Fibroids

GYNECOLOGY IN PRACTICE: SERIES EDITOR AYDIN ARICI

Fibroids

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Series Foreword

In recent decades, massive advances in medical science and technology have caused an explosion of information available to the practitioner. In the modern information age, it is not unusual for physicians to have a computer in their offices with the capability of accessing medical databases and literature searches. On the other hand, however, there is always a need for concise, readable, and highly practical written resources. The purpose of this series is to fulfill this need in the field of gynecology.

The *Gynecology in Practice* series aims to present practical clinical guidance on effective patient care for the busy gynecologist. The goal of each volume is to provide an evidence-based approach for specific gynecological problems. "Evidence at a Glance" features in the text provide summaries of key trials or landmark papers that guide practice, and a bibliography at the end of each chapter provides a springboard for deeper reading. Even with a practical approach, it is important to review the crucial basic science necessary for effective diagnosis and management. This is reinforced by "Science Revisited" boxes that remind readers of crucial anatomical, physiological or pharmacological principles for practice.

Each volume is edited by outstanding international experts who have brought together truly gifted clinicians to address many relevant clinical questions in their chapters. The first volumes in the series are on chronic pelvic pain, one of the most challenging problems in gynecology, *Disorders of Menstruation*, *Infertility*, and *Contraception*. These will be followed by volumes on *Sexually Transmitted Diseases*, *Menopause*, *Urinary Incontinence*, *Endoscopic Surgeries*, and *Fibroids*, to name a few. I would like to express my gratitude to all the editors and authors, who, despite their other responsibilities, have contributed their time, effort, and expertise to this series.

Finally, I greatly appreciate the support of the staff at Wiley-Blackwell for their outstanding editorial competence. My special thanks go to Martin Sugden, PhD; without his vision and perseverance, this series would not have come to life. My sincere hope is that this novel and exciting series will serve women and their physicians well, and will be part of the diagnostic and therapeutic armamentarium of practicing gynecologists.

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Preface

A newspaper reporter once asked me, "*Why* do you study uterine fibroids?" My reply was, "Because of the patients I treat with fibroids. Patients with fibroids suffer a great deal and treatment options are so limited – we need to develop new treatments!" I rather suspect the reporter was looking for another response, perhaps an erudite scientific rationale, but many women with fibroids experience significant health consequences. The following stories reflect the pain and suffering caused by uterine fibroids.

> Because of my fibroids my cycle was very heavy which meant that I had to visit the ladies room every one to two hours to change my tampon and pad. I feared that my clothes would get soiled in public so I would rarely socialize. I was severely anemic and had no energy so I felt weak, lethargic and lacked enthusiasm most of the time. In addition, I frequently had the urge to urinate only to find out it was just a few drops of urine, and not to mention it would take an act of congress to have a bowel movement. I felt bloated, my stomach got bigger and I always had a feeling of discomfort. I did not know when to expect the bleeding so I was always nervous as to when it would happen. I felt lots of pressure in my pelvic area and was not interested in sex because I feared that I would bleed.

In addition to acute issues, fibroids can be a life-altering disease, as is so poignantly illustrated by the next story.

> I am 73 years old. Persons my age look back upon life and *weigh* pleasures and disappointments, joys *and sadness and satisfactions and regrets. My greatest* regret is that I never had children of my own. I never had children because I lost the capacity to bear children. A large fibroid causing great pain, pressure and debilitating bleeding necessitated a hysterectomy in my thirties. At the time of surgery the fibroid was measured as 14 by 14 centimeters. At the time of my surgery my widowed mother cried as I would not have children. I do not regret the hysterectomy because I felt so much better physically. But the loss of the ability to have at least one child has haunted me.
>
> My gynecologists were caring people for their time. I had been told 4 years before the surgery that I had a "questionably slightly enlarged fibroid on the left side but this is not for sure." I put this in quotes as it is comes directly from my medical record, copies of which I have kept in my files all these years.
>
> Seven months later the fibroid was "probably 3–4 centimeters." Almost 2 years later it was either "5–6 centimeters" or "7 x 7 centimeters" depending on the examining gynecologist. I was told that I should have a baby and then come back for surgery. Well, the pregnancy option was not so easily arranged. I had just broken off a relationship, but even if I had still been involved with that particular person I was not really sure that marriage to him was a good idea. Throughout this whole period of time my friends and colleagues kept asking me: Isn't there a medical treatment? Why can't you just take a pill? Why is hysterectomy the only treatment?
>
> While I grieve my lack of biological children it is even harder today to come to terms with the lack of knowledge available to physicians practicing in 1975 regarding the biology of fibroids, knowledge that would have provided the foundation for non-surgical treatment possibilities. While physicians and scientists over the past 37 years have learned more about these benign but burdensome tumors called by various names – leiomyomata, myomas or simply fibroids – and there are currently imaging techniques that allow precise measurement of fibroid size and growth, nonsurgical medical therapies still elude us. Fibroids are so common and affect over 70–80% of women. I cannot accept the fact that more has not been done. I grieve that society in general and funding agencies in particular have not been able to provide the really extensive resources needed to find medical treatment. Thirty seven years is a long time.

As a physician caring for women with fibroids, it is painful to bear witness to the pain, frustration, and angst caused by uterine fibroids. Without question, more needs to be done. The issue is further magnified by the prevalence of uterine fibroids, which now affect one in every two women in the US. There are millions of women who have been affected and have stories to tell about the adverse impact of fibroids in their lives.

Strangely, for a condition that affects millions of women worldwide, few books have been written

about fibroids and their treatment. There is a need to shed light on this extremely prevalent condition, not only to educate providers but also to explain options for treatment for women who suffer from the condition. For this reason, I enthusiastically accepted the invitation of Dr Arici to edit this book.

The intent of this book is to provide a succinct, pithy summary of current understanding and evidence-based treatment of fibroid disease. In addition, it is my hope that the book will help to stimulate interest for future research and development of understanding of these enigmatic tumors.

To bring the reader up to date with current understanding of fibroids, Chapter 1 includes a description of the pathophysiology of the disordered growths we call fibroids.

Fibroids are a very diverse disease with a complexity that is almost infinite. That is, the location, size, and number of fibroids are so extremely varied between patients that what might otherwise be a simple disease to treat is actually extremely complex. In Chapter 2, the clinical spectrum of fibroids is examined to lay the foundation for Chapter 3, in which an evidence-based approach to fibroid management is provided. Since the effects of fibroids upon reproductive health vary greatly depending on the age of the woman, Chapter 4 examines pregnancy-related consequences of fibroids, whereas Chapter 5 focuses on considerations unique to fibroid disease in the older woman.

Currently, there is no effective preventive therapy for fibroids. Accordingly, available treatment options are reviewed in detail, with particular attention paid to the evidence supporting the different options and the expected benefit, beginning with medical therapy in Chapter 6. Nonsurgical treatment options, uterine artery embolization and magnetic resonance-guided focused ultrasound are discussed in Chapters 7 and 8, respectively. Some patients will require surgical intervention, and newer methods of minimally invasive surgery are reviewed in Chapter 9. Notably, the treatments reviewed in Chapters 6 through 9 are not typically associated with a long recuperation, and use of such treatment approaches will minimize the disruption caused by a lengthy recovery period.

Should the more patient-friendly options reviewed in Chapters 6 through 9 not be sufficient, standard surgical treatments, abdominal myomectomy and hysterectomy, are reviewed in Chapter 10, with discussion of expected outcomes and attendant complications. Although uncommon, in some cases fibroids are associated with rare genetic conditions that require a different approach, and current understanding of these diseases is discussed in Chapter 11.

Finally, counseling of the patient with fibroid disease is reviewed in Chapter 12, an important chapter given the varied nature of the disease. The role of diet and current understanding of prevention are reviewed in detail. Still, more needs to be done. Research and understanding are vital to the future treatment and ideally prevention of uterine fibroids.

In closing, I would like to acknowledge the contributors to this book for their work and dedication that made this possible; specifically, the students, residents, fellows, and faculty who share my passion for advancing understanding and treatment of fibroid disease. Finally, it is important to acknowledge key individuals who have, at critical times, kindled and supported my research interest on uterine fibroids. Drs Phyllis Leppert and Vivian Pinn have had a profound and lasting stimulation on my research on uterine fibroids. There have been many individuals at NIH who have supported our research on fibroids, most notably Drs Alan DeCherney, Duane Alexander, Yvonne Maddox, and George Chrousos. These mentors and leaders have provided guidance, inspiration, and ideas, and by so doing, have established a foundation for future research that is so desperately needed for this debilitating condition.

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1

Understanding Uterine Fibroids

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Introduction

Uterine leiomyoma, commonly called fibroids, consist of an abundant but altered extracellular matrix. Fibroids are benign monoclonal tumors believed to be of myometrial origin. They develop in women of reproductive age, a fact that led to the concept that their growth was predominantly driven by reproductive hormones. The first systematic study of their pathology was described in 1793 and the first abdominal myomectomy was reported in 1838. By the early 1900s, because of advances in surgery and anesthesia, many surgeries were done for uterine leiomyoma, as reported in the first book on the subject, *Fibroids and Allied Tumors*, by Cuthbert Lockyer in 1918. While the prevalence of fibroids in the United States is often quoted to be 35–50%, in fact the prevalence is likely much higher. In 1990 Cramer reported a study of hysterectomies in which fibroids were detected in 77% of uterine specimens. More recently, the group led by Baird reported that the cumulative incidence of fibroids by age 50 was 70% in US Caucasian women and approximately 80% in African-American women. Currently, one in every two women of reproductive age in the US has uterine fibroids, making the condition the most common disease of the female reproductive tract. In this chapter, we review what is known about causes of fibroids, their features, and pathophysiology.

Fibroid etiology and pathophysiology

Despite their remarkable prevalence, the etiology of fibroids remains unknown. Nonetheless, the past decade has witnessed a significant increase in published scientific investigations of uterine fibroid biology, initiating factors, fibroid growth and development as well as new treatment modalities. Several seminal breakthroughs in understanding of fibroid pathophysiology have occurred. Most significantly, Baird and coworkers reported that uterine fibroids grow at various rates even in the same women and that the growth rate patterns are different in Caucasian and African-American women. A second scientific observation that changes the way scientists think about fibroids were reports that these benign tumors are composes of altered collagen fibrils and display many differences in other extracellular molecules compare to normal myometrium. In addition, mechanical forces appear to play a role in the development and growth of these benign tumors. This has led to the appreciation that fibroids can be considered a fibrotic disease. Furthermore, numerous cytokines and integrins have been reported to be significantly changed in fibroids, leading to the concept that the inflammatory response also plays an important role in the etiology and pathophysiology of fibroids.

It is essential to appreciate that the molecules involved in the inflammatory response are the same

Fibroids, First Edition. Edited by James H. Segars.

as those involved in tissue remodeling during development and after injury. Thus the concept of inflammation actually fits into a theory of fibroid development based on an altered response to noxious stimuli; possibly tissue injury from extravasated menstrual blood into the myometrium or hypoxia leads to altered repair and fibrosis. The two advances discussed above suggest further studies and the need for the development of a unified systematic approach to the etiology of fibroids.

Genetics

Uterine fibroids are monoclonal in origin. Approximately 40% of fibroids are cytogenetically abnormal. Cytogenetics studies demonstrated that fibroids have similar chromosomal rearrangements to other benign lesions but are distinct from the complex rearrangements and aneuploid karyotypes characteristic of leiomyosarcomas. Genetic polymorphisms in the estrogen receptor gene, insulin-like growth factor gene, and androgen receptor gene have been reported to be related to the development of fibroids.

Most of the cytogenetic alterations involve chromosome 12. Translocations involving this chromosome identified members of the high mobility group gene family, which include HMGA1 and HMGA2. Both HMGA1 and HMGA2 are aberrantly expressed in fibriods and other benign lesions such as lipomas. Three loci on chromosomes 10q24.33, 22q13.1 and 11p15.5 revealed genome-wide significant associations with uterine fibroids. It is possible that the 60% of uterine myomas with a normal karyotype may harbor a subtle genetic abnormality such as point mutation or changes in the regulatory regions of certain genes.

Some types of fibroids, such as those found in individuals with hereditary leiomymoma and renal cell carcinoma (HLRCC) syndrome, are associated with genetic mutations (see Chapter 11). It is not clear, however, if genetic susceptibility gene abnormalities will be discovered for all fibroid subtypes. Specifically, the fact that fibroids are extremely common suggests that genetic factors alone are unlikely to be a significant component of their overall etiology. Thus, further investigations are needed before the question of whether or not genetic susceptibility genes exist can be answered. What is interesting, however, is the fact that small RNAs, called microRNAs, are present in fibroids collected at the time of hysterectomy. These microRNAs regulate gene expression and their role in fibroid development and growth is intriguing but remains to be defined.

Recently it was reported that MED12, the mediator complex subunit 12 gene, is mutated at a high frequency in uterine fibroids. Eighteen fibroids from 17 subjects were evaluated. Ten tumors had a mutation in this gene and eight of these mutations were in codon 44. Next, an additional 207 fibroids were evaluated for codon 44 mutations. While this report has generated much interest, the results need to be confirmed in future studies with larger sample sizes, by fibroid subtype, as well as data from different populations.

Growth factors

Transforming growth factor (TGF) beta has a central role in the enlargement of fibroids. TGF-beta stimulates the production and deposition of extracellular matrix (ECM) and is considered to be a major growth factor in the development of fibrotic disease. Compared to normal myometrium, fibroids have a greater density of TGF-beta receptors. The downstream targets of TGF-beta signaling are many and include tissue inhibitor of matrix metalloproteases (MMPs) and plasminogen activator inhibitor (PAI), which promote the deposition of the ECM by complex mechanisms. Interleukin (IL)-11, under the regulatory control of TGF-beta, plays a role in the development of fibrosis and is overexpressed in fibroids. Interestingly, gonadotropin-releasing hormone (GnRH) agonists inhibit the expression of TGF-beta. GnRH agonists also change osmotic forces and decrease the water content of fibroids. Furthermore, reduced TGF-beta expression results in reduced ECM production and shrinkage of the fibroid size, indicating again the major role of TGF-beta in fibroid growth.

CAUTION #1

In evaluating investigations of fibroid surgical specimens, it is important to bear in mind that the tissue was obtained at one point in time and that in most cases it is not known whether the particular tissue studied was from a growing, static or regressing fibroid. Since size of the fibroid also does not agree with growth state, small size *per se* does not imply a new or actively growing fibroid. Future studies will need to gather information on fibroid size and location, and growth rate over time.

Several growth factors are also vasoactive and angiogenic. Therefore, they may contribute to the profuse menstrual bleeding. Examples of such growth factors include basic fibroblast growth factor (bFGF) which promotes angiogenesis, prolactin which is a proangiogenic factor, and parathyroid hormone-related protein which acts as a vasorelaxant.

The growth factors that are known to act on the myometrial cells are the following: epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), acidic fibroblast growth factor (aFGF), and basic fibroblast growth factor (bFGF). The effect of growth factors on a target tissue is the production of cytokines including IL-1, IL-6, IL-11, IL-13, IL-15, interferon (IFN)-delta, tumor necrosis factor (TNF)-alpha, and granulocyte macrophage colony-stimulating factor (GM-CSF). These cytokines have been documented in the myometrium and fibroids.

The role of sex steroids

Sex steroids promote the local production of growth factors, which act in autocrine or paracrine mechanisms resulting in cellular growth. Fibroids are responsive to sex steroids, estrogen and progesterone but the precise mechanisms that lead to growth are unclear. Expression of a dominant negative estrogen receptor inhibited fibroid cell growth *in vitro* and *in vivo*. We do know that fibroids express higher levels of cytochrome P450 aromatase, which consequently catalyzes androgen to estrogen. Leptin is a regulator of aromatase; it also stimulates collagen production and may therefore play a role in fibroid formation. Treatment of primary fibroid cells with leptin resulted in increased aromatase expression.

Although estrogen has traditionally been identified as the most important sex steroid for fibroid growth, progesterone seems to have the dominant steroidal influence on fibroids. This dominance is supported by the increased mitotic rates in fibroids during the secretory phase of the menstrual cycle. The clinical response of mifepristone, a progesterone antagonist, in inhibiting fibroids growth supports this theory. Progesterone may influence leiomyoma growth by upregulating EGF and TGF-beta 3 expression. In contrast, progesterone reduced IGF-1 expression in cell culture. Progesterone receptor (PR) ligands regulate gene expression in leiomyoma cells by forming PR-ligand complexes that interact with gene promotors. Progesterone also inhibits MMPs. The action of MMPs on the ECM is complex but the end result is that they affect matrix assembly and deposition.

SCIENCE REVISITED #1

Retinoic acid and fibroid growth?

Surgical specimens of fibroids demonstrated reduced expression of gene products involved in retinoic acid production and increased expression of gene products involved in retinoic acid degradation. Fibroids exhibited more rapid metabolism of retinoic acid after addition of the hormone, compared to myometrium. When retinoic acid was added to fibroid cells in tissue culture, expression of genes involved in retinoic acid production increased to expression levels similar in fibroids. Retinoic acid treatment of immortalized fibroid cells altered expression of many genes encoding ECM proteins, and levels of expression resembled expression levels observed in myometrial cells. In contrast, treatment of immortalized myometrial cells with TGF-beta 3 caused immortalized myometrial cells to develop a leiomyoma-like ECM phenotype.

Antiprogestins have important therapeutic effects on fibroids. Selective progesterone receptor modulators represent a class of PR ligands that exerts clinically relevant tissue-selective progesterone agonist, antagonist or partial (mixed) agonist/antagonist effects on various progesterone target tissues, depending on the biological action studied.

Selective progesterone receptor modulators (SPRMs) such as asoprisnil, ulipristal and telapristone have been shown to reduce fibroid volume *in vivo* and to induce apoptosis *in vitro*. The synthesis of mifepristone, the first glucocorticoid and PR antagonist, was a starting point of drug discovery and research programs in the area of progesterone antagonists. Interestingly, the mifepristone effects were accompanied by a reduction in uterine blood flow, suggesting that progesterone plays an important role in the regulation of uterine perfusion.

In clinical studies (see Chapter 6), asoprisnil significantly suppressed both the duration and intensity of uterine bleeding as well as the uterine volume of the largest fibroid, and consequently the symptoms of pressure and bloating. Administration of ulipristal acetate for 3–6 months controlled bleeding, reduced fibroid size, and improved quality of life. Variations in SPRM biological effects may be due to differences in fibroid cells, binding kinetics or ECM characteristics. Although these drugs are not FDA approved and are not on the market, their effects on fibroids show that progesterone is an important regulator of fibroid growth. Recent studies have confirmed beneficial clinical effects and these compounds may be available clinically in the future.

Myometrial hyperplasia: a possible precursor to fibroids

Myometrial hyperplasia, a common structural variation of the myometrium, is an irregular area of myometrial hypercellularity and increased nucleus/cell ratio and was first described by Cramer in 1995. It is diagnosed by a pathologist by observation of increased blue areas on H&E slides and on scanning magnification. These areas can be correlated with bulges and firm pale areas of the fixed gross specimens. With further light microscopic observation, a dramatic difference in cellularity and nucleus/cell ratio between these blue-staining areas and adjacent myometrium is apparent. Finally, microscopic pressure effects of vascular dilation (ectasia) and interstitial edema are noted in the outer myometrium.

The onset of myometrial hyperplasia occurs in adolescence around the time of menarche. After years of careful observation, Cramer reported the association of fibroids <1 cm in size or seedling myomas with myometrial hyperplasia, which suggests that myometrial hyperplasia is a precursor lesion for fibroids. It is quite intriguing that both myometrial hyperplasia and uterine fibroids produce evidence of the pressure effects of vascular dilation and interstitial edema in tissue specimens. Although not accepted as a discrete entity by all pathologists, myometrial hyperplasia deserves to be more fully scrutinized and investigated.

Fibroid growth

As noted above, Baird and colleagues recently published a report on the growth of fibroids that has changed thinking about this condition. By showing that fibroids grow at different rates in the same woman and that some grow, some are static and some actually regress in size, despite a uniform hormonal milieu, their study indicated that growth is not dependent on circulating levels of systemic hormones, but that other factors are at work. In the same study, they report that while black and white women less than 35 years of age had the same fibroid growth rates, growth rates declined with age in white women even before menopause but not in blacks, and that fibroid size did not predict fibroid growth. The same group also reported that fibroids regress in size in pregnancy. This study suggests that the effect of reproductive hormones on fibroid growth is not as straightforward as previously thought.

EVIDENCE AT A GLANCE

Fibroid growth is variable and not wholly dependent on circulating sex steroid levels

Baird and colleagues tracked the growth of 262 fibroids that ranged in size from 1 to 13 cm in diameter from 38 black women and 34 white women. They measured fibroid volume by MRI scans over 12 months. Median growth rate was 9% with the large range of –89% to +138%. 7% of the fibroids regressed in size with a >20% shrinkage. Tumors from the same woman grew at different rates as within-woman variation was twice that of the variation among different women ($p < 0.001$). The odds among whites of a tumor growing >20% in 6 months decreased with age but not for blacks ($p < 0.01$) (Peddada et al., 2008).

Classification of fibroids

Fibroids arise from a very heterogeneous disease process. In fact, clinical acumen suggests there are different fibroid phenotypes, one being a uterus that is chock-full of multiple fibroids of all sizes and a second condition where only one fibroid is present. Currently, there is not a universally accepted classification for fibroids that is agreed upon by clinicians and scientists working in the field of fibroid biology. The most commonly used system classifies fibroids in relation to where the fibroid is located in the uterine myometrium: submucosal, intramural,

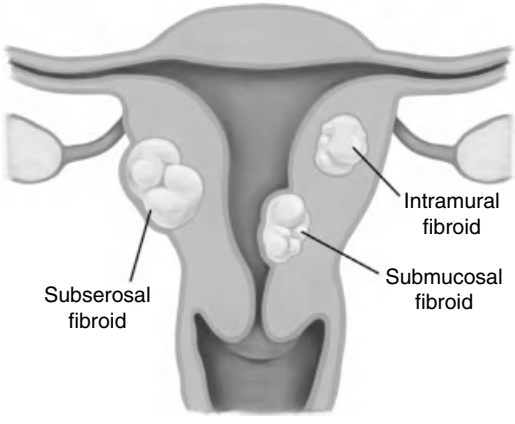

Figure 1.1 Uterine leiomyoma may be classified based on location in the uterine muscle. Submucous, intramural, and subserosal types of fibroids are shown. Such a system is useful for communication but does not account for fibroid size or overall uterine size in cases of more severe disease when multiple fibroids are present (Drawing provided by Anne Kelley).

and subserosal. Submucosal refers to the region that is below the endometrium but the term is actually a misnomer as the uterus does not contain any mucosal tissue, so the term "subendometrial" would be more accurate. Intramural fibroids are those that do not distort the endometrial cavity whatsoever, and have <50% protrusion beyond the serosal surface. Subserosal fibroids are then defined as those with >50% protrusion beyond the serosal surface of the uterus (Figure 1.1).

Submucosal fibroids have been further classified and subdivided, to allow for distinction and for clinically relevant surgical approaches (see Chapters 9 and 10). Submucosal fibroids distort the uterine cavity and have been subclassified into three types – type 0, type I, and type II – based on the ESHRE/ESGE classification. Type 0 are >90% within the uterine cavity and are also called pendunculated or intracavitary fibroids. Type I are sessile submucosal fibroids that are >50% in the cavity, and type II are <50% in the cavity. A more detailed classification system known as STEPW, that includes fibroid size, location and depth of invasion, has been proposed with the goal of more accurately predicting the success of treatment. While the ESHRE/ESGE system is very useful for hysteroscopic surgery, no current systems account for disease burden (number of fibroids) or fibroid size, which is related to severity of disease, bleeding, and pressure symptoms. There is a great need to characterize and develop a complete classification of fibroids that will enable scientists and clinicians to deeply understand the molecular biology and natural history of fibroid phenotypes as it is apparent that every fibroid is not the same as another. Whereas the basic underlying physiology may be identical, the actual triggering mechanisms of fibroid development between patients or state of growth of a particular fibroid may vary among other fibroids in a single uterus.

Pathology of uterine fibroids

Grossly, fibroids are monoclonal smooth muscle tumors that appear as firm circumscribed nodules arising in and from the myometrium. They may be single or multiple and are of various sizes. A pseudocapsule surrounds them and upon incision, the fibroid consists of characteristic firm, pink or tan circular swirling or whorling smooth muscle bundles and connective tissue. There is a large network of blood vessels surrounding the fibroid nodule under the pseudocapsule familiar to all surgeons who have performed myomectomies. The vessels in the fibroid itself tend to be small without muscular walls and do not appear to have the classic gradient of vessels found in myometrium and are not easily noted at the level of gross examination (Plate 1.1).

Microscopically, the uterine fibroid is a well-circumscribed nodule with interlacing bundles of spindle-shaped cells with no mitotic activity and no nuclear atypia in a stroma with varying degrees of fibrosis. In fact, the presence of 10 or more mitoses per 10 high-power fields indicates malignancy, and this feature differentiates leiomyosarcomas from leiomyoma in addition to nuclear atypia. Light microscopy of uterine fibroids and adjacent myometrium using stains for collagen revealed collagen to be abundant in the leiomyoma tissue, while the myometrium had sparse, well-aligned collagen bundles adjacent to smooth muscle cells. Small blood vessels do not have well-defined muscular walls and are often ectatic or dilated. This vascular ectasia is considered to be due to compression (Plate 1.2).

When viewed using electron microscopy, fibroids feature an ECM with widely dispersed and short

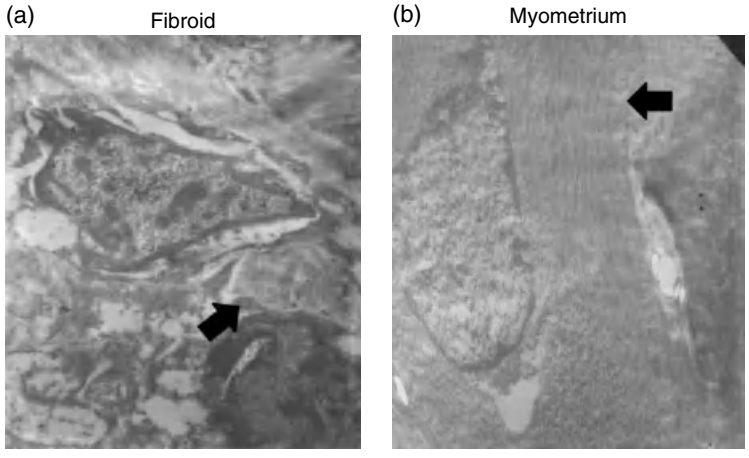

Figure 1.2 Electron microscopy images of matched fibroid and myometrial tissues.
(a) The fibroid cell nucleus is angular and notched. Also, note the disordered structure of the ECM and collagen fibers in the fibroid tissue (*black arrow*; ×15,000). (b) Image of myometrium from the same patient. Note the well-aligned, ordered collagen fibers (*black arrow*) and the more rounded nucleus (×11,000).

collagen fibers. Consistent with the presence of an abnormal ECM, collagen fibers are arranged in a nonparallel manner in fibroids. In contrast, those of the myometrium are well packed and parallel to each other. Thus, the abundant collagen in fibroids is altered in contrast to the collagen structure and orientation of myometrium. Fibroid cells have a myofibroblast-like appearance (Figure 1.2).

Pathologists also identify different types of what has traditionally been called degeneration that can occur in uterine fibroids: hyaline (a histological term meaning that cytoplasm becomes glassy and homogeneous in appearance), myxomatous (mucus is observed), calcific (evidence of calcium deposits), cystic, fatty, or red degeneration and necrosis. The mildest form of degeneration of a myoma is hyaline degeneration. The most acute form is red infarction which is classically thought to be due to rapid outgrowth of its blood supply. It is often a common form of fibroid degeneration in pregnancy and is associated with sudden pain. Two-thirds of all myomas show some degree of degeneration, with the three most common types being hyaline degeneration (65%), myxomatous degeneration (15%), and calcific degeneration (10%).

Extracellular matrix of fibroids

Fibroid cells do not proliferate rapidly. Importantly, growth more than 5 cm is mainly due to excessive production of the disorganized ECM. It is the overproduction of the ECM that contributes extensively to uterine fibroid volume expansion and is what makes these tumors a fibrotic disease. In addition to altered collagen, uterine fibroids are tumors enriched in ECM proteins. The ECM is composed predominantly of collagens, proteoglycans, matrix glycoproteins, and matricellular proteins (Plate 1.3).

Fibroids not only exhibit increased levels of ECM gene expression by microarray analysis but contain fibronectin and proteoglycans such as dermatopontin, decorin, versican and matricellular proteins such as thrombospondin-1 (TSP-1) and SPARC. TSP-1 not only activates latent TGF-beta but also plays a significant role in angiogenesis. The ECM plays a dynamic role in serving as a repository for cytokines and growth factors which, when activated, stimulate signaling to initiate cell regulatory pathways. Collagen, fibronectin, and proteoglycans serve to confine these cytokines and growth factors in the vicinity of fibroid cells by binding tightly to them and preventing them from diffusion to distant sites. Most importantly, the ECM sequesters TGF-beta and it is only when TGF-beta dissociates from the ECM that it becomes available to bind to its receptors. Proteoglycans, such as heparin sulfate, which binds to several growth factors such as bFGF, TGF-beta and PDGF, play an important role in tumorigenesis.

SCIENCE REVISITED #2

Collagens

Collagens are the most abundant protein in mammals, making up about 25–35% of the body's protein content. Collagens are encoded by at least 30 genes. Fibril-forming collagens are synthesized as pro-collagen molecules that are secreted into the ECM by fibroblasts, smooth muscle cells and chondrocytes, where these propeptides undergo processing and self-assembly and result in the formation of the mature collagen. Fibrillar collagens (types I, II, III, IV, V) are the most abundant collagens and function as structural proteins. The predominant collagens in a normal uterus are types I, III, and V. Type IV collagen is found predominantly in basement membranes.

Because ECM accumulation is the most consistent feature of all fibrotic conditions, the basis for tissue fibrosis possibly involves not only increased connective tissue deposition but also decreased ECM degradation of newly secreted and poorly cross-linked collagen. This deposition of stiff ECM produces mechanical stress on the cells and increased mechanical stress has been shown to be involved in the growth of many tumors. Mechanical stress of cells changes the cell shape by inducing changes in the signaling of molecular pathways. It is known that this mechanism of cell signaling change will increase production of ECM and as this ECM is produced, the microenvironment of the cells compresses the cells, leading to increased mechanical stress. Recently, peak strain and pseudodynamic modulus of fibroid tissue was demonstrated to be significantly higher than that of adjacent myometrium. This study also demonstrated that in addition to these properties of fibroid stiffness, fibroids that have been obtained at the time of hysterectomy, and by definition were causing symptoms, have an attenuated sensitivity to mechanical stress, suggesting that fibroid cells have become adapted to their very stiff environment and are insensitive to more moderate or more subtle mechanical cues. These findings imply that mechanical stimulation, which in other cells types changes cell signaling behavior (known to cause more production of collagen), could be downregulated in fibroid cells.

By histochemical and immunofluorescence methods, the glycoproteins, proteoglycans, and collagen of the ECM of leiomyoma have different distribution when compared to normal myometrium. So far, studies of the types of collagen in fibroids show that type V collagen is increased and there is evidence that the ratio of type I to type III collagen is different from that found in myometrium. These changed ratios are similar to those found in tissue remodeling and early wound healing. This research is ongoing and time will provide a more complete understanding of the development and growth of fibroids. Based on existing evidence, however, it is clear that the ECM plays an important and critical role in fibroid growth, and possibly development.

Effects of uterine fibroids on reproductive tissues

Depending on their location, fibroids have been associated with bleeding, pain, pressure symptoms, recurrent pregnancy loss, miscarriage, infertility, and pregnancy complications. The strong effect of fibroid location upon fertility has been consistently observed in many studies. Many hypotheses have been proposed to explain the possible adverse effect of fibroids on fertility and pregnancy, including impaired and/or obstructed gamete transport, dysfunctional uterine contractility, abnormal vascularization, chronic inflammation and abnormal hormonal milieu, but in most cases the hypotheses have not been rigorously tested.

One pathophysiological mechanism has been established. Studies have shown that submucosal and intramural fibroids that distort the endometrial cavity are associated with lower pregnancy, implantation and delivery rates; furthermore, removal of a submucous fibroid improved implantation and pregnancy rates. These studies implied that the mechanism by which submucous fibroids reduce implantation and endometrial receptivity is not simply due to a local effect but involves a signaling mechanism to the entire endometrium accompanied by abnormal endometrial development. Specifically, global endometrial expression of HOXA10 and HOXA11 (which are homeobox-containing transcription factors) was altered in biopsies from patients with submucous fibroids, compared to controls, both in endometrium overlying the fibroid and from the adjacent endometrium. Histology

alone cannot effectively and reliably assess endometrial receptivity and molecular evaluation of the endometrium is crucial to identifying defects in endometrial receptivity.

Basic transcriptional element binding protein 1 (BTEB1) and leukemia inhibitor factor (LIF) also play a role in embryonic uterine development, and endometrial development during each menstrual cycle and implantation. In support of a critical role of these factors in early pregnancy, targeted mutations of the genes in mice resulted in infertility due to implantation failure. In contrast, subserosal fibroids that do not impinge on the endometrial cavity do not affect fertility outcomes and removal does not confer benefit to the patient. The clinical evidence describing the effects of fibroids on pregnancy and fertility is detailed in Chapters 2–4.

CAUTION #2

Clinicians should be aware that there are no universally accepted animal models for fibroids. The most frequently cited model is the Eker rat, which develops spontaneous tumors. This model was established originally as a model of leiomyosarcoma. However, the tumors do not have a well-defined abundant collagen and other ECM components, which is why some scientists do not accept this as a satisfactory model of fibroids. There are animals that do spontaneously develop fibroids, such as dogs that develop tumors in the vagina, great apes, and mature pot-bellied pigs. However, these tumors do not arise frequently in these animals. Primary cultures from tissue collected at surgery will exhibit growth factors expressed by the particular fibroid collected. Cell lines will transform in culture over time. These facts do not mean that the studies are not useful in the quest for knowledge regarding fibroids, but only that their particular limitations need to be considered.

In addition, fibroids are associated with abnormal uterine bleeding, pelvic pain, and pressure. The pathophysiological mechanism for pressure seems straightforward as such symptoms appear to be related to effects on adjacent pelvic organs, such as bladder and bowel. The pathophysiological mechanism accounting for heavy bleeding is less clear, although tumors that distort or impinge upon the endometrium are more likely to be associated with bleeding. It is possible that the mechanism may be related to the altered endometrial development described in the preceding paragraphs, since the thin, poorly developed endometrium overlying a submucosal fibroid has been known for over 100 years. Current thinking is that normal endometrial development does not occur, which leads to altered vascular responses and excessive bleeding (see Chapter 6).

The economic burden of fibroids

Epidemiologists, demographers, and clinicians are beginning to provide a clearer picture of the true cost to society of uterine fibroids. Approximately 200,000 hysterectomies and 30,000 myomectomies are performed annually for uterine leiomyoma in the US. Women with uterine fibroids undergo surgery, require frequent outpatient visits and hospitalization, are prescribed medications for symptom control, and miss work. Furthermore, uterine fibroids have additional obstetric and reproductive complications that adversely affect women's health.

Approximately 588,000 women annually seek treatment for uterine fibroids. The most commonly performed surgery is hysterectomy, followed by myomectomy, endometrial ablation, and uterine artery embolization. Reimbursement rates for myomectomy were most expensive, followed by hysterectomy. Approximately 36.97–77.64% of women manage their symptoms without surgery, but the exact extent of the symptoms of these women is not known. Nor do we know whether or not the symptoms interfere with their work or daily activities, or if they would seek treatment if other options were available to them.

Most of the published studies on the economic burden of disease used a lower prevalence for fibroids than the often quoted 35–50%, which may have underestimated the total costs of fibroids. A more recent study suggests that the costs of uterine fibroids in the US are quite high, indicating an urgent need for additional therapies including therapeutic combinations to alleviate the symptoms of fibroids. In this study, direct, indirect, and obstetric costs were estimated in 2010 dollars. The

direct costs, which include surgery, outpatient visits, hospitalizations, and medications, were estimated to be $4–9.3 billion each year. The costs of absenteeism and short-term disability ranged between $1.5 and $17 billion annually. Obstetric complications, such as preterm delivery, miscarriage and cesarean delivery, result in an additional $8.7 billion. Thus, the total annual cost ranged between $5.8 and $34.3 billion. These figures are well above cost estimates in previous studies.

Obstetric complications due to fibroids, such as preterm delivery, miscarriage, cesarean delivery and labor and delivery visits due to pain, may increase the cost to society to as much as $8.7 billion per year. As reported by the US Centers for Disease Control, this results in a minimum total annual cost of $13.6 billion compared to $18 billion for asthma and $76.6 billion for hypertension which are also common health problems in the US. With all the above costs considered, uterine fibroids contribute considerably to the cost of healthcare for women in the United States.

Conclusion

Although uterine leiomyomas are benign tumors, fibroids can lead to multiple and disabling difficulties. While sex steroids play an important role in the pathogenesis of uterine fibroids, the ECM, growth factors, and cytokines all contribute to their development. Specifically, the interaction of hormones, growth factors, cytokines, and ECM components appears to be crucial for the growth of fibroids. Within a given uterus, some fibroids may be growing while others may be shrinking. Fibroids clearly reduce fertility, increase preterm labor and delivery, and markedly increase the risk for cesarean delivery. The effect of fibroids on fertility is most likely a global endometrial effect that can be detected at the molecular level, resulting in abnormal endometrial development and receptivity. Fibroids represent a tremendous public health burden on women and the annual cost to society may approach $34.3 billion.

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2

The Clinical Spectrum of Fibroid Disease

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Introduction

Uterine fibroids are widespread in the United States. Women who have symptomatic fibroids bear an enormous disease burden and reduced quality of life. It is not uncommon to incidentally diagnose untreated uterine fibroids of considerable size. What may be more surprising is that many patients with uterine fibroids are asymptomatic. This chapter will review the clinical spectrum of fibroid disease, including the symptoms, diagnosis, interval changes, and epidemiology of fibroid disease.

Symptoms

In the presence of uterine fibroids, a woman may experience recurrent pregnancy loss, adverse obstetric outcomes, decreased fertility or sterility, chronic pelvic pain, abnormal uterine bleeding, urological or gastroenterological complications, and sizeable pelvic masses. These symptoms are neither mutually inclusive nor exclusive, and can cause significant disruption to a patient's wellbeing and quality of life. In fact, although available data are limited, it is estimated that 20–50% of patients with uterine fibroids experience symptoms that can be directly attributed to the presence of uterine fibroids. However, it is currently believed that many women with uterine fibroids do not experience, or perhaps do not report, adverse symptoms attributable to fibroids. Clinical experience suggests that symptoms relate somewhat to the size or location of fibroids, such that "asymptomatic" fibroids are more likely to be smaller tumors, perhaps located in the subserosal or intramural portions of the uterus. Conversely, a 1 cm intracavitary fibroid can cause heavy menses or pregnancy loss. One study has estimated that each year, approximately 0.9% of women affected with fibroids will consult with a provider because of symptomatic fibroids, and of those who seek care, over 90% will be treated with medical or surgical therapy (Carls et al., 2008).

To assess the impact that symptomatic fibroids had on patient quality of life and to quantitatively measure symptoms related to fibroid disease, the research team led by Spies developed the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire (Spies et al., 2002). The UFS-QOL revealed that women with fibroids experienced significantly elevated levels of symptom distress and lower health-related quality of life when compared to patients without fibroids.

Abnormal uterine bleeding

Abnormal uterine bleeding (AUB) is the most common symptom associated with uterine fibroids, and is experienced in approximately 30% of patients with the disease (Gupta et al., 2008). AUB is described as cyclical bleeding of increased quantity, menorrhagia, and/or duration. Excessive bleeding can cause reduction in a woman's quality of life

Fibroids, First Edition. Edited by James H. Segars.

by requiring significant lifestyle modifications, including frequent tampon and/or peripad changes (see Table 2.1). AUB can be life threatening since it may lead to acute blood loss, hemorrhage, and symptomatic anemia, requiring emergency blood transfusion and hospitalization. Bleeding can vary with the location of the fibroid. In a study of premenopausal women with abnormal bleeding, both intramural and submucosal fibroids were more prevalent in symptomatic patients over asymptomatic patients. It has been suggested that fibroids with a greater intracavitary extension can cause more bleeding (Bukulmez and Doody, 2006). However, this association has been questioned and at least one study found that symptoms of heavy bleeding were equally present in patients regardless of the fibroids' presence in the uterine cavity (Wegienka et al., 2003).

CAUTION #1

Much confusion exists among gynecologists when the terms abnormal uterine bleeding, menorrhagia, and dysfunctional uterine bleeding are used. A recently convened panel even suggested discarding these terms and replacing them with other universally accepted descriptors (Table 2.1). Therefore it is imperative to know the normal menstrual bleeding patterns of women, in order to differentiate them from the abnormal.

Pelvic pain/pressure

Pelvic pain is a very general and encompassing term describing pain and discomfort located in the pelvic region. Pelvic pain such as dysmenorrhea, dyspareunia, and noncyclic pelvic pain have all been associated with fibroids. Earlier studies reported pelvic pain and or dysmenorrhea in 34% of fibroid clinic patients. However, a population-based study, analyzing the entire population and not just care-seeking patients, reported that dyspaurenia and noncyclic pain were more bothersome to the fibroid population. Dysmenorrhea was experienced equally among the general population. Of note, there appeared to be no relationship between pelvic pain and the total volume and quantity of fibroids present (Lippman et al., 2003).

Bulk symptoms

Fibroids can cause pelvic pressure and "bulk symptoms" due to a mass effect. These bulk symptoms, as their name suggests, are due to displacement of tissues caused by fibroids in the abdominal cavity. Fibroids can physically exert pressure and disrupt nearby organs and organ systems. Anterior fibroids can cause urinary symptoms due to their proximity to the bladder. Symptoms can vary from urinary frequency to difficulty emptying the bladder, and in very rare but extreme situations, cause urinary obstruction leading to hydronephrosis and chronic kidney disease (Bansal et al., 2009). Posterior fibroids may exert pressure on the rectum, causing constipation. Lower back pain has also been associated with fibroid bulk symptoms. There are a few reports in the literature regarding the frequency or prevalence of these symptoms, but multiple case reports document the successful alleviation of symptoms after treatments to reduce fibroid size or remove fibroids.

Bulk symptoms can cause a great deal of pain. The larger the fibroid, the more disruptive and irritating it can be. Additionally, fibroids can outgrow their blood supply and thereby degenerate, causing excruciating pain. Such pain must always be considered in the setting of acute-onset pain and history of fibroids. However, it is always important to bear in mind that not all pelvic pain is due to fibroids and other etiologies must be considered.

CAUTION #2

When evaluating a patient with suspected and/or confirmed fibroids, it is important to consider the entire differential diagnoses, before assuming that her symptoms are due to fibroids. A complete workup of abnormal bleeding should evaluate for all possible sources of bleeding, including but not limited to polyps, hyperplasia, carcinoma, and adenomyosis. The evaluation of pelvic pain should exclude pain originating in the urinary, gastrointestinal or musculoskeletal systems, before concluding that fibroids are the cause.

Fibroids and sexual function

Multiple studies support a relationship between dyspareunia and fibroids. According to the

Table 2.1 Suggested "normal" limits for menstrual parameters in the midreproductive years

Clinical dimensions of menstruation and menstrual cycle	Descriptive terms	Normal limits (5th to 95th percentiles)
Frequency of menses (d)	Frequent Normal Infrequent	<24 24–38 >38
Regularity of menses, cycle-to-cycle variation over 12 mo (d)	Absent Regular Irregular	— Variation ± 2–20 days Variation >20 days
Duration of flow (d)	Prolonged Normal Shortened	>8.0 4.5–8.0 <4.5
Volume of monthly blood loss (mL)	Heavy Normal Light	>80 5–80 <5

UFS-QOL study previously mentioned, sexual dysfunction was one of many symptoms afflicting fibroid patients (Spies et al., 2002). Lippman et al. (2003) also found that fibroid patients were more likely to complain of dyspareunia than unaffected patients. Moreover, a recent study relating myomatous uteri to sexual dysfunction found that women with myomatous uteri had more pain during, and were less satisfied with, sexual intercourse than their nonfibroid counterparts. However, it is worth noting that there was no difference in the fibroid patients' arousal or orgasmic phases when compared to nonmyomatous uteri patients (Ertunc et al., 2009). Additionally, a case report confirming alleviation of dyspareunia with myomectomy further supports the association between fibroids and dyspareunia (Yildiz et al., 2009). Conversely, conflicting results were reported when 307 preoperative patients were compared with one another; patients with fibroids did not exhibit an increased prevalence or severity of dyspareunia (Ferrero et al., 2006). However, these differences between studies may be accounted for by the utilization of different sexual function scoring systems as well as the possible inclusion of chronic pelvic pain patients in some of the studies.

Infertility

Reduced fertility has been noted in some fibroid patients. Strong, consistent evidence demonstrates a negative impact on clinical pregnancy and delivery rates as well as an increased risk of spontaneous miscarriages when submucosal and sizeable intramural fibroids are present in the uterus. There is a consensus that patients with subserosal fibroids using assisted reproductive technologies (ART) appear to have similar outcomes to patients with no fibroids. The evidence for the effects of fibroids on fertility will be discussed in greater depth in Chapter 3.

Intrapartum and postpartum complications

Despite a reduction in fertility, fibroid patients can conceive and deliver. However, such pregnancies may be complicated by a number of adverse obstetric outcomes. Though many of these adverse outcomes are clearly inter-related, each poses a significant risk to mother and fetus in the intrapartum and peripartum state. Preterm labor, preterm delivery, placenta previa, placental abruption, intrauterine growth retardation (IUGR), breech presentation, premature rupture of membranes (PROM), and increased rate of cesarean section are of specific concern, and are increased with the presence of leiomyomas. Pregnancy-related complications of fibroid disease are discussed in depth in Chapter 4.

Diagnosis

As with any condition, it is important to make the correct diagnosis before proceeding with a plan of management. The gynecologist must integrate and synthesize the patient's clinical presentation and physical exam, and conclude what, if any, imaging would help to further characterize the

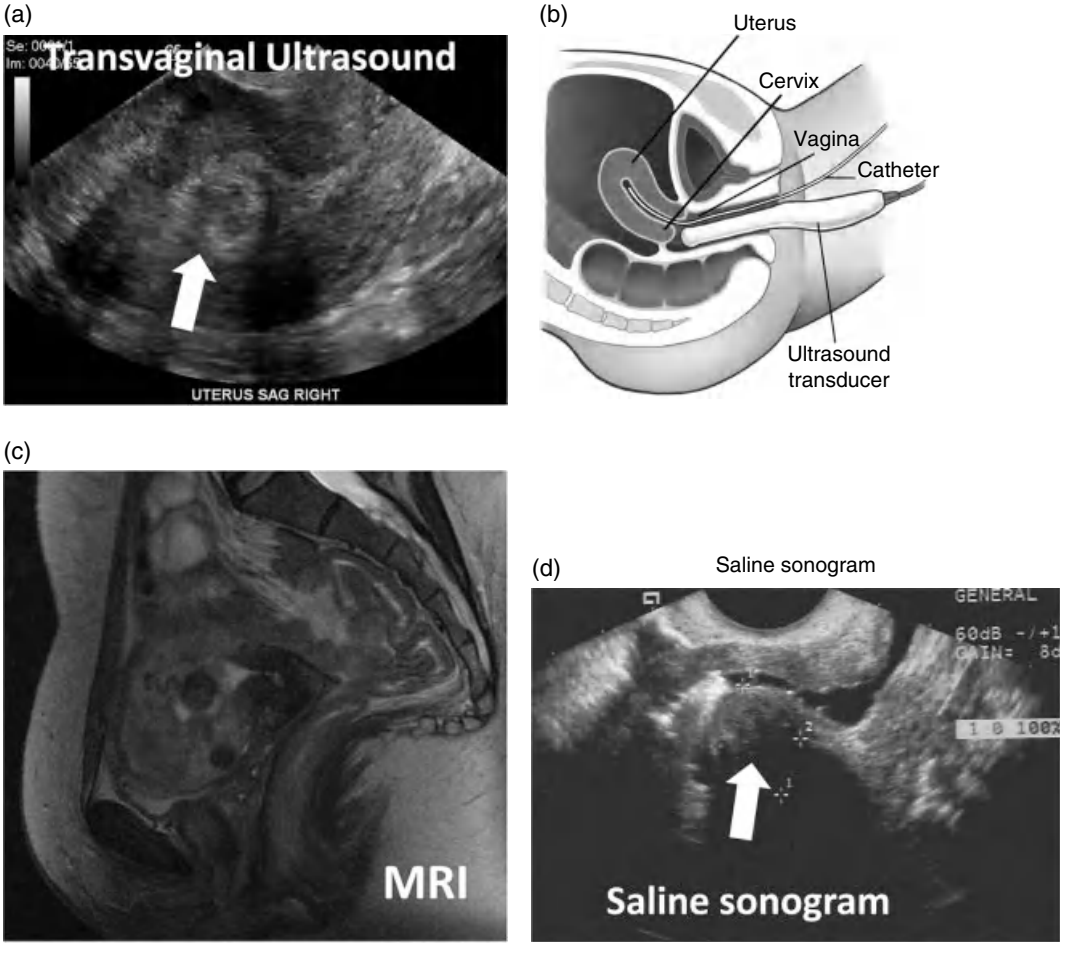

Figure 2.1 Three imaging studies of a uterine leiomyoma. (a) Sagittal view of the uterus using transvaginal ultrasound. The white arrow indicates a uterine fibroid in the uterus. The endometrium is more echodense (white) compared to the myometrium. (b) Sagittal view of the uterus in the same patient using MRI. Note the fibroid appears to be distorting the endometrial cavity (Drawing courtesy of Anne Kelley). (c) Schematic diagram of saline infusion sonogram (SIS; also known as hysterosonography). A long catheter is threaded into the uterine cavity and connected to a syringe of sterile normal saline. Next, a transvaginal probe is placed in the vagina and under visualization, saline is slowly injected. The cavity is visualized by the sonolucency of the normal saline. (d) Sagittal view of the uterus of the same patient imaged in (a) and (b) with saline infusion. The fibroid is indicated by the white arrow. The infused saline renders a black appearance in the image surrounding the fibroid. Note that with this imaging method, the fibroid is clearly distorting the uterine cavity. Management of this particular case is described in greater detail in Chapter 3.

disease. The physical exam is very important since it can demonstrate the location, size, and mobility of the fibroids and uterus. The physicial exam, accompanied with appropriate imaging (Figure 2.1), equips the physician with the information needed to properly counsel and manage patients with uterine fibroids. There is a strong correlation between an experienced examiner's presurgical assessment of leiomyomatous uteri and the pathological specimens' measurements.

Ultrasound

Several imaging modalities are available, each with their own strengths and weaknesses. The mainstay of diagnosis is ultrasound imaging. Two ultrasound imaging approaches are used: transvaginal and abdominal. Other variations of ultrasound include two-dimensional (2D) and three-dimensional (3D) ultrasound, saline infusion sonography (SIS) or sonohysterogram (HSN). SIS and 3D ultrasound, for the evaluation of myomas, are typically approached transvaginally. The relative advantages of the ultrasound are its wide availability, ease, and nominal expense.

Since ultrasound is based on sound waves, the proximity of the wave to its target is crucial. The close proximity to the target organ afforded by the transvaginal approach is a considerable advantage over the abdominal approach. It allows for better resolution and excellent characterization of pelvic organs. Additionally, it is a more tolerable exam for patients because a full bladder is not needed. An obvious advantage of the abdominal approach is its less invasive nature; the patient may be more comfortable during the course of the exam.

The 2D transvaginal ultrasound has been the standard since its introduction to clinical practice in the 1980s. However, following the more recent advent and integration of 3D imaging, debate emerged regarding 3D's merits and benefits. Earlier studies were only suggestive of an added advantage of 3D imaging but lacked statistical significance. Recently, data have emerged demonstrating that 3D SIS is comparable with diagnostic hysteroscopy, a clear advantage over 2D SIS. 2D had an accuracy of 98.8%, sensitivity of 75%, and positive predictive value (PPV) of 100%, compared with 100% accuracy, sensitivity, and PPV for 3D, SIS, and diagnostic hysteroscopy (El-Sherbiny and Nasr, 2011). The 3D ultrasound's accuracy is now being compared to the current gold standard, hysteroscopy. Future research will determine if these results are substantiated as the imaging methods are integrated into clinical practice.

☆ TIPS & TRICKS #1

Periodically, patients being evaluated for abnormal uterine bleeding may be reluctant to undergo a hysteroscopy. In those situations, the clinician should consider 3D ultrasound because of its diagnostic advantages and relatively noninvasive approach.

Saline infusion sonography has proven to be an effective method for evaluating the uterine cavity. SIS involves inserting a small catheter into the uterus and distending its cavity with a sterile solution under real-time ultrasound imaging (see Figure 2.1). This method has been used as an alternative to the more invasive diagnostic hysteroscopy. A recent study reported SIS to have a sensitivity of 99% and PPV of 96%, compared to transvaginal ultrasound values of 95% and 92%, respectively (Bingol et al., 2011). These results attest to the routine use of SIS in the current evaluation of abnormal uterine bleeding, as there is a clear advantage. Though the literature is varied on the exact sensitivity and specificity of SIS, one principle emerges: SIS was always equal to or more sensitive and specific than transvaginal ultrasound alone.

Magnetic resonance imaging

In spite of the clear benefits described above, ultrasound has several limitations. It can fail to detect small fibroids and subserosal fibroids. Ultrasound may also be imprecise when mapping fibroids from very large uteri and distinguishing fibroids from sarcomas and adenomyosis. These shortcomings are overcome by the use of magnetic resonance imaging (MRI). However, given the significant cost associated with MRI, the clinician must weigh the cost benefits of MRI versus other less expensive imaging. Of note, computed axial tomography (CT) has limited contrast resolution when evaluating pelvic organs, and is severely limited in its diagnosis and characterization of fibroids, unless there is calcification (Griffin et al., 2010).

Magnetic resonance imaging is the most accurate imaging modality available for the diagnosis, mapping, and characterization of uterine fibroids. Its excellent soft tissue contrast resolution allows for precise preoperative evaluation of quantity, size, and location of fibroids (Dueholm et al., 2002; Vitiello and McCarthy, 2006). MRI and ultrasound were equally able to identify the presence of fibroids, but MRI far exceeded ultrasound regarding fibroid position and myometrial wall invasion. To detect the mere presence of fibroids, MRI had a sensitivity of 99% and specificity of 86%, compared to transvaginal ultrasound respective values of 99% and 91%, attesting to the equivalence in their qualitative abilities. However, MRI correctly identified fibroid position and wall embedment with a mean value of

2.92 compared to ultrasound's mean of 1.98. In that same study, MRI far exceeded ultrasound's ability to determine the precise quantity of myomas as uterine volume increased, with statistical significance noted when uterine volume was greater than or equal to 375 mL (Dueholm et al., 2002). Additionally, MRI accurately detected pedunculated, subserosal, and submucosal fibroids (Griffin et al., 2010).

Currently, imaging modalities are being evaluated for their ability to distinguish benign pelvic pathology from more serious neoplastic conditions, such as sarcomas. In one study, MRI was able to distinguish between the various subtypes of leiomyomata with 70% accuracy and 100% accuracy in distinguishing leiomyosarcoma from benign leiomyoma. However, while MRI findings can be suggestive of sarcoma, a reliable diagnosis is still lacking (Vitiello and McCarthy, 2006). A role for positron emission tomography (PET)/CT using fluorodeoxyglucose has emerged in this differentiation; however, more investigation is needed given two recent reports. One report suggested a role for PET/CT with a 91.3% confirmation of uterine sarcoma in a selected group of patients (Yoshida et al., 2011). Yet other reports have cautioned against PET/CT's use since benign leiomyomas showed similar uptake as their neoplastic counterparts.

Epidemiology

Nationally

One of the many problems in the epidemiological investigation of fibroids is lack of a universally accepted disease classification. Fibroids present in various locations, sizes, and quantities, but are not categorized as such when being studied. This lack of uniformity unfairly assumes that all fibroids are the same. Fibroids are not all the same. Fibroids occur in varied locations and are truly a protean disease. See Chapter 1 for discussion of fibroid classification. Failure to properly classify fibroids in a study could lead to inconsistent research outcomes.

Since the mid 1990s, the epidemiological investigation of fibroids has advanced considerably. Fibroids are now assessed more accurately; current analysis focuses on a broader range of the general population and not simply on symptomatic patients. This possibility was created by our increased ability to diagnose fibroids through sonographic screening of the general population. Early studies, based on analysis of symptomatic patients, concluded that fibroids were prevalent in 0.002–0.012% of patients. We now know this to be a gross underestimation of fibroid prevalence. By the age of 50, women who were screened sonographically had a cumulative incidence of 70% in whites and 80% in African-Americans (Day Baird et al., 2003). Though this study underscored the fact that African-American women have a higher prevalence than white women, it is remarkable how prevalent fibroids are in women from the US. The reason for this difference in disease prevalence among African-American women is not currently understood.

Internationally

Fibroids appear to be less prevalent in European women than in American women. Two European studies, one originating from Italy and the other from Sweden, analyzed fibroid prevalence using ultrasound screening of the general population. The Italian group studied 341 women aged 30–60 years old and found that only 21.3% had fibroids. The Swedish group, which divided the study group of 335 women into two age groups, detected an even lower percentage. Only 3.3% of the 25–32 year olds and 7.8% of the 33–40 year olds had fibroids. These results suggest that fibroids were significantly less prevalent in European populations, compared to American women. Interestingly, a Finnish group investigating twins between the ages of 40 and 47 years old found a fibroid prevalence of 67%, which was much more comparable to American women (see Payson et al. (2006) for review).

With regard to other races and ethnicities, there are limited data regarding fibroid prevalence. A study of women between the ages of 18 and 42 in the first trimester of pregnancy noted that Hispanics in the south east US appear to have fibroid characteristics similar to white women (Laughlin et al., 2009). An older study that may not necessarily reflect the actual prevalence, given our newer screening methods, suggested there was a similar rate of fibroid disease in the white, Hispanic, and Asian populations in the US, with rates of 12.5%, 14.5%, and 10.4%, respectively. However, more investigation is needed to further elucidate the prevalence among these subpopulations.

In the course of epidemiological study, it is imperative to highlight which geographic and ethnic populations are at greatest risk. This comes with

the discovery of various medical characteristics and risk factors in these populations. These topics will be discussed further at the end of this chapter.

Growth of uterine fibroids

Women of reproductive age have a 30–70% chance of developing uterine fibroids. While the precise molecular events involved in the generation of uterine fibroids remain enigmatic, it is accepted that fibroids are, in part, derived from clonal expansions of myometrial cells. These benign tumors, referred to as uterine fibroids or leiomyoma, have been grossly described based on size and location. It is still not fully understood whether fibroids present a typical smooth muscle response to multiple disorders or a distinct disease.

SCIENCE REVISITED

Some genetic syndromes have been associated with uterine fibroid formation, such as hereditary leiomyomatosis and renal cell cancer. These examples show that there can be a genetic predisposition for uterine fibroid formation, but for common fibroids, no genetic causes have been identified.

Growth rates

One of the most interesting aspects of uterine fibroids is that growth is highly variable, as some fibroid tumors grow, some shrink, and others may remain static for years. Significant variation exists in fibroid growth rates but the tendency for fibroids to grow is clear. One study concluded that the average growth of uterine fibroids was 1.2 cm over the course of 2.5 years (DeWaay et al., 2002). This average was calculated from a wide variation of growth rates that existed among individual fibroids. The tendency towards overall fibroid growth was further highlighted in a study among 262 fibroids, which found that 34% were rapidly growing while only 7% were spontaneously regressing; this resulted in an overall median growth rate of 9% per 6 months (Peddada et al., 2008). An overall increase in uterine size, as previously mentioned, was also detected. The increase in uterine size was most likely due to the overwhelming growth of the majority of the fibroids in comparison to the fewer regressing ones. Interestingly, this variation exists even when fibroids are exposed to a uniform hormonal milieu. A single patient can have fibroids of varying sizes, including some undergoing regression (Peddada et al., 2008).

Growth spurt

To complicate matters even more, fibroids may undergo growth spurts (≥30% volume increase/3 months) while others maintain a consistent growth rate. One possible explanation for this variability is the fact that each fibroid is derived from a single myometrial cell that has undergone clonal expansion. Individual cells may experience different microenvironments, factors, and cell cycle abnormalities, and may therefore exhibit different patterns of growth but currently, the reason for the different behavior of fibroids remains unknown. The variable growth of fibroids can make treatment quite challenging. If a woman has multiple fibroids, as is often the case, each fibroid may exhibit a different rate and pattern of growth, as mentioned earlier. Moreover, a woman who has at least one rapidly growing tumor has a 14% higher uterine growth rate than a woman without a rapidly growing tumor (Davis et al., 2009).

It is more common for a woman to present with multiple uterine fibroids than a single fibroid. It may seem surprising that a woman with several potentially large pelvic masses most commonly presents with few to no symptoms. A recent study noted that over 90% of the women enrolled had multiple uterine fibroids. Almost one-third of these participants had more than 10 fibroids. It remains unclear whether multiple fibroids or single fibroids are more likely to cause symptoms and progression of disease.

TIPS & TRICKS #2

Growth spurts are not as likely to occur in large tumors (>5 cm diameter).

Hormones and growth

It has been known for many years that ovarian steroids play a key role in uterine fibroid growth and formation. It is widely accepted that the ovarian steroid, estrogen, is the primary modulator of uterine fibroid growth. While estrogen is not the only factor in the development of fibroids, understanding its role is vital to understanding the

growth and maintenance of uterine fibroids. Recent evidence indicates that progesterone may also be critical for fibroid growth, and may act synergistically with estrogen to promote preservation of fibroid volume. Progesterone may even be more important than estrogen. Consistent with a dependency on sex steroids, gonadotropin-releasing hormone (GnRH) agonists are commonly used to treat uterine fibroids. GnRH agonists lower circulating estrogen and progesterone levels. Fibroids will typically shrink up to 30% of pretreatment volume after 3 months of GnRH agonist therapy. Upon cessation of GnRH therapy, the fibroids usually return to pretreatment size. Such growth is not to be confused with a spontaneous growth spurt, since it is induced by cessation of GnRH agonist therapy (response of fibroids to GnRH therapy is discussed in detail in Chapter 6).

Regression

While progesterone has a demonstrated role in fibroid formation, studies have shown that pregnancy actually reduces the risk of fibroid disease. One current study showed that 72% of women who were pregnant (or recently pregnant) were likely to have >50% regression of pre-existing fibroids. Recent reports have also indicated a correlation between fibroid location within the uterus, fibroid type, and chance of fibroid regression. Fibroids located in the lower segment of the uterus had a greater reduction in size than fibroids located in the corpus or fundus. Submucous fibroids also appear to have a greater likelihood of size reduction in comparison with the more common subserosal fibroids. Postpregnancy follow-up studies showed that 36% of fibroids were no longer detectable (Laughlin et al., 2010). Those fibroids that could still be detected had a median reduction of 0.5 cm.

It is not clear why pregnancy causes a reduction in fibroid disease but one possibility is that the postpartum fall in progesterone levels, which is accompanied by a wave of apoptosis in the uterus, may promote the reduction in fibroid size. The reduction in fibroid size observed post pregnancy is more likely to occur in women with more recent pregnancies. Of note, fibroids can return to their pre-pregnancy size in the years following a pregnancy. Recent studies have shown that when a progestin is used in the postpartum period, there is less reduction in size of the fibroids, indirectly supporting the hypothesis that the postpartum fall in progesterone may explain the pregnancy-related fibroid reduction. Women with gestations that lasted ≥41 weeks and women who miscarried were also less likely to experience fibroid regression. Current studies have not been able to document a correlation between breastfeeding and return of menses with fibroid regression.

☆ TIPS & TRICKS #3

While postpartum progestin use is associated with a reduction in fibroid regression, no interference with fibroid regression has been detected with postpartum combined estrogen-progestin use.

Current studies have shown that fibroid size, type, and location do not necessarily correlate with a fibroid's ability to undergo a growth spurt or indicate its average growth rate. A typical pattern of growth has also been described as consistent during a woman's premenopausal years with an increased growth rate during the fifth decade of a woman's life. After menopause, however, tumors tend to regress and are less likely to be diagnosed due to their small size. Of note, spontaneous regression of fibroids does occur even in the premenopausal woman, just with less frequency than their postmenopausal counterparts (Baird et al., 2011; Davis et al., 2009).

☆ TIPS & TRICKS #4

Watchful waiting may be the best approach for perimenopausal women if there is no immediate threat due to the presence of the fibroid(s). Since it is likely that fibroids will regress once menopause is reached, the patient may be able to avoid surgery by waiting. Notably, a recent report has suggested that postmenopausal regression may not occur in African-American women, so watchful waiting may not be as efficacious for this group.

Even with varying growth rates, patterns, and numbers, fibroids are not prone to malignancy. In fact, less than 1% of fibroids actually become malignant. Nonetheless, a proper understanding of benign uterine fibroid growth is paramount since some treatment options are preferred over others, based on fibroid size, fibroid number, location, and the patient's desire for fertility preservation.

☆ TIPS & TRICKS #5

Recent studies have shown a correlation between pelvic pain, uterine bleeding, and elective surgical intervention. Better pain and bleeding management may allow for more nonsurgical methods to be employed in both African-American and Caucasian women.

Fibroids and ethnicity

As mentioned earlier in this chapter, there are limited studies regarding ethnicities other than in Caucasian and African-American women. The higher prevalence of fibroids in African-American women is well established. By age 50, a cumulative incidence of 70% in white and 80% in black women has been reported (Day Baird et al., 2003). Additionally, African-American women typically present at a younger age and with multiple fibroids in comparison with age-matched Caucasian women. In fact, fibroids have been detected, via ultrasound, 10–15 years earlier in African-American women than in white women; the fibroids also tend to be larger in African-American women (Peddada et al., 2008). The reason why African-American women bear a greater disease burden is not understood, and more research needs to be conducted to elucidate the cause of this health disparity.

Even though African-American women have been found to have an increased number of uterine fibroids, and may have a nine-fold increased risk of developing uterine fibroids, a recent study suggested that symptom scores were similar to white women (Davis et al., 2009). That is, one group did not perceive higher pain or disability from uterine fibroids than the other. Furthermore, the study did not find a significant difference in surgical interventions between black and white women. This may have been due to the fact that women with large (>5 cm diameter) fibroids were recruited for the study. However, African-American women have been reported to undergo hysterectomies and myomectomies at an earlier age than white women, and may have an up to three-fold higher chance of hysterectomy. Notably, the main reasons for seeking treatment for uterine fibroids, in both black and white women, were pain and bleeding.

Fibroid regression following pregnancy has been well established in the literature. However, African-American women were less likely than white women to have fibroid regression during pregnancy. The reason for this difference is unclear at present. On a similar note, fibroids have been found to have slower growth rates with age in white compared to black women. According to one study, the chances of a tumor growing rapidly (>20% over a 6-month time period) stay the same in black women with age, but fall as white women age (Peddada et al., 2008). This may in part explain the increased fibroid burden faced by African-American women.

Lastly, African-American women who choose to use assisted reproductive technology (ART) experience fewer live births and a statistically significant increase in spontaneous abortions. One study found that African-American women who had an adverse outcome using ART were three times more likely to have uterine fibroids (Feinberg et al., 2006). Whether the outcomes are due to the presence of the fibroids or whether this simply reflects the population's increased risk of developing uterine fibroids is currently unknown. Collectively, the racial and ethnic differences in disease prevalence, severity, and response to pregnancy underscore the acute need for research directed toward understanding of this health disparity.

Risk factors for uterine fibroids

While many researchers have explored the various risk factors associated with fibroids, conclusive evidence enabling the creation of a definitive list of risk factors is lacking. Nonetheless, recent studies have suggested some risk factors worth further exploration. Each section below represents a possible risk factor and relevant information regarding its role in fibroid formation. New studies will proffer more information about each of these

potential risk factors and may serve to add to, or subtract from, this list.

Obesity

Although there seems to be an association between obesity and uterine fibroid development, study results have been inconsistent. Some earlier studies found little or no increased risk with elevated body mass index (BMI). However, a recent report cited an 18% increase in the risk of uterine fibroid development for every 10 kg increase in weight (Payson et al., 2006). Another report demonstrated that women with a BMI in the upper quartile had a 2.3 times higher risk of fibroid development than women in other quartiles. Researchers have proposed that the hormonal alterations seen in these obese patients could account for the increased hormonal availability, thereby creating an environment where fibroids can thrive (Payson et al., 2006).

Hormones

Hormone replacement therapy (HRT) during menopause has been implicated in increasing the risk of uterine fibroid development. This risk is thought to increase when women continue HRT for 8 or more years, and have a BMI of <24. However, studies on this topic are conflicting.

The relationship between oral contraceptives (OCP) and fibroids has been studied extensively without any clear consensus. The results of various studies have ranged from increased, to similar, to decreased risk of fibroids when compared to non-OCP users. A large study of 95,000 women did, however, find that OCP use from the ages of 13–19 is a significant risk factor for the development of uterine fibroids (Marshall et al., 1998). Additionally, a later study found that OCP use after the teenage years was protective. Interestingly, a study in Thailand reported a significant reduction in risk associated with the use of depot medroxyprogesterone acetate (DMPA), an injectable progestin contraceptive (Lumbiganon et al., 1996). The risk of fibroids declined with increasing duration of DMPA use, with a reportable 90% reduction after 5 years of use.

Finally, fibroid onset has been seen to correlate with increasing luteinizing hormone (LH) levels. This correlation, however, seems to indicate fibroid onset and not necessarily fibroid growth. It is unknown if LH itself is important for tumor initiation or if it is a marker for a hormonal environment favorable to fibroid development, since chronic elevations of LH are associated with anovulation and polycystic ovary syndrome. Further research is under way to elucidate this relatively new finding.

Age

It is well established that increased age is a risk factor for fibroids. This is likely due to fibroids enlarging and becoming more symptomatic as a woman advances in age, thereby causing incidence to increase along with a woman's age. Women of reproductive age are most commonly diagnosed with uterine fibroids, either due to symptoms caused by the uterine fibroids or incidentally. Moreover, women who experienced menarche at an earlier age have a higher risk of uterine fibroid growth. However, if a woman reaches her late 40s without fibroids, she has a low risk of developing fibroids thereafter (Ryan et al., 2005).

Alcohol

While there are conflicting data on alcohol use and fibroid development, several studies have found that there may be a correlation between beer and fibroids. The Black Women's Health Study found that women who consumed more than seven beers per week had an increased risk for fibroid growth (Key et al., 2006). Another study showed that women in the highest tertile of alcohol consumption had a higher risk of having fibroids than the women in the lower tertile (Nagata et al., 2009). More research in this area is needed to determine if these outcomes can be repeated in a larger population of women with varying racial and ethnic backgrounds.

Vitamin D

Hypovitaminosis D has been implicated as a risk factor in the development of uterine fibroids due to vitamin D's ability to inhibit cell growth in human leiomyoma (HuLM) cells. In the absence of appropriate vitamin D concentration, cells may be more likely to overgrow which ultimately leads to development of uterine fibroids. An increased level of vitamin D has been shown to be protective and may be useful as a nonsurgical treatment option for fibroids. A recent preclinical study with vitamin D showed significant shrinkage of uterine leiomyoma

size in the Eker rat model (Halder et al., 2012). Not all studies have had the same results, indicating a need for more research in this field.

Other

Multiple studies have also shown hypertension to be a risk factor for fibroid development. In one study, women with hypertension had a 24% increased risk of fibroid development compared to normotensive women. Hypertension associated with fibroid development tends to be chronic and is treated with antihypertensive agents. It is thought that hypertension can cause cytokine release or even injure the smooth muscle of the uterus, thereby encouraging fibroid development. Recent studies have also shown that fibroid development can be correlated with diastolic blood pressure levels. For every 10 mmHg that diastolic blood pressure increases, the patient has an 8–10% increased risk of fibroid development.

Additionally, daily talc use has been implicated as a uterine "irritant." This irritation, in turn, is thought to cause fibroid formation. Both profibrotic and proinflammatory factors have been suggested in the creation of leiomyoma. Further research in this area is indicated for the development of possible nonsurgical treatment options.

Infection has recently been explored as a possible risk factor for fibroid development. A case-controlled study of 318 women reported an increased risk of fibroids in women with a history of pelvic inflammatory disease (PID); risk appeared to increase with the number of infections a woman had experienced. This did not prove to be true for external infections, such as genital warts or herpes, in the same group, thereby suggesting that irritation of the uterus by an infectious process could indeed increase risk for fibroids. The Chagas disease parasite can infiltrate the uterine smooth muscle and is proposed to promote fibroid development. Twenty-seven percent of women with a positive history (and confirmation via serology) of Chagas disease, an infection brought about by a parasite endemic to some parts of South America, presented for uterine fibroid surgery. Of the control group, 16% had a positive history confirmed by serology data. It was also found that white women with fibroids were 40% more likely to have Chagas disease than other ethnic groups (10%) (Payson et al., 2006).

Stress has also been suggested as a possible risk factor in fibroid development. However, there is a paucity of data on this topic. It is hypothesized that stress could act on the adrenal gland to increase activity that would increase progesterone levels and thereby increase fibroid development.

Conclusion

By the time of menopause, approximately one in two women in the US will have developed uterine fibroids. Estimates are that 20–50% of women will suffer symptoms due to fibroid disease. The symptoms are varied and include abnormal uterine bleeding, pain, recurrent pregnancy loss, adverse obstetric outcomes, decreased fertility or sterility, urological or gastroenterological complications, pelvic pressure, and sexual dysfunction. Fibroid-related symptoms significantly affect the lives of millions of women, resulting in loss of work and disability. Each year fibroid-related symptoms will cause approximately 1% of affected women to seek treatment for the condition. Moreover, healthcare related to fibroids has been estimated to account for around 320,000 hospital procedures in the US.

Given the considerable morbidity caused by uterine fibroids, it is clear that more research is vital in order to determine the etiology and proliferative abilities of uterine fibroids. It is equally important to understand the differences among different racial and ethnic groups and any associated risk factors for uterine fibroid formation. A better understanding of the disease process and development of strategies for disease prevention are a pressing need.

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3

Evidence-Based Indications for Treatment of Uterine Fibroids in Gynecology

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Introduction

Fibroids are commonly found in women and cause a multitude of symptoms. Symptoms include bleeding, pain, genitourinary and gastrointestinal symptoms, sexual problems, and infertility. Many options for treatment of uterine fibroids exist, including surgical and medical therapies, as well as newer options such as uterine artery embolization and magnetic resonance imaging (MRI)-guided focused ultrasound. These therapies will be discussed in detail in Chapters 6–9.

Practitioners are often faced with the dilemma of determining whether treatment for uterine fibroids is indicated based on symptoms or associated complications, and how to choose the most appropriate treatment modality. In this chapter, we will review evidence-based indications for treatment of uterine fibroids based on the patient's symptoms.

The gynecological patient

Considerations for the treatment of uterine fibroids include age, desire for future fertility, and presenting symptoms. These variables must be taken into account when determining whether treatment is indicated. The location, size, and number of uterine fibroids in a given patient also drastically affect treatment recommendations.

Fibroids are often found incidentally via abdominal or pelvic exam, ultrasound or MRI. Many uterine fibroids are asymptomatic and may not require treatment. However, in patients with severe anemia from menorrhagia related to fibroids or hydronephrosis caused by obstruction of a ureter from an enlarged fibroid uterus, prompt medical treatment is essential (Parker, 2007). Data on the long-term outcomes of expectant management are limited, but have shown that up to 77% of women choosing observation had no significant change in symptoms at 1 year (Parker, 2007). Fibroids are typically slow growing and often regress in patients following menopause. Expectant management remains an option in a patient with mild-to-moderate symptoms who desires to postpone treatment.

Bleeding in patients with fibroids

Abnormal uterine bleeding is the most common reason why patients present for treatment of uterine fibroids. Over 30% of women with fibroids will experience menstrual abnormalities. The most common bleeding pattern seen with fibroids is menorrhagia or hypermenorrhea (Stewart, 2001). Bleeding with uterine fibroids can be both acute and chronic in nature. Such bleeding can result in severe anemia as well as major alterations in the lifestyles of patients (Stovall, 2001). Uterine bleeding can be objectively measured using blood loss questionnaires such as the Ruta Menorrhagia Questionnaire, using the alkaline hematin method, or pictorial blood loss

Fibroids, First Edition. Edited by James H. Segars.

assessment charts. Studies have shown increased heavy bleeding in patients with fibroids compared to those without fibroids. The risk of heavy bleeding increases with the size and location of fibroids. Submucosal fibroids more commonly cause menorrhagia than fibroids in other locations (Stewart, 2001).

SCIENCE REVISITED

Whereas initial reports implicated venous lakes as the cause for abnormal bleeding in patients with uterine fibroids, recent research has uncovered other causes. Abnormal uterine bleeding may be caused by altered endometrial signaling. In 2010, Rackow and Taylor reported that the presence of uterine fibroids not only affects endometrial development over the fibroid but also alters endometrial development throughout the cavity.

Evaluation of abnormal uterine bleeding

In patients who present with abnormal uterine bleeding, causes other than fibroids must first be considered. A pelvic exam can help the practitioner determine the size and location of larger fibroids. Laboratory tests such as beta-human chorionic gonadotropin (hCG) and complete blood count (CBC) are helpful in women of reproductive age. A detailed menstrual history can be a clue that a patient is experiencing anovulatory bleeding. Anovulatory bleeding is typically noncyclic and can be the result of obesity, polycystic ovary syndrome (PCOS), and thyroid disease, among other causes. Coagulation abnormalities such as von Willenbrand disease and thrombocytopenia may cause abnormal uterine bleeding. A CBC with platelets, prothrombin time (PT), and partial thromboplastin time (PTT) may identify a coagulation abnormality. Sampling the endometrium via endometrial biopsy or dilation and curettage is an important consideration to exclude hyperplasia and cancer.

Atrophic endometrium is the most common cause of abnormal uterine bleeding in postmenopausal women and can be evaluated by ultrasound or endometrial biopsy. Transvaginal ultrasound with saline infusion sonogram will identify the location of any intracavitary fibroids. In patients with large fibroids, MRI is often helpful to map the location of fibroids. Other structural uterine lesions, such as uterine polyps and adenomyosis, can also cause abnormal bleeding similar to uterine fibroids. The practitioner must determine the number of uterine fibroids present, the location, and the percentage of the fibroid that is located in the uterine cavity. Submucosal fibroids may distort the endometrium, causing abnormal bleeding. Classification systems such as the Wamsteker system used by the European Society of Gynaecological Endoscopy (ESGE) help determine the likelihood of successful removal of submucosal fibroids by hysteroscopic myomectomy (Lasmar et al., 2011).

CASE REPORT

A 40-year-old woman, gravida 0, with a BMI of 25, presented with increasing dysmenorrhea and menorrhagia. Menses were regular but lasted 7–8 days with heavy bleeding accompanied by the passage of clots, resulting in loss of work on a regular basis. Prior to 3 years ago, menses occurred every 28–30 days, lasted 5 days and were heavy for 2 days, but then lightened. Gynecological history was otherwise unremarkable. There was a history of orthopedic surgery for an injury but no suggestion of coagulopathy. The patient took vitamins but no other medications. A hematocrit was 32. Pelvic examination revealed the uterus to be slightly enlarged but of normal contour. Ovaries were not enlarged. A transvaginal ultrasound in the office revealed a 3 cm submucous-intracavitary leiomyoma. Sixty percent of the leiomyoma was located in the uterine cavity. Two smaller, distinct 1 cm and 2 cm leiomyomas were located intramurally. The patient desired relief of the pain and bleeding but did not want a hysterectomy and wished to preserve the possibility of child bearing. Because of the anemia, medical therapy was initiated for 3 months while the patient took iron therapy. The leiomyoma was reduced slightly to 2.6 cm in size and bleeding was reduced while on therapy. The patient underwent hysteroscopic resection of the leiomyoma using a hysteroscopic morcellator. Postoperatively, the patient had considerable relief of dysmenorrhea and a significant reduction in menorrhagia and was well pleased with the operative result.

Management of bleeding

Medical management of uterine fibroids is often indicated in patients who have uterine bleeding and severe anemia associated with fibroids. Studies have shown that menorrhagia associated with fibroids responds well to gonadotropin-releasing hormone (GnRH) agonists, causing amenorrhea in up to 97% of women by 6 months. However, menses resume in most patients 4–8 weeks following discontinuation (Parker, 2007). GnRH agonists may be particularly helpful in anemic patients prior to surgery. GnRH agonist therapy given for 3–4 months preoperatively has been shown to significantly improve preoperative hemoglobin and reduce operating times and length of hospitalization. Over 74% of women given GnRH agonists plus iron were shown to have an improvement in hemoglobin from 10.2 g/dL to greater than 12 g/dL in a period of 12 weeks. Use of danazol may also be helpful in patients with fibroids, demonstrating an increase in mean hemoglobin values from 10.8 g/dL to 11.5 g/dL after 6 months of therapy (La Marca et al., 2003). Mifepristone has been shown to be effective, and induces amenorrhea in 60–65% of patients (Olive et al., 2004). Long-term use of mifepristone may be limited by the potential for development of endometrial hyperplasia.

The levonorgestrel intrauterine system (LNG-IUS) has been shown to decrease uterine bleeding in patients with fibroids. Blood loss was demonstrated to be significantly less in patients using the LNG-IUS, using both menstrual pictograms and mean hemoglobin values. Mean hemoglobin value, increased from 12.6 g/dL to 13.2 g/dL as early as 3 months following initiation of treatment. Amenorrhea was seen in 10% of these patients by 3 months, 20% by 6 months, and 40% by 12 months (Grigorieva et al., 2003).

☆ TIPS & TRICKS #1

In perimenopausal women, medical therapies such as GnRH agonists and the LNG-IUS can temporize bleeding and prevent surgery. If GnRH agonists are used for longer than 6 months, the practitioner can consider low-dose hormone replacement, which has not been shown to cause significant fibroid regrowth. The LNG-IUS remains an excellent option for patients requiring therapy for greater than 1 year, as the concern of bone loss associated with GnRH agonist use is not an issue.

Uterine artery embolization (UAE) has been successfully used to reduce symptoms of bleeding in patients with fibroids. Over 96% of patients with menorrhagia who underwent UAE were improved or symptom free at 2 years, while 83% were improved or symptom free at 5 years following the procedure (Van der Kooij et al., 2011; Volkers et al., 2007). UAE is minimally invasive and can be effective in patients with both acute and chronic bleeding. However, the amenorrhea associated with UAE, as well as unclear effects of UAE on fertility and pregnancy, make this option less desirable in patients considering future child bearing.

Surgical procedures are often necessary in patients with severe anemia. Treatment of fibroids by myomectomy in patients with bleeding is again dependent on the location of fibroids. The most common indication for hysteroscopic removal of submucosal fibroids is abnormal uterine bleeding. Most studies show a reduction in uterine bleeding after hysteroscopic myomectomy. Studies using pictorial assessment of bleeding have shown a decrease in bleeding in 82% of women following hysteroscopic resection of submucous pedunculated fibroids, 86% with sessile fibroids, and 68% with sessile/intramural fibroids (Vercellini et al., 1999). Endometrial ablation used with hysteroscopic myomectomy may help to further decrease menorrhagia in patients not desiring future child bearing. Laparoscopic and abdominal myomectomy can be utilized as well for those patients presenting with abnormal uterine bleeding who have intramural or subserosal fibroids.

☆ TIPS & TRICKS #2

Severely anemic patients require rapid volume resuscitation, as well as emergency measures to terminate bleeding. In addition to blood and fluid infusion, the Cell Saver blood salvage machine can be utilized to recirculate lost blood. GnRH agonists and iron therapy may also be helpful in severely anemic patients prior to surgical management.

Endometrial ablation can be performed in patients with menorrhagia or menometrorrhagia caused by benign conditions who have completed child bearing and have either failed medical

therapy or are not appropriate candidates for medical therapy. Satisfaction rates with endometrial ablation in patients with fibroids approach 95%, but the rates of amenorrhea following this procedure are low at only 15–60% (Stovall, 2011). Endometrial ablation is often not the best option for patients with submucosal fibroids as the cavity is often abnormal, but some ablative methods have been approved for patients with submucosal fibroids less than 2 cm (Stovall, 2011).

Uterine bleeding can be definitively relieved by hysterectomy but this will not be an option for all patients, such as those who desire future fertility or uterine conservation. Hysterectomy is associated with significant cost as well as morbidity to patients.

EVIDENCE AT A GLANCE #1

Medical therapy	Mechanism of action
Gonadotropin-releasing hormone (GnRH) agonists	Downregulate pituitary GnRH receptors, causing decreased ovarian estrogen and progesterone production
Danazol	Androgenic steroid that creates a high androgen and low estrogen environment, resulting in fibroid shrinkage (not commonly used)
Mifepristone SPRMs: asoprisnil, ulipristal acetate	Progesterone receptor modulator (antagonist and partial antagonist for SPRM) with primarily antagonistic properties on the progesterone receptor, causing a decrease in fibroid size
Levonorgestrel intrauterine system (LNG-IUS)	Exhibits a profound progestational effect on the endometrium and can cause fibroid shrinkage
Letrozole	Aromatase inhibitor which reduces estrogen biosynthesis within the fibroid

Pelvic pressure in patients with fibroids

Pelvic pressure is commonly seen in patients with fibroids due to a mass effect. The severity and location of this pressure are usually related to the size and location of the fibroids (Stovall, 2001). Patients often complain of insomnia and other sleep-related disturbances due to pressure from fibroids. Symptoms of pressure are more commonly seen than those of pain in patients with uterine fibroids.

Evaluation of pelvic pressure

The evaluation of a patient with pelvic pressure can help to guide management. A pelvic exam will offer information on the size and location of large fibroids. Radiological evaluation, including transvaginal ultrasound and possibly MRI, is helpful as well. Laboratory tests such as blood urea nitrogen (BUN) and creatinine may be necessary in a patient with very large fibroids to determine if renal injury has been caused by ureteral obstruction.

CAUTION

Significantly enlarged fibroids can cause complications other than pelvic pressure. Obstruction of ureters may occur in patients with very large fibroids, leading to hydronephrosis and eventual renal damage. Elevated blood urea nitrogen or serum creatinine may be indicative of a renal insult.

Management of pelvic pressure

Many pharmacological treatments successfully reduce fibroid size and uterine volume, which can help to relieve feelings of pressure. The hypoestrogenic state induced by GnRH agonists is associated with a 35–65% reduction in fibroid volume, mostly occurring in the first 3 months following treatment (Olive et al., 2004). Danazol, an androgenic steroid, has been shown to decrease fibroid volume by 37% and uterine volume by 29% after 6 months of therapy (La Marca et al., 2003) but is not commonly used for fibroids due to androgenic side-effects. Mifepristone, a progesterone receptor antagonist, caused a 57% reduction in fibroid volume and 36% reduction in uterine volume (Esteve et al., 2012). Medical treatment of fibroids will be covered in greater detail elsewhere, but two selective progesterone receptor

modulators (SPRMs), ulipristal acetate (formerly known as CDB-2914) and asoprisnil, have been shown to cause a significant reduction in fibroid volume and significantly reduce bleeding symptoms (Chwalisz et al., 2007; Levens et al., 2008). Uterine volume was reduced as much as 41% with LNG-IUS use but fibroid volume was not significantly reduced (Magalhães et al., 2007). A recent study showed letrozole, an aromatase inhibitor, to be beneficial in the treatment of fibroids. The study showed a 46% reduction in fibroid volume and a 21% reduction in uterine volume after 3 months of treatment (Parsanezhad et al., 2010).

Noninvasive procedures offer further options to patients with pressure symptoms associated with fibroids. Following UAE, over 54% of patients noted volume reduction of fibroids at 1 year, and over 60% at 2 years after the procedure (Van der Kooij et al., 2011). Surgical options such as myomectomy may be helpful in patients who do not achieve adequate reduction in fibroid size with medical management to relieve symptoms of pressure. Laparoscopic or abdominal myomectomy may be employed to remove large intramural or subserosal fibroids causing pressure. Symptoms of pressure can be nearly completely relieved with hysterectomy but this is often not necessary as patients have many other alternatives, as demonstrated above (Kjerulff et al., 2000).

Pain in patients with fibroids

Fibroids are typically asymptomatic but may cause pain due to the mass effect of the uterus on adjacent organs. Noncyclic pelvic pain and dyspareunia are increased in patients with fibroids (Lippman et al., 2003). Over 40% of white women and 59% of black women presenting for hysterectomy due to fibroids reported severe pelvic pain. Women with fibroids have been reported to be 40% more likely to have mild dyspareunia and 80% more likely to have moderate or severe dyspareunia than women without fibroids (Lippman et al., 2003). Patients with fibroids were also twice as likely to report moderate or severe noncyclic pelvic pain as patients without fibroids. Acute pain can occur with degeneration of fibroids or with torsion of a pedunculated fibroid (Stewart, 2001).

Evaluation of pelvic pain

Evaluation of pain in a patient with uterine fibroids is similar to the evaluation of a patient with pressure symptoms. Pelvic and abdominal exams can help the practitioner determine the exact location of pain. Ultrasound can assist in determining whether fibroids are present, and their size and location if identified. MRI may be helpful in cases of very large fibroids that cannot be adequately characterized via ultrasound. It is important to quantify and document the quality, severity, location, and duration of pain so that this information may be used in the future to judge treatment success.

Management of pain

Medical management of fibroids in patients with pain symptoms can be beneficial. As with patients who present with symptoms of pressure, reducing the size of fibroids can alleviate pain. As outlined above, GnRH agonists, danazol, mifepristone, and letrozole are all efficacious in reducing fibroid size. The LNG-IUS has been shown to reduce uterine size but not overall fibroid volume. Medical management is noninvasive and may be effective in relieving pain symptoms prior to surgical management.

Surgical management may be necessary in patients with significant pain due to fibroids. Pain scores as measured by the Short Form-36 (SF-36) questionnaire have been shown to markedly improve at 12 months following treatment in patients who undergo uterine artery embolization, myomectomy, or hysterectomy for treatment of uterine fibroids (Spies et al., 2010). Although patients who underwent hysterectomy showed slightly greater improvement in pain scores, this difference was not significant. Pain scores per the SF-36 questionnaire are significantly improved in patients undergoing MR-guided focused ultrasound at 1, 3, and 6 months following the procedure when compared to baseline scores prior to treatment (Stewart et al., 2006).

Sexual problems in patients with fibroids

Patients with uterine fibroids have been noted to have significant impairment in sexual function, with high rates of dyspareunia (Lippman et al., 2003). Women with gynecological problems, such as fibroids, often feel different and less attractive than other women. These feelings of inadequacy may affect the arousal and desire phases of sex. The location of fibroids may be an indicator of the degree of sexual impairment. Studies have shown

that patients with fundal and anterior fibroids have noted more intense deep dyspareunia than patients with fibroids in other locations (Ferrero et al., 2006). These patients have been noted to have less overall satisfaction with sexual intercourse due to discomfort. Patients with fibroids score consistently lower on UFS-QOL sexual function tests than controls without uterine fibroids (Spies et al., 2010). The UFS-QOL provides an objective, validated measure by which researchers can compare patients.

Evaluation of sexual problems

Female sexual dysfunction involves social, psychological, and physical factors. Evaluation should begin with a sexual history, which may help to elucidate problems with body image, relationships, and sexual abuse. Multiple questionnaires are available to evaluate sexual function, including the Female Sexual Function Index (FSFI) and the UFS-QOL. Physical exam may uncover a structural abnormality such as a cystocele or rectocele, which can interfere with sexual function. Also, patients who are menopausal often experience vaginal atrophy and dryness. Cervical and vaginal swabs can be used to diagnose infections, which may cause dyspareunia. Fibroids may be palpable on physical exam and can cause dyspareunia due to mass effect. As above, patients with fibroids may have a significant psychological component to their sexual dysfunction, as they often feel less attractive than other women.

Management of sexual problems

Studies have shown that sexual function scores improve markedly following treatment, approaching those of normal controls. Sexual function scores following myomectomy showed no change in desire, arousal, lubrication, or orgasm following surgery. However, overall satisfaction scores were improved following myomectomy. Overall sexual functioning scores were also improved following UAE, with significantly higher scores on sexual questionnaires seen at 3 months following the procedure than prior to UAE. Significantly improved scores were seen in the areas of frequency of sexual desire, frequency of sexual activity, duration of lubrication, frequency of orgasm, and pain in the genital area following UAE (Voogt et al., 2009). This study also showed a significant correlation between sexual and psychological well-being.

Many women are concerned that removal of the uterus may affect their sexual wellbeing and attractiveness. Early reports on sexual function suggested that the uterus may play a role in vaginal orgasm, and that uterine removal may negatively affect a woman's ability to achieve orgasm. Hysterectomy alters the local nerve supply and anatomy of the pelvic organs, which may play a role in sexual function. Questions have arisen as to whether removal of the cervix alters sexual function. Studies have both supported and refuted the removal of the cervix at the time of hysterectomy for improved sexual function. Despite concerns about altered orgasmic function, a recent study reported significantly improved sexual function in all patients independent of the type of hysterectomy. Although sexual function improved markedly following hysterectomy, the rate of dysfunction remained disturbingly high. This study demonstrated the prevalence of sexual problems including lubrication, orgasm, sensation, and arousal to be 43% in patients following vaginal hysterectomy, 41% following supracervical abdominal hysterectomy, and 39% following total abdominal hysterectomy (Roovers et al., 2003).

In studies comparing hysterectomy, myomectomy, and UAE, sexual functioning scores after treatment were found to be highest in those patients who underwent hysterectomy (Spies et al., 2010). Sexual function scores have also shown significant improvement over baseline following treatment with MR-guided focused ultrasound (Stewart et al., 2006).

EVIDENCE AT A GLANCE #2

Procedure	Prevalence of postoperative sexual dysfunction
Vaginal hysterectomy	43%
Supracervical hysterectomy	41%
Total abdominal hysterectomy	39%

Data from Roovers et al. (2003).

Genitourinary symptoms in patients with fibroids

Urinary symptoms related to uterine fibroids often result from a mass effect of the fibroid on the bladder, ureters or urethrovesical junction. Patients

may experience urinary incontinence, early urge to void, difficulty voiding or renal dysfunction secondary to compression of the ureters (Stovall, 2001). Many patients with fibroids complain of nocturia, which significantly affects their quality of life. Urinary symptoms more commonly arise from the mass effect of anterior fibroids (Stewart, 2001).

Evaluation of genitourinary symptoms

When evaluating urinary symptoms in a patient with fibroids, it is important to first exclude other causes. A careful history and physical exam will help to delineate the timing, frequency, severity, and location of symptoms. Urinalysis can help to determine the presence of infection, which is a very common cause of dysuria and urinary frequency. Vaginal cultures may be used to identify the presence of sexually transmitted infections and other vaginal infections. Ultrasound, intravenous pyelography, and plain films may be used to evaluate stones, diverticula, and hydronephrosis. Cystoscopy allows direct visualization of the urethra and bladder, which may be important in diagnosing conditions such as interstitial cystitis. Ultrasound, computed tomography (CT), and MRI can be useful in identifying fibroids which are compressing the bladder or obstructing ureters, causing hydroureter or hydronephrosis.

Management of genitourinary symptoms

Medical management may reduce fibroid size, which can alleviate compression of the bladder and ureters in nearly half of treated patients. GnRH agonists are associated with a 35–65% reduction in fibroid volume, danazol is associated with a 37% reduction in fibroid volume, and mifepristone is associated with a 57% reduction in fibroid volume. Also, the LNG-IUS is associated with a 41% reduction and letrozole with a 46% reduction in fibroid volume.

Improvements in urinary function have been demonstrated to occur mainly during the first 6 months in patients following both UAE and hysterectomy (Hehenkamp et al., 2008). Incontinence symptoms at 18 months following UAE were significantly improved in patients using the incontinence impact questionnaire. At 24 months following their procedure, 53% of women who underwent UAE with incontinence at baseline still reported incontinence, while 82% of women who underwent hysterectomy with incontinence at baseline still reported incontinence (Hehenkamp et al., 2008). Myomectomy may be used to remove fibroids that are compressing the bladder or ureters, or to reduce overall uterine size, which may alleviate urinary symptoms.

Gastrointestinal symptoms in patients with fibroids

Gastrointestinal symptoms related to uterine fibroids often involve defecatory dysfunction, which includes both constipation and diarrhea. Defecatory dysfunction is often the result of a mass effect from posterior fibroids. Patients may also report symptoms of abdominal bloating and increasing abdominal girth. These symptoms can be particularly distressing to patients and life altering if not addressed.

Evaluation of gastrointestinal symptoms

Evaluation of defecatory dysfunction begins with a focused history and physical exam. Questions about the timing, location, quality, and severity of symptoms may help to elucidate the cause. Practitioners should perform both vaginal and rectal exams in a patient with defecatory dysfunction. Vaginal exam may demonstrate a symptomatic rectocele, which is often the cause of constipation. Rectal exam and hemoccult stool testing will help to determine if a rectal sphincter defect, hemorrhoids, or colonic malignancy are present. Colonoscopy allows direct visualization of the lower gastrointestinal tract and can be diagnostic of polyps, ulcerative lesions, and malignancy. Ultrasound, CT, and MRI may all be useful in determining if uterine fibroids are compressing the gastrointestinal tract. Large fibroids, often palpable on pelvic exam, frequently cause feelings of abdominal fullness or bloating.

Management of gastrointestinal symptoms

Medical management may be efficacious in reducing fibroid size and relieving gastrointestinal symptoms. GnRH agonists, danazol, mifepristone, and letrozole have all been proven to reduce fibroid volume. A reduction in overall uterine volume may help to alleviate symptoms of abdominal fullness and bloating.

Several studies have been performed which demonstrate the effectiveness of UAE on improving defecatory function. A recent study has shown

that at 24 months following UAE, 91% of patients reported similar or improved quality of defecatory function, while 83% of patients reported similar or improved defecatory function following hysterectomy. The use of laxatives was shown to decrease from 10% at baseline to only 1%, 24 months following UAE (Hehenkamp et al., 2008). Myomectomy may also be effective in the removal of posterior fibroids that are known to cause defecatory dysfunction, or in the reduction of overall uterine volume. Abdominal bloating has been shown to improve by as much as 81% after a period of 24 months following hysterectomy but other alternatives have been proven effective and should be considered first (Kjerulff et al., 2000).

Other symptoms in patients with fibroids

Fibroids can affect many other areas of patients' lives, including activity level, energy, mood, and self-consciousness. All these factors were found to markedly improve per the UFS-QOL questionnaire after treatment of fibroids with UAE, myomectomy or hysterectomy. Improvement was observed to be greatest in each of these areas in patients who underwent a hysterectomy as opposed to other methods (Spies et al., 2010). However, hysterectomy is often not the best option for patients as it involves significant surgical risk and does not allow future fertility. Patient scores in the areas of general health, vitality, social functioning, mental health, and emotional role were all seen to markedly improve per the SF-36 questionnaire in patients with fibroids after treatment with UAE, myomectomy or hysterectomy (Spies et al., 2010). Patients with uterine fibroids undergoing MR-guided focused ultrasound have also been shown to have significantly improved UFS-QOL scores in the areas of control, activities, energy, mood, concern, and self-consciousness at 3 and 6 months following therapy, when compared to baseline scores (Stewart et al., 2006).

Fibroids in the patient considering pregnancy

Fibroids are commonly encountered in women considering pregnancy, and have been reported in over 10% of women undergoing ultrasound in the first trimester of pregnancy (Cook et al., 2010). Fibroids are known to cause many complications in pregnancy, including increased risk for spontaneous abortion, preterm labor, and fetal malpresentation.

Evaluation of a patient with fibroids who is considering pregnancy typically involves a pelvic exam, supplemented by ultrasound to further define the location and size of fibroids. Once a patient has become pregnant, determining the location of fibroids in relation to the placenta and cervical canal will offer clues to the risk for placental abnormalities.

Obstetric outcomes and uterine fibroids

Data indicate that fibroids increase the risk of pregnancy loss. Women with fibroids in all locations have a relative risk of spontaneous abortion approaching 1.7 compared to women without fibroids (Pritts et al., 2009). Patients with fibroids also have a significantly lower livebirth rate, with the relative risk of livebirth approaching 0.7 when compared to controls without fibroids. A correlation has been demonstrated between the location of fibroids and risk of pregnancy loss. Patients with both submucosal and intramural fibroids have significantly higher spontaneous abortion rates and significantly lower livebirth rates compared to women without fibroids. However, women with subserosal fibroids show no difference in spontaneous abortion or livebirth rates compared to women without fibroids (Pritts et al., 2009).

Fibroids have been shown in several studies to increase the risk for preterm labor, especially if fibroids are large, multiple fibroids are present or the site of placentation is adjacent to or overlying a fibroid. Other studies have shown an increased risk for preterm labor but not preterm birth. A recent meta-analysis showed no significant difference in rates of preterm delivery in patients with fibroids in all locations compared to women without fibroids (Pritts et al., 2009).

Large submucosal fibroids that distort the uterine cavity have been associated with fetal malpresentation. Studies have shown an odds ratio of 3.98 for fetal malpresentation in women with fibroids compared to women without fibroids (Ouyang et al., 2006). Fetal malpresentation may increase risk for cesarean section, which carries increased maternal morbidity.

Fibroids may exhibit growth during pregnancy, which can cause a significant increase in pain. However, fibroid regression has been demonstrated in 70% of women following livebirths. These women had more than a 50% reduction in fibroid volume between early gestation and 3–6 months postpartum (Laughlin et al., 2011). Significantly less fibroid regression was observed in patients who used postpartum progestins or who had a miscarriage (Laughlin et al., 2011).

Patients with symptomatic uterine fibroids considering pregnancy typically undergo myomectomy for resection. Resection of submucosal fibroids can be performed via hysteroscopic myomectomy, while resection of intramural or subserosal fibroids can be performed via laparoscopic or abdominal myomectomy. Hysteroscopic resection of submucosal fibroids is associated with a low rate of complications and rapid recovery. There are no reported cases of uterine rupture following hysteroscopic myomectomy, so patients may attempt a vaginal delivery following this procedure (Stewart, 2001). The risk of uterine rupture in pregnancy following abdominal myomectomy is low, approximately 0.002%. While this occurrence is lower than the risk of uterine rupture following a previous cesarean section, approximately 0.1%, patients with a transmural incision following abdominal or laparoscopic myomectomy are typically counseled to undergo a cesarean section for delivery (Stewart, 2001). Furthermore, adhesive disease following myomectomy may have a detrimental effect on fertility.

Fibroids in the infertile patient

Many studies have been performed to elucidate the relationship between fibroids and infertility and several excellent meta-analyses have been published. Fibroids are present in approximately 5–10% of patients with infertility, and are the only abnormality seen in 1–2.4% of patients with infertility (Cook et al., 2010). Fibroids affect fertility through obstruction of fallopian tubes, impaired gamete transport, abnormal endometrial receptivity, distortion of the endometrial cavity, impaired uterine contractility, impaired blood supply to the endometrium, and abnormal hormonal milieu (Somigliana et al., 2007). Fibroids in the infertile patient must be considered in both patients who are utilizing assisted reproductive technology (ART) and those who are not.

Clinical pregnancy, implantation, and livebirth rates are significantly impaired in women with any location of fibroid (Pritts et al., 2009; Somigliana et al., 2007). The location of fibroids is thought to greatly affect fertility, with submucosal fibroids or intracavitary fibroids having the greatest effect. Patients with submucosal fibroids have a relative risk of 0.36 of achieving clinical pregnancy, and a relative risk of 0.32 of having a livebirth when compared to nonfibroid controls (Pritts et al., 2009). The effect of intramural fibroids on infertility remains unclear, but may be clearer in those patients undergoing ART. Current studies examining intramural fibroids differ in the size and location of the fibroids, as well as the method used for classifying them as intramural (Lasmar et al., 2011). Subserosal fibroids are thought to have little to no effect on fertility but the classification of some fibroids as subserosal is controversial. Patients with fibroids that have no intracavitary involvement nonetheless had significantly lower implantation and livebirth rates compared to nonaffected controls. Clinical pregnancy rates did not significantly differ in patients with no intracavitary involvement (Pritts et al., 2009).

The size of fibroids is also thought to affect fertility. Patients with intramural fibroids greater than 4 cm have significantly lower pregnancy rates than those with fibroids less than or equal to 4 cm. Patients with fibroids greater than 4 cm have pregnancy rates of only 12%, while those with fibroids less than or equal to 4 cm have pregnancy rates over 30%. Treatment of fibroids not encroaching on the uterine cavity that are greater than 3–4 cm is generally recommended in patients pursuing fertility.

Treatment of fibroids in infertile patients involves myomectomy, as other less invasive techniques have not been approved for those attempting pregnancy. Myomectomy is not without risk, as there is potential for blood loss and infection at the time of surgery, and adhesion formation postoperatively. Patients who undergo myomectomy for submucosal fibroids have been shown to have higher clinical pregnancy rates, with a relative risk of 2.03, compared to women

with fibroids *in situ* who did not undergo myomectomy (Pritts et al., 2009). However, livebirth rates and spontaneous abortion rates in patients following myomectomy for submucosal fibroids are not significantly altered compared to those with fibroids who did not undergo myomectomy. When compared to infertile women without fibroids, data indicate that clinical pregnancy rates, livebirth rates, and spontaneous abortion rates will normalize in patients with submucosal fibroids following myomectomy.

It remains unclear whether myomectomy for intramural fibroids is beneficial in the patient with infertility. Studies examining this issue often do not contain information regarding the fibroid number, location or size that is necessary to affect fertility. Also, studies often include women with fibroids who are older than controls, which would adversely affect their ability to achieve clinical pregnancy or successful livebirth (Bulletti et al., 2004). There are published reports of improved fertility following myomectomy for intramural fibroids. Casini et al. (2006) demonstrated a trend towards higher pregnancy rates in patients with intramural fibroids who underwent myomectomy, with clinical pregnancy rates of 56% in those undergoing myomectomy compared to 41% in those who did not undergo myomectomy (Casini et al., 2006).

It is generally accepted that subserosal fibroids have little effect on fertility, and that their removal offers little benefit to pregnancy, livebirth or spontaneous abortion rates (Cook et al., 2010).

EVIDENCE AT A GLANCE #3

Effect of fibroids on fertility based on location (relative risk)

	Submucosal fibroids	No intracavitary involvement
Clinical pregnancy	0.36	0.89
Livebirth	0.32	0.78
Spontaneous abortion	1.68	1.89

Data from Pritts et al. (2009).

Fibroids in the assisted reproduction patient

Patients considering assisted reproductive technologies must contend with the detrimental effects of fibroids as well (Ezzati et al., 2009). Altered endometrial receptivity is thought to cause infertility in patients undergoing ART, as other causes such as abnormal gamete transfer and blockage of fallopian tubes are bypassed by ART. Recent studies have suggested that submucosal and intramural fibroids may cause a global reduction in HOX gene expression (Rackow and Taylor, 2010). The impaired endometrial receptivity and subsequent infertility associated with fibroids could result from the effect of this signaling molecule on the entire endometrium, rather than a focal area overlying the fibroid (Rackow and Taylor, 2010). Altered endometrial receptivity can adversely affect embryo implantation, lowering the rate of successful pregnancy.

In patients undergoing ART, the location of fibroids is paramount. Patients with submucosal fibroids that distort the uterine cavity have been shown to have an odds ratio of 0.3 for clinical pregnancy, and 0.3 for delivery. Intramural fibroids have a less substantial effect on pregnancy outcomes in patients undergoing ART. Patients with intramural fibroids have an odds ratio of 0.8 for clinical pregnancy, and 0.7 for delivery. Subserosal fibroids likely play no role in patients pursuing ART, with an odds ratio of 0.92 for clinical pregnancy, and 0.94 for delivery (Somigliana et al., 2007).

However, the size of fibroids that would cause lower implantation rates remains unclear. Myomectomy prior to *in vitro* fertilization (IVF) in patients with intramural fibroids greater than 50 mm has been shown to be beneficial to pregnancy outcomes (Bulletti et al., 2004). This study showed that patients who underwent myomectomy prior to ART had a clinical pregnancy rate of 33% and a livebirth rate of 25%. These success rates were significantly greater than those in patients who did not undergo myomectomy prior to ART, who had a 15% clinical pregnancy rate and 12% livebirth rate (Bulletti et al., 2004). Myomectomy is likely to be effective in improving pregnancy outcomes in those patients undergoing ART with submucosal fibroids, and those with intramural fibroids greater than 4 cm. Myomectomy for subserosal fibroids likely has no effect on pregnancy outcomes.

EVIDENCE AT A GLANCE #4

Effect of fibroids on ART outcome based on location (odds ratio)

	Submucosal	Intramural	Subserosal
Clinical pregnancy	0.3	0.8	1.2
Delivery	0.3	0.7	1.0

Data from Somigliana et al. (2007).

Conclusion

Uterine fibroids affect quality of life, as well as obstetric and fertility outcomes. There is considerable evidence on which to base clinical intervention for symptoms caused by fibroids, such as bleeding, pain, sexual dysfunction, and infertility. The most appropriate treatment for each patient will be largely influenced by her symptoms, age, and desire for fertility or to retain her uterus. Evidence-based treatment of fibroids depends on the size, location, and number of fibroid(s) present. Thus, accurate assessment of the size, number, and location of the fibroid(s) is necessary to design individualized management and treatment of patients with fibroids to obtain optimal outcomes.

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4

Management of Fibroids in Pregnancy

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Introduction

Uterine leiomyomas are the most common benign pelvic tumors in women, occurring in approximately 20–25% of women of reproductive age. Fibroids affect approximately 0.1–3.9% of all pregnancies (Coronado et al., 2000), but prevalence varies depending on the study referenced. However, as more women begin to delay the onset of child bearing, incidence will likely increase because age is an independent risk factor for fibroid development. Women who develop fibroids during pregnancy are more likely to be older than 35 years of age, nulliparous, or of African-American descent (Table 4.1). In addition, women with fibroids are more likely to have higher body mass indices, gestational diabetes, and chronic hypertension.

Although the majority of pregnant women with fibroids are asymptomatic, and most affected pregnancies will be uneventful, serious complications can occur during pregnancy leading to poor outcomes. Complications occur in approximately one out of every 500 pregnancies related to myomata. Some studies have shown that 10–40% of women with known fibroids experience complications during pregnancy (Sheiner et al., 2004). Findings on specific complications associated with leiomyomata are inconsistent, but examples of commonly cited complications include pelvic pain related to red or carneous degeneration, increased risk of spontaneous abortions, preterm labor, placental abruption, malpresentation, increased risk of cesarean section, retained placenta, increased risk of postpartum hemorrhage, and delivering a neonate with low Apgar scores. Less common complications such as acute renal failure, fetal limb anomalies, and hypercalcemia have also been reported in the literature. A woman's risk of developing pregnancy complications increases when the fibroids are larger than 3 cm. Nonetheless, women with leiomyomata larger than 10 cm can achieve a vaginal delivery in approximately 70% of cases.

General management

It is still unclear how best to manage pregnancies with symptomatic fibroids to decrease the risk of adverse events. In addition to the use of ultrasound to identify women at risk for fibroid-related complications, the gold standard for initial management has traditionally been conservative treatment for pain symptoms. However, treatment options are dependent on multiple factors such as location, position of the tumor relative to the lower uterine segment, size, severity of symptoms, and the patient's desire for nonconservative treatment. Fibroid disease manifests heterogeneously; women can have a solitary myoma or multiple myomata, which can concurrently present with adenomyosis. Therefore, different forms of the disease probably exist, particularly between different ethnic groups. Chromosomal abnormalities have been found in

Fibroids, First Edition. Edited by James H. Segars.

Table 4.1 Obstetric risk factors with and without fibroids

	Sheiner et al. (2004)			Qidwai et al. (2006)			Coronado et al. (2000)			Stout et al. (2010)		
Characteristic	Myomas (%)	No myomas (%)	Odds ratio (OR)	Myomas (%)	No myomas (%)	Odds ratio (OR)	Myomas (%)	No myomas (%)	Odds ratio (OR)	Myomas (%)	No myomas (%)	Odds ratio (OR)
Maternal age >35	44.3	12.6	1.2	5.6	NR	NR	36.9	9.9	5.3	62.0	28.7	4.1
African-American race	NR	NR	NR	24.2	15.7	1.7	9.8	3.7	2.9	34.5	20.3	2.1
Nulliparity	30.4	24.3	4.0	57.4	53.7	1.2	57.7	38.7	2.2	NR	NR	NR
Chronic HTN	7.2	1.8	1.9	2.2	0.9	2.4	2.6	0.9	3.0	4.9	2.3	2.2
Diabetes mellitus	4.6	1.3	1.4	9.8	6.1	1.7	3.7	2.5	1.5	7.4	5.1	1.5
Previous CS	18.7	10.2	2.0	NR	NR	NR	14.7	6.9	2.3	NR	NR	NR

CS, cesarean section; HTN, hypertension; NR, not reported.

approximately 40% of cases, indicating that fibroids most likely have a genetic component. Examples of syndromes associated with fibroids are discussed in detail in Chapter 11.

Differences in disease presentation make treating fibroid disease extremely challenging, since physicians will need to tailor their management to meet the needs of each individual patient. The absence of management guidelines is largely due to a relative paucity of large randomized trials exploring the benefits of surgery during pregnancy. Further research is needed to elucidate and distinguish overall risk and benefit of surgical intervention versus expectant management. However, several case series in pregnancy suggest that myomectomy may be indicated for the appropriate patient.

Pregnancy and fibroids

Parity, or the number of times that a woman has given birth, has been consistently associated with a 20–40% decrease in risk of developing fibroids (Baird and Dunson, 2003). This risk is further decreased as the total number of births increases, and shorter intervals between births have been reported as being protective against fibroid development. There is a relative risk reduction of 40–50% in situations where women older than the age of 35 give birth for the first time. However, these protective effects may be inflated, because it is well documented that if a woman does not have fibroids she is more likely to have conceived and delivered a child. Fibroids have been implicated as the primary cause of infertility in 12–25% of women.

Response to pregnancy

Longitudinal studies using ultrasonography have consistently reported that most fibroids do not undergo significant growth, defined as >10% volume increase. However, significant growth does occur in up to one-third of symptomatic cases, and this growth has been noted to be greatest during the first trimester. A recent study by de Vivo et al. (2011) reported that 71.4% of myomas increased in size between the first and second trimesters, whereas growth between the second and third trimesters was found in only 66.6% of myomas. Fibroid growth has been reported to be greater in younger women and in those of African-American descent. Parity has been shown to be protective against significant changes in growth. Nonetheless, studies indicate that myoma growth rates tend to taper towards the end of pregnancy, and may even reverse during the postpartum period. Fibroid regression can be attributed to a remodeling process that is initiated during the puerperal period when uterine involution is occurring. Prolonged intervals between births may enable fibroids to grow to a size too large to undergo remodeling and resolution.

EVIDENCE AT A GLANCE

Fibroid response to pregnancy

Exacoustòs and Rosati (1993)

- 12% increase in myoma volume in up to one-third of cases during first trimester
- Greatest change in growth occurs during the first 10 weeks of gestation → tapers off/reverses by the third trimester

Laughlin et al. (2010)

- Fibroids seen at postpartum ultrasound were generally smaller than at the initial ultrasound examination
- 36% of fibroids resolved beyond the ability to detect them on ultrasound postpartum

De Vivo et al. (2011)

- 71.4% of myomas increased in size, and 28.6% remained unchanged or decreased in size between the first and second trimesters
- 66.6% of myomas grew between the second and third trimesters
- Myoma growth negatively related to parity, and positively related to high pre-pregnancy BMI
- Changes in growth were greater in younger women and in African-Americans

Laughlin et al. (2011)

- 72% of women showed >50% myoma regression by 3–6 months postpartum
- 12% of women had ≤50% myoma regression postpartum
- 10% of women showed an increase in fibroid volume >50% postpartum
- Progestin contraception diminished fibroid regression postpartum

In general, fibroids seen postpartum have been shown to be smaller than at initial ultrasound. For example, Laughlin et al. (2010) found that 36% of fibroids resolved to sizes below the ability to detect them on ultrasound. The underlying mechanism that causes fibroids to recede during uterine involution postpartum is unknown. A current theory suggests that the primary cause is ischemia of the myometrium and myomas that occurs at delivery as the uterus involutes and elicits vascular remodeling. Fibroids contain abnormal vasculature that is reduced in density compared to the myometrium, making fibroids more susceptible to ischemia and necrosis (Burbank, 2004). However, this is not the only accepted explanation for fibroid regression.

Shynlova et al. (2004) suggested that the phenotypic changes seen in the myometrial structure are regulated by both hormonal and mechanical factors. Progesterone (P_4) levels vary between the pregnant and nonpregnant state, and these hormonal fluctuations are believed to modulate and induce changes in expression of certain extracellular matrix (ECM) proteins. In particular, proteins such as elastin, fibronectin, laminin, and collagen types I, III, and IV are thought to be key participants in the signaling pathway for uterine remodeling. In the nonpregnant state, these ECM proteins are expressed at very low levels. However, during pregnancy temporal changes are seen in the secretion of laminin, fibronectin, and collagen IV. Fibronectin is a glycoprotein that is involved with the process of collagenolysis late in pregnancy, which is thought to play a vital role in uterine remodeling. Mechanical stretch has also been implicated as a modulator of the expression of ECM proteins in several types of tissue. A considerable increase in collagen formation and uterine weight has been demonstrated in nonpregnant uteri distended with uterine wax injections (Cesen-Cummings et al., 2003). Thus, another plausible theory is that the uterus alternates between contractile and synthetic pathways as it transitions from a nonpregnant to a pregnant state. The synthetic state occurs during early pregnancy when smooth muscle cells (SMC) detect increasing levels of P_4. At the end of pregnancy, P_4 levels precipitously drop, eliciting an increase in basement membrane proteins such as collagen and laminin. This enables the uterus to revert back to its previous contractile state, preventing any further growth of uterine fibroids. Nonetheless, some leiomyomata fail to undergo growth arrest in the postpartum state and continue to proliferate. Cells within the fibroids become unregulated when myometrial cells re-enter the G_D phase of the cell cycle instead of undergoing apoptosis.

Another explanation for postpartum fibroid reduction is that abnormal proliferation occurs when myometrial cells undergo injury, which initiates changes in growth factors such as transforming growth factor (TGF) beta. Data from microarray studies suggest that 25% of genes expressed differentially between myomas and the myometrium are related to TGF-beta signaling and collagen or ECM proteins [10]. Other studies using Eker rat uteri have hypothesized that the inability of SMCs within fibroids to regulate cell growth may be related to an impaired response to prostaglandins. Under normal physiological conditions, parturition and involution of the uterus are thought to be initiated by increasing levels of prostaglandins, which are synthesized in response to estradiol in the myometrium by COX enzymes in the arachidonic acid cascade. Prostaglandins are produced at the end of gestation when P_4 levels fall, shifting the estrogen/progesterone ratio within the myometrium. Fibroids appear to lack the ability to either make or respond to these prostaglandins, keeping the SMC of the myomata in a constant state of proliferation instead of undergoing contraction like normal myometrial cells (Cesen-Cummings et al., 2000).

Leiomyoma cells express several myometrial contraction proteins such as the oxytocin receptor (OTR), connexin 43, and cyclo-oxygenase (COX)-1, which may play critical roles in modulating tumor growth. However, tumor cells fail to express COX-2, the enzyme necessary to increase specific uterine prostaglandins responsible for initiating parturition and uterine involution, as well as apoptosis during myometrial remodeling. Lack of COX-2 expression may allow fibroids to escape apoptosis, which has been found to be defective in Eker rat leiomyomas. Moreover, activation of the OTR signaling pathway appears to suppress tumor cell proliferation induced by estrogen, which further exemplifies the possible protective role of pregnancy in fibroid disease. However, other signaling pathways have also been implicated as potential mediators of neoplastic growth.

SCIENCE REVISITED

Evidence for fibroid regression

Burbank (2004)

- Fibroid regression caused by ischemia and vascular remodeling within myometrium and myomas seen with uterine involution at parturition

Shynlova et al. (2003)

- Increased expression of ECM proteins at parturition induced by decreasing P_4 levels
- Mechanical stretch of the uterus stimulates expression of ECM proteins causing contraction of uterine SMC

Cesen-Cummings et al. (2003)

- Increased production of basement membrane proteins is elicited by decreasing P_4 levels at the end of pregnancy and converts the uterus into a contractile state
- Uterus alternates between synthetic and contractile pathways as it transitions from the pregnant to nonpregnant state

Cesen-Cummings et al. (2000)

- Tumorigenesis is linked to activation of the OTR signaling pathway by estrogen at the end of pregnancy

Recent studies from Japan suggest that there may be an association between adiponectin, a hormone derived from adipocytes, and fibroid development (Wakabayashi et al., 2011). Adiponectin plays an important role in regulating several metabolic pathways, involving glucose and fatty acid catabolism; low levels of the hormone have been implicated in the development of metabolic syndrome and type 2 diabetes, which are conditions also associated with a higher risk of fibroid development. It has been found that adiponectin inhibits rat uterine leiomyoma cell growth in a dose-dependent fashion. Thus, pathways associated with adiponectin could possibly serve as therapeutic targets against fibroid development in the future. Burroughs et al. (2002) suggest that insulin-like growth factor (IGF)-1 may be a potential modulator of the effects of steroid hormones on uterine fibroids. IGF-1 is a well-known growth promoter that both regulates proliferation and inhibits apoptosis in target cells via an autocrine signaling pathway. Studies have shown that IGF-1 is bound with greater affinity by fibroids than normal myometrium, suggesting that overexpression of the IGF-1 receptor may occur in tumorigenesis. However, the regulation of IGF-1 expression in myomas is still elusive, and may vary significantly depending on local sex steroid hormone levels throughout the menstrual cycle and pregnancy. Therefore, it is important to note that although existing theories are the first breakthroughs to understanding the pathology of fibroid disease, the literature is quite controversial and scant. As a result, further research investigating metabolic signal pathways is necessary to develop a better understanding of the mechanism of disease and identify new therapeutic targets for treatment.

First trimester

Miscarriage

In addition to pelvic pain, fibroids in the first trimester have also been associated with pregnancy loss and bleeding. Early pregnancy loss is more common in women who have fibroids located in the uterine corpus than in the lower uterine segment. Certain types of fibroids also increase the risk of having a spontaneous abortion. For example, the risk of miscarriage increases for both intramural and submucous fibroids but not for subserous fibroids. Olive and Pritts (2010) performed a meta-analysis of the literature and reported that intramural fibroids have a relative risk of 1.60 for spontaneous abortion. Submucous fibroids may alter and reduce the volume of the intrauterine cavity. Furthermore, incidence of miscarriage was higher when multiple myomas were present compared to a solitary myoma (Lee et al., 2010).

The relationship between spontaneous abortion and fibroids in established pregnancy is not entirely clear, while there is clearly an increased likelihood of miscarriage (reviewed in Chapter 3). Possible explanations include increased uterine irritability and contractility, and compromised blood supply to the placenta and fetus due to altered endometrial development at the implantation site. If placental

implantation occurs close to a fibroid, there is a greater propensity for bleeding in early pregnancy to occur. Exacoustòs and Rosati (1993) found that 17% of pregnant women with myomas experienced a threatened abortion compared to 10% of controls. Furthermore, vaginal bleeding occurred in 72% of pregnant women who had retroplacental fibroids compared to 9% of patients who had fibroids that were nonretroplacental. The risk of placental abruption may also increase due to decreased placental surface area directly contacting the underlying endometrium, which causes ischemia and decidual necrosis, further compromising fetoplacental perfusion. In patients who have multiple pregnancy losses, it is imperative to further investigate the underlying cause. If the presence of fibroids is determined to be the only explanation for the losses, then the patient may benefit from a myomectomy prior to conceiving again. Early first-trimester miscarriage is clearly increased in cases with submucous fibroids and those that encroach on the uterine cavity. Furthermore, there are a few controlled studies to support myomectomy in such cases, with a reduction in subsequent loss rates in patients undergoing myomectomy versus controls (see Chapter 3). In addition, existing evidence does not suggest that there is an increased risk of pregnancy loss in patients who have undergone myomectomies. There are very few reports of myomectomy after pregnancy is established. Glavind et al. (1990) reported an incidence of pregnancy loss in 18% of patients treated both conservatively and with myomectomy during pregnancy.

Management

The first trimester of pregnancy is defined as the period from conception to week 13. It is important to note that most fibroids do not change in size throughout pregnancy, but changes in growth occur in one-third of cases during the first trimester. De Vivo et al. (2011) observed that 71.4% of uterine myomas increased in size between the first and second trimesters with a growth rate of 7.4% weekly change in volume. Another group (Exacoustòs and Rosati, 1993) noted that growth was most pronounced throughout the first 10 weeks of gestation, but that this increase in size ceases by the onset of the third trimester. Approximately 5–15% of pregnant woman with uterine fibroids require hospitalization at some point for pain management. In fact, the most common complaint attributed to fibroid growth was localized abdominal pain associated with red degeneration, which is typically seen with large, pedunculated subserosal myomas greater than 5 cm. Leukocytosis, nausea and vomiting, and mild fever may also be reported with this myoma pain syndrome.

Several explanations have been postulated to elucidate the underlying cause of severe pain in red degeneration. One cause may be that rapid fibroid growth leads to the tumor outgrowing its blood supply, resulting in ischemia, necrosis, and infarction. A second possible explanation purports that the growing uterus elicits unfavorable changes such as kinking in the fibroid's blood supply, which subsequently causes ischemia and necrosis of the myoma. The last explanation contends that pain is caused by the release of prostaglandins from cellular insults occurring within the fibroid. Evidence supporting this theory is illustrated by the fact that prostaglandin synthetase inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) are effective at controlling fibroid pain. In fact, the initial treatment for pain symptoms is conservative and usually consists of bed rest, hydration, and analgesics. It is recommended to avoid prolonged use of NSAIDs during the third trimester, specifically after 34 weeks, due to concern over the increased risk of premature closure of the patent ductus arteriosus, pulmonary hypertension, necrotizing enterocolitis, and oligohydramnios.

Myomectomy in the first trimester

If conservative treatment fails, then the physician must explore other options to better manage the patient's pain. At this point, manual removal of the tumors by myomectomy is typically the next step. Criteria for surgery include recurrent, intractable pain, large or rapidly growing myomas, and large or medium-sized myomas within the lower uterine segment or deforming the placental site. In addition, it is recommended to remove only solitary, pedunculated subserous myomas with stalks that are less than 5 cm in diameter. Tumors near the fundus and ostia of the tubes should also be avoided to prevent adhesions and future fertility problems.

In general, surgery is reserved for situations in which there are acute complications primarily because there is concern over risk of injury to the

Table 4.2 Evidence for outcomes of myomectomy during pregnancy

Author	Study design	Intervention	# Case patients (n)	# Controls (n)	Blood loss, study vs control	Blood transfusion (n), study vs control	Other adverse outcomes, study vs control	Successful outcomes, study vs control
Danzer et al. (2001)	Case report	1st trimester myomectomy	1	0	NR	None	Fetal limb anomaly; hydrocephalus	2 term livebirths via cesarean
Fanfani et al. (2010)*	Case report	2nd trimester myomectomy	1	0	NR	None	None	1 term livebirth via SVD
Febo et al. (1997)	Retrospective case control	2nd trimester myomectomy, cesarean myomectomy	13	14	NR	None	1 fetal loss/0 fetal losses	12 term livebirths via cesarean/14 term livebirths via cesarean
Hasbargen et al. (2002)	Case report	2nd trimester myomectomy	1	0	ΔHct 13.6	None	Fetal limb anomaly	1 term livebirth via cesarean
Burton et al. (1989)	Case series	Exploratory laparotomy, antepartum myomectomy, cesarean myomectomy	27	0	NR	1/0	5 fetal losses	21 term livebirths
Suwandinata et al. (2008)	Case report	2nd trimester myomectomy	1	0	1000 mL	None	Cesarean at delivery	1 term livebirth via cesarean
Wittich (2000)	Case report	2nd trimester myomectomy	1	0	ΔHct 7.0	None	None	1 term livebirth
Michalas et al. (1982)§	Case series	2nd trimester myomectomy	18	0	NR	NR	2 fetal losses	16 term livebirths
Michalas et al. (1995)	Case report	2nd trimester myomectomy	1	0	NR	None	None	1 term livebirth via cesarean
Lolis et al. (1994)†	Case control	2nd trimester myomectomy	18	14	Hemorrhage (n) 3/0	3/0	1 fetal loss/3 fetal losses uterine atony→2 subtotal hysterectomies	17 term livebirths/11 term livebirths
Son et al. (2011)‡	Case report	2nd trimester myomectomy	1	0	NR	None	None	1 term birth via SVD

Hct, hematocrit; NR, not reported; NS, not statistically significant; SVD, spontaneous vaginal delivery.

*Patient remained in the hospital for 10 days.

§Patient remained in the hospital for 7 days.

†There were no subsequent surgeries in the study group and 14.3% subsequent surgeries (either myomectomy or hysterectomy) in the control group.

‡Patient was discharged from hospital on day 3.

fetus or pregnancy loss, as well as other serious postoperative complications such as uterine dehiscence, hemorrhaging, preterm labor, placental abruption, and subsequent need for cesarean section (Table 4.2). Incidence of uterine rupture has been found to occur in one out of 15,000 births, and is more likely at birth in women of high parity and in cases where uterotonic agents such as oxytocin are used to stimulate labor. There are conflicting opinions regarding whether or not laparoscopic myomectomies increase the risk of uterine rupture compared to laparotomies. Roopnarinesingh et al. (1985) reported a 5.3% incidence of rupture at birth with laparotomies. However, physicians have not consistently reported cases of uterine rupture with laparoscopic myomectomies in the literature, making it difficult to compare the efficacy of both surgeries and ascertain the true risk of rupture associated with laparsocopy. Dubuisson et al. (2000) reported a single case of rupture out of 100 laparoscopy procedures performed.

Regardless of the type of myomectomy performed, there is still a high incidence of cesarean section following surgery. Some studies indicate that the risk of intraoperative and postpartum hemorrhage may be reduced by using techniques such as applying interrupted sutures around the fibroid to achieve hemostasis. Furthermore, Mollica et al. (1996) showed that elective myomectomies performed during weeks 15–18 of gestation did not result in a higher incidence of pregnancy loss, but rather indicated an improved overall fetal and neonatal outcome. Of 18 antepartum myomectomies performed, no miscarriages occurred, compared to a 13.6% pregnancy loss in the conservative treatment group. Furthermore, the incidence of preterm delivery was 5.6% in the surgical cohort, whereas preterm delivery occurred in 22.7% of those managed expectantly.

Despite the positive outcomes observed in several small retrospective studies, there are still reports to suggest that the risk of having an adverse complication is not negligible. For example, one case report of a myomectomy performed on a twin pregnancy at 12 weeks gestation by Danzer et al. (2001) relates fetal limb anomalies seen in the neonate at birth to similarities seen with chorionic villus sampling in early pregnancy. This raises concerns over what time frame during pregnancy is safest to undergo surgical interventions such as myomectomies. However, leaving myomas in place also poses risks; other small case series report similar fetal anomalies between fibroids and those induced experimentally via early withdrawal of amniotic fluid, compressing the developing limbs. Matsunaga et al. (1980) reported embryo malformations in 6.2% of cases with known uterine fibroids compared to 3.3% in the control group.

Second trimester fibroid management

The second trimester is defined as the time between 14 weeks and 27 weeks of gestation. Standard prenatal care typically includes a fetal survey at 20 weeks' gestation to investigate potential neural tube defects and organ abnormalities. Ultrasound is an effective tool that can accurately detect the presence of uterine leiomyomata with a detection limit of 1×1 cm. Given that many women with fibroids are asymptomatic, a second-trimester ultrasound may be the first time that a patient is made aware of the presence of fibroids. Early detection provides an opportunity for extensive counseling on risks and potential adverse pregnancy outcomes. Nonetheless, practicing physicians may have differing approaches to fibroid management throughout pregnancy. This further underscores the need to design and implement better studies to investigate how to effectively decrease the incidence of deleterious complications associated with fibroids in pregnancy.

The most commonly encountered problem with fibroids during the second trimester is pain caused by red degeneration. The approach to treatment is conservative, and consists of bed rest, hydration, and analgesics. If there is concern over a potential infection associated with fibroid necrobiosis, then antibiotics can be supplemented to the rest of the regimen. If conservative therapy fails, and the patient desires further management of her pain symptoms, surgery should be offered as the next step. The patient must be extensively counseled on the risks and benefits associated with the myomectomy such as pregnancy loss, hemorrhage, infection, uterine rupture, premature rupture of the membranes, and increased risk for cesarean delivery. She should also be made aware that antenatal myomectomy is not routinely performed during pregnancy due to lack of large studies on surgical benefits, despite its recent gain in popularity. In

addition, the physician must take into consideration the quantity of myomas present, location, and the fibroid's proximity to large uterine vessels in order to best assess who is an ideal candidate for myomectomy.

The ultimate goal is to avoid as many complications as possible. Therefore, the same general rules and inclusion criteria for the first trimester pertain to the second trimester as well (see Table 4.2). Criteria for surgery include recurrent, intractable pain, large or rapidly growing myomas, and large or medium-sized myomas within the lower uterine segment or deforming the placental site (Burton et al., 1989). Surgeons should remove only solitary, pedunculated subserous myomas with stalks that are less than 5 cm in diameter. Most myomectomies have typically been performed between 12 and 19 weeks' gestation without incident. Celik et al. (2002) recommend that the optimum time to perform myomectomies is between the fourth and sixth months of pregnancy, which is in agreement with other small case series that suggest doing the procedure around the 14th or 15th week of gestation. The literature reports that outcomes for surgeries completed during pregnancy within this time frame are comparable to those of conservatively managed patients, and this may be a promising treatment modality in the right patient.

CASE REPORT

Fibroid pain in pregnancy

A 41-year-old primigravid woman presented at 16 weeks' gestation with worsening lower abdominal pain for 1 week. Abdominal examination showed a uterine size larger than dates and focal tenderness and guarding at the uterine fundus. Abdominal ultrasound confirmed a viable singleton intrauterine pregnancy consistent with dates. A single 8.4 × 6.2 cm subserosal/intramural fibroid was identified with internal echogenic changes suggestive of degenerative change (see Figure 4.1). The placenta was fundally located and marginally inserted in the region of the fibroid. The patient was treated symptomatically for 6 days with tylenol and oral narcotic analgesics, as needed; nonsteroidal anti-inflammatory agents were avoided. The pain resolved spontaneously. The patient was followed with serial growth scans every 3–4 weeks after 24 weeks' gestation, because of the potential risk of uteroplacental insufficiency. Induction of labor was recommended at 38–2/7 weeks' gestation for new-onset oligohydramnios (AFI 4.6 cm); the estimated fetal weight and fetal nonstress testing were within normal limits. A viable male infant was delivered vaginally without incident. Birth weight was 3150 g. Apgar scores were assigned at 8 and 9 at 1 and 5 minutes, respectively. The placenta was delivered by manual extraction because of prolonged third stage of labor (40 minutes) and excessive bleeding (estimated blood loss 800 mL). Sharp curettage was performed because of retained placental fragments in the region of the fibroid. Her postpartum course was otherwise uncomplicated. She did not require a blood transfusion.

Third trimester fibroid management

The third trimester is defined as the period from 28 weeks to the end of the pregnancy, typically 40 weeks' gestation. Women with fibroids in late pregnancy are more likely to develop preterm labor and to deliver preterm than women without fibroids (Chen et al., 2009). Preterm labor is defined as regular contractions of sufficient frequency and intensity leading to cervical change at <37 weeks' gestation. Independent risk factors for preterm labor include having multiple myomas and fibroids contacting the placenta. Incidence also appears to increase with size of the leiomyoma, where risk is greatest in fibroids larger than 3 cm in diameter.

The association between preterm labor and fibroids is uncertain, but several theories purport to explain plausible causes. For example, one explanation suggests that fibroids make the uteri less distensible than normal uteri, which leads to premature labor and delivery via a similar mechanism seen in women who have congenital Müllerian defects. Another hypothesis suggests that localized increases occur in oxytocin levels due to decreased oxytocinase activity in fibroid uteri during pregnancy. Recently, a reduction in cervical length has been associated with fibroids (Shavell et al., 2012). Although there is conflicting evidence, most studies

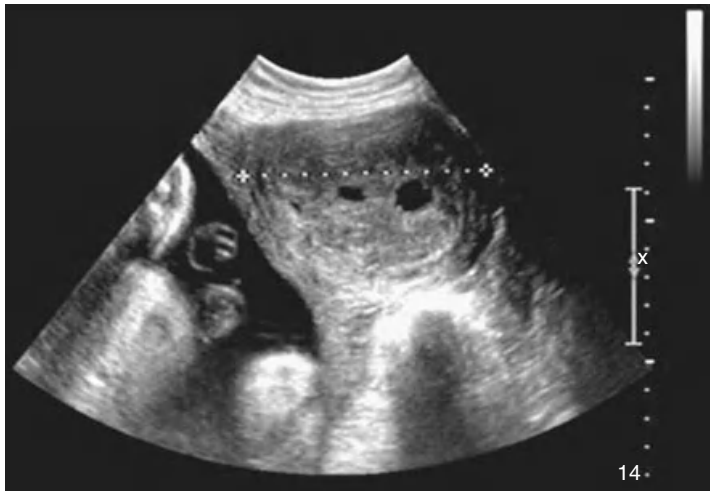

Figure 4.1 Sonographic image illustrating echogenic patterns indicative of degenerative changes in a single 8.4 × 6.2 cm subserosal/intramural fibroid, as shown by calipers. The fetus can be seen to the left of the image.

suggest that fibroids also increase the risk of placental abruption up to three-fold, which is associated with a higher incidence of fetal death (Coronado et al., 2000). Abruptions affect 1% of all pregnancies but are more common when submucosal myomas, retroplacental myomas, and myomas with volumes greater than 200 cm^3 are present.

The underlying mechanism of placental abruption is unclear but it is possible that diminished blood flow to the myoma elicits ischemia and necrosis in placental tissues overlying the tumor. It is important to note that uterine leiomyomata do not appear to cause decreased fetal growth after taking into consideration that intrauterine growth retardation (IUGR) is increased with maternal age.

Symptomatic patients in the third trimester are also managed conservatively with regard to pelvic pain and pressure. In an example described by Febo et al. (1997), a patient was given an analgesic infusion by peridural catheter for 4 weeks to alleviate intense pain until she reached term. Myomectomies are generally not performed during this trimester of pregnancy, although they have been performed at the time of cesarean delivery, which will be discussed in depth in the next section.

Puerperal complications and management of fibroids at time of delivery

If a woman has no contraindication to a trial of labor and vaginal delivery, then she should be allowed to attempt vaginal delivery. However, fibroids have been found to increase the risk of cesarean section before labor up to 5.3 times over the baseline incidence (Table 4.3). For instance, Qidwai et al. (2006) estimate that approximately 20,000 cesarean sections are attributed to fibroids each year if the prevalence of fibroids in pregnancy is approximately 3%. Increased occurrence of cesareans in pregnancies complicated by fibroids has been attributed to multiple factors such as: increased risk of placenta previa, malpresentation, and having tumors in the lower uterine segment below the fetal presenting part (Vergani et al., 2007). Larger tumors have a greater effect on risk of cesarean, especially when fibroids reach a size greater than 5 cm. It has been shown that risk can increase up to 26% for every 1 cm increase in diameter of the tumor (Vergani et al., 2007). However, it is unclear whether or not knowledge of the presence of a large uterine fibroid may decrease an individual clinician's threshold to

Table 4.3 Risk of obstetric outcomes

Outcome	Increased risk with fibroids
Preterm labor	1.04–3.36
Malpresentation	1.58–4.39
Placenta previa	1.78–4.0
Placental abruption	0–15.29
Cesarean section	1.37–5.34
Postpartum hemorrhage	1.15–3.0
Retained placenta	2.0–2.4
Low neonate Apgar score	0.52–3.2

Table 4.4 Complications at parturition associated with fibroids

Puerperal complication	Coronado et al. (2000)	Olive and Pritts (2010)	Stout et al. (2010)	Rice et al. (1989)	Exacoustos and Rosati (1993)	Vergani et al. (2007)	Sheiner et al. (2003)	Qidwai et al. (2006)	Klatsky et al. (2008)
Preterm labor	1.5	1.9	1.5	4.0	1.0	1.0	1.4	1.5	1.9
Malpresentation	4.0	2.9	1.5	2.0	NR	2.7	NR	NR	2.9
Placenta previa	1.8	2.3	2.2	NR	NR	3.9	NR	1.9	2.3
Placental abruption	3.9	3.2	2.1	16.5	8.9	0.5	2.6	0.8	3.2
Cesarean section	6.4	3.7	1.2	2.5	1.1	2.3	6.7	1.6	3.7
Postpartum hemorrhage	1.6	1.8	NR	NR	NR	4.0	NR	2.6	1.8
Retained placenta	NR	2.3	NR	NR	NR	2.0	NR	2.7	2.3

All values are OR unless stated otherwise.
NR, not reported.

pursue a cesarean under the deduction that the patient will develop labor dystocia.

In addition to higher risk of delivering via cesarean, fibroids also increase the risk of intrapartum and postpartum hemorrhage which may be associated with placental abnormalities (see Table 4.4). One example is placenta accreta, which occurs when the placental villi abnormally adhere to the myometrium due to a partial or total loss of decidua basalis and defective development of the Nitabuch layer. Placenta accreta complicates births unaffected by myomas in one out of every 2500 births, which is a 10-fold increase from 50 years ago. Increased risk of placenta accreta has been attributed to the steep rise in cesarean deliveries, occurring in 25% of women who have had previous cesareans. The underlying cause is thought to be related to formation of adhesions in the uterine wall, which are then invaded and strongly adhered to by placental villi. However, increased risk of placenta accreta has also been attributed to subserosal uterine myomas, previous myomectomies, previous uterine scarring, Asherman syndrome, maternal age >35 years, and placenta previa. Approximately one-third of pregnancies affected by placenta previa go on to develop placenta accreta. Incidence of placenta accreta is also higher as parity increases, where one-fourth of women who are gravida 6 or greater develop placental complications. Placenta accreta can result in significant maternal morbidity and mortality associated with massive hemorrhage during delivery. Severe blood loss is frequently due to uterine atony and retained placenta, which usually results in an emergency hysterectomy and blood transfusion. Mortality risk can approach 7% depending on the severity of blood loss, with a massive hemorrhage being defined as >500 mL of blood loss with vaginal delivery or >1000 mL of blood loss with cesarean. Several studies suggest the use of ultrasound to screen and identify women at greater risk of placenta accreta. Early diagnosis would enable physicians to prepare for a complicated delivery in women who are at high risk. Sensitivity for diagnosing placenta accreta with sonography has been shown to be 82–93% (Amal Al-Serehi et al., 2008) when one of the following markers is present: loss of normal hyoechoic retroplacental line; thinning of the uterine serosa–bladder interface; presence of multiple placental lacunae; and presence of focal masses.

A patient may undergo a myomectomy at time of cesarean section, although this procedure is controversial and has traditionally been discouraged due to concerns over risk of uterine atony and severe hemorrhage that may result in postpartum hysterectomy (Table 4.5). Preventing large blood volume loss is of primary concern during delivery, because by the end of the third trimester cardiac output is increased to approximately 7.34 L/min, with 17% of the total output supplying the pregnant uterus. The highest risk of hemorrhage occurs with the removal of intramural fibroids; therefore, extreme caution should be employed when attempting to remove these tumors. However, most myomectomies have been limited to symptomatic pedunculated fibroids to avoid bleeding complications.

Despite legitimate apprehensions regarding morbidity, some physicians believe that myomectomies can be safely performed using techniques oriented at decreasing blood loss both intraoperatively and postoperatively. Such techniques include using a tourniquet, electrocautery, and intraoperative suturing circumferentially around the myoma to achieve hemostasis. Sapmaz et al. (2003) investigated the efficacy of using a tourniquet versus uterine artery occlusion to control intraoperative and postoperative blood loss. Intraoperative success was similar between the two groups, but blood loss was better controlled postoperatively with uterine artery occlusion due to the permanence of the procedure. However, larger controlled studies will be necessary to confirm the validity of these claims. Other arguments supporting the efficacy of myomectomies at cesarean are gaining popularity. Some clinicians believe that leaving fibroids alone at time of cesarean is poor management, since many myomas will go on to grow and require either myomectomy or hysterectomy at a later time. Desai et al. (2010) found that fibroids grew an average of 34% over a period of 38.5 months after cesarean. Furthermore, existing myomas may also complicate subsequent pregnancies if left untreated.

Uterine artery ligation (UAO) has been reported at time of cesarean because it can reduce postpartum blood loss, as well as minimize the need for future surgery (see Chapter 7). Other benefits include reducing dominant myoma volume postoperatively. However, this is a permanent procedure and is recommended only for women who do not desire future fertility. Uterine artery ligation has been

Table 4.5 Evidence for management of fibroids at time of parturition

Author	Study design	Intervention	Case #	Control #	Blood loss	Successful outcomes, study vs controls
Sapmaz et al. (2003)*	Prospective randomized control	Uterine artery ligation + cesarean myomectomy vs cesarean myomectomy + tourniquet	26	26	361 ± 35/ 366 ± 37 mL Hemorrhage 0/1	26 livebirths/26 livebirths
Ehigiegba et al. (2001)	Case series	Cesarean myomectomy	25	0	876 ± 312 mL	25 livebirths; 3 subsequent pregnancies
Ande et al. (2004)	Case report	Repeat myomectomy at cesarean	1	0	500 mL	1 livebirth
Hassiakos et al. (2006)	Retrospective case–control	Cesarean myomectomy	47	94	Hemorrhage (n) 5/9 ΔHb 1.0 ± 0.3/0.8 ± 0.4 g/dL	47 livebirths/94 livebirths
Roman et al. (2004)	Retrospective case–control	Cesarean myomectomy	111	257	Hemorrhage (n) 14/32.9 ΔHct 5.5/6.1	Livebirths NR
Ortac et al. (1999)	Retrospectivecase series	Cesarean myomectomy	22	0	324.2 ±131.1 mL	22 livebirths
Kwawukume (2002)	Prospective case–control	Cesarean myomectomy	12	12	ΔHb 1.83/1.73 g/dL	12 livebirths/12 livebirths
Lin et al. (2010)§	Prospective case–control	Uterine artery ligation + cesarean myomectomy	36	36	ΔHb 1.3 ±0.4/ 1.2 ± 0.5 g/dL	36 livebirths/36 livebirths
Kaymak et al. (2005)	Retrospective case–control	Cesarean myomectomy	40	80	Hemorrhage 5/9 ΔHb 1.6 ± 0.7/1.5 ± 0.7 g/dL	40 livebirths/80 livebirths
Brown et al. (1999)	Retrospective case–control	Cesarean myomectomy	16	16	403 ± 196/356 ± 173 ΔHb 1.64 ± 1.7/1.4 ± 1.3 g/dL	16 livebirths/16 livebirths
Liu et al. (2006)†	Case series	Uterine artery ligation at cesarean	26	22	254 ± 92.3/278 ± 160.5 mL ΔHb NS	26 livebirths/22 livebirths
Li et al. (2009)	Retrospective case–control	Cesarean myomectomy	1242	396	Hemorrhage (n) 14/2 ΔHb 6.2/(5.4–6.7) g/dL	Livebirths NR

Hct, hematocrit; Hb, hemoglobin; NR, not reported; NS, not statistically significant.

*3.8% of the controls underwent a subsequent surgery (1 emergency laparotomy for postpartum hemorrhage); 1 postpartum hemorrhage occurred in the control group.

§2.8% of the study cohort and 41.7% of controls underwent a subsequent surgery (either myomectomy or hysterectomy).

†7.7% of the study group and 40.9% of controls underwent a subsequent surgery (either myomectomy or hysterectomy).

associated with a high incidence of early pregnancy loss in some studies. Laparoscopic occlusion of the uterine arteries is thought to work by causing a state of localized ischemia to the myometrium by impeding blood flow through the myometrial arteries and veins. As time passes, stagnant blood in these vessels forms clots. However, this ischemic state is transient since blood flow is sustained in the communicating ovarian vessels and small collaterals in the surrounding broad ligament. Blood flow through these vessels enables the clots to lyse, restoring perfusion to the myometrium. Myomas are unable to survive this brief ischemic event, which is believed to explain why pain symptoms resolve after this procedure. The ability to undergo repeated alternating states of ischemia and reperfusion is unique to the uterus, which makes the organ suitable for childbirth (Burbank, 2004). Success rates for alleviating pain symptoms for laparoscopic UAO have been found to be comparable to those of UAE. Myomas and the myometrium may also differ in their ability to lyse and break down clots due to a higher concentration of tissue plasminogen activator in the myometrium compared to myomas. This would enable the myometrium to better restore perfusion than myomas that subsequently succumb to prolonged ischemia. Recent case studies propose that using UAO and myomectomy concurrently at the time of cesarean may give the best outcome with regard to symptom relief and minimizing blood loss and need for future surgery. However, larger studies are necessary to confirm these claims.

Recurrence of myomas post surgical resection

The 5-year incidence of fibroid recurrence after myomectomy has been reported to range from 5% to 51% of cases. However, these are not large randomized control studies, making it difficult to ascertain specific cumulative probability of disease recurrence. In addition, the large variability between studies may be attributed to the following: employment of different criteria for diagnosis of recurrence, implementation of more sensitive transvaginal ultrasonography for improving identification of recurrent myomas, and ethnic population being studied, with greater recurrence noted in African-Americans. Fedele et al. (1995) reported a 5-year cumulative probability of recurrence (CPR) of 51%, but recurrence was decreased to 42% in women who had a subsequent pregnancy and delivery after myomectomy. In addition, the CPR increased when women were nulliparous, had submucous myomas, had multiple myomata, and when women were older at the time of myomectomy. However, the risk of recurrence should not be a deterrent to surgical resection since many myomas take years to develop, and subsequent surgery such as hysterectomy for symptoms is necessary in only one-third of cases. Thus, if a symptomatic woman still desires future fertility at the time of cesarean section, then uterine-preserving procedures such as myomectomy should not be ruled out as a treatment option. Nonetheless, future studies investigating the underlying mechanism of fibroid pathology are necessary to help identify women at higher risk of recurrence and to develop new therapeutic targets to prevent fibroid development.

Conclusion

Fibroids are a common finding throughout a woman's reproductive years, and are becoming more prevalent during pregnancy as more women delay child bearing. Although the majority of fibroids do not change in growth and many remain asymptomatic throughout pregnancy, fibroids clearly contribute to the development of adverse pregnancy outcomes such as early pregnancy loss, pain, preterm labor, placenta previa, placental abruption, cesarean section, and postpartum hemorrhage. However, data in the literature are conflicting regarding risk of developing such complications if a woman is found to have fibroids when she becomes pregnant. Most studies of fibroids in pregnancy have been small, retrospective case series, making it difficult to draw clear conclusions about how fibroids negatively affect pregnancy outcome. It is also unclear why there is such disparity in disease incidence and pregnancy outcomes between different ethnic groups. African-Americans tend to develop fibroid disease more frequently and at a younger age than whites. African-Americans also appear to have a higher incidence of pregnancy complications associated with myomas. There is some evidence to suggest that different forms of the disease exist, and differences between ethnic and racial groups may be explicated by genetics. Understanding the cause of tumor development will help identify potential

therapeutic targets that could be used in pregnancy. Currently, management of fibroid disease and its associated complications in pregnancy is based on limited data, summarized in this chapter. The physician should tailor treatment to each individual patient. Treatment has traditionally been oriented at managing pain symptoms with heavy reliance on bed rest, hydration, and analgesics.

Guidelines regarding fibroid management are lacking, especially regarding when to proceed with surgery, if at all, during pregnancy. Currently available evidence supports the treatment algorithm outlined in Figure 4.2. Myomectomies during pregnancy and at time of cesarean section are extremely controversial primarily because there are no large, randomized studies concerning the efficacy of the

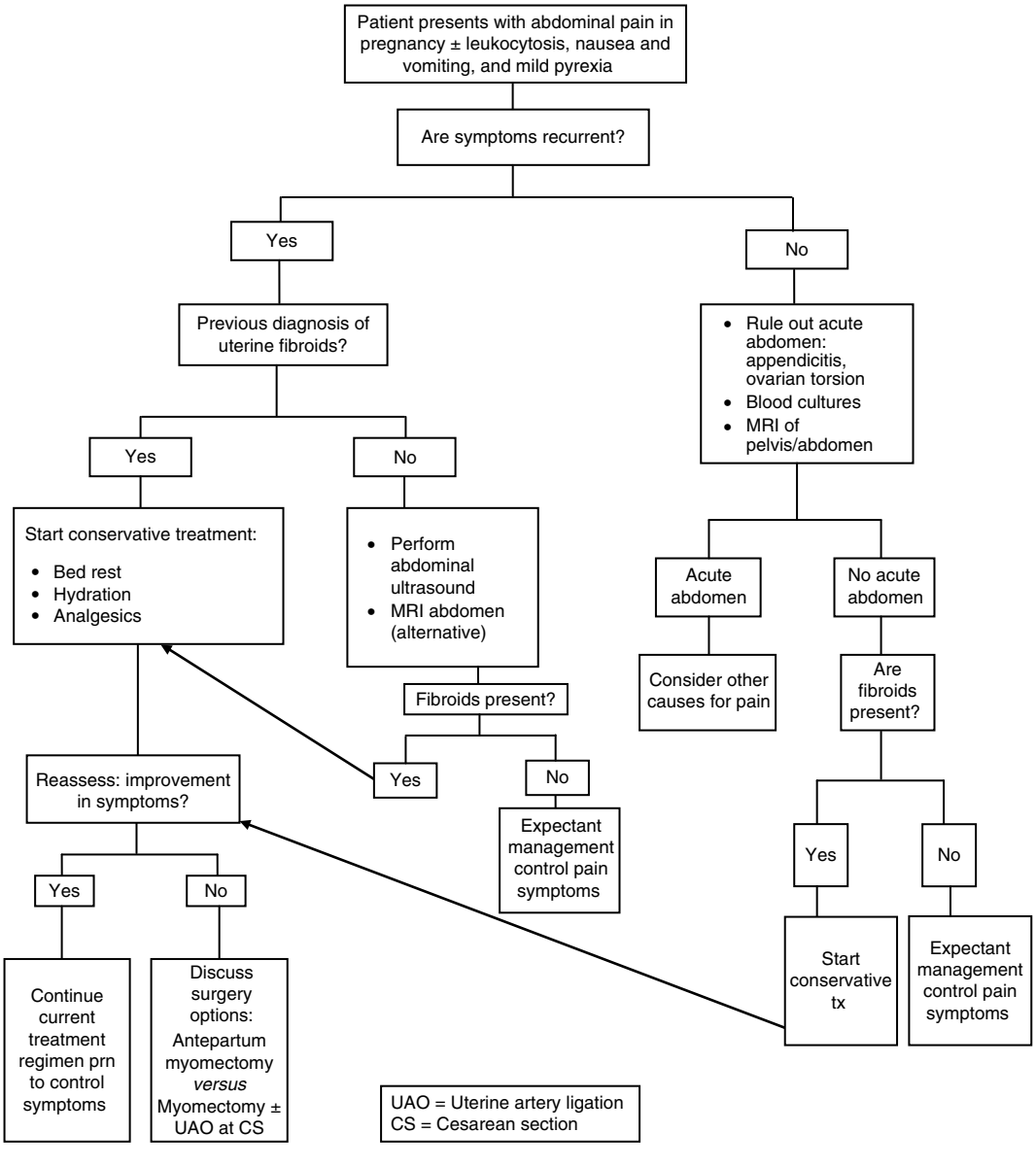

Figure 4.2 Evidence-based algorithm for treatment of women presenting with symptomatic fibroid disease in pregnancy.

procedure and risk of bleeding complications. Most clinicians agree that antepartum myomectomies should be reserved for patients with intractable pain unresponsive to medical therapy, and those with large subserosal or pedunculated fibroids within the first and second trimesters. Despite concerns over severe morbidity and mortality associated with hemorrhage, some case series suggest that in the appropriate patient population, the procedure can be effectively and safely performed with minimal sequelae. Uterine artery occlusion is also gaining popularity as a complementary procedure to perform simultaneously with myomectomies at time of cesarean section since it decreases intraoperative and postoperative blood loss and the need for future surgery. Even so, few studies have been done to effectively illustrate both procedures' advantages and safety compared to conservative treatment modalities. Further research using prospective, randomized controlled trials is necessary to substantiate the relative risk of performing myomectomies, and to identify new treatment modalities that may pose fewer risks to the fetus and mother when fibroids become symptomatic during pregnancy. However, these studies are unlikely to be pursued due to the ethics of potentially exposing and endangering viable pregnancies to unnecessary risk of harm.

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5

Management of Uterine Fibroids in the Older Woman

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Fibroids in the perimenopausal woman

The presence of a fibroid in the older woman who is perimenopausal and has completed child bearing may not require any intervention provided she is asymptomatic following this diagnosis. However, management of symptomatic fibroids in the older woman requires special considerations. As with all patients who present with a gynecological problem, a proper history and examination are crucial, and both of these in conjunction with simple investigations will determine a course of action best suited for the woman.

Several key points should be ascertained when taking a history from a perimenopausal patient with fibroids. The cyclicity, heaviness of her menses, and symptoms that may be impinging on her activities of daily living should be established. Specific questioning regarding the above may further target and refine treatment options. These include the presence of intermenstrual bleeding, dysmenorrhea, menorrhagia, urinary or bowel symptoms and dyspareunia. Factors affecting the quality of life of a patient and reasons why she decided to seek medical advice from a gynecologist should be explored. These factors should be used in conjunction with a comprehensive history in order to establish what the patient's ideas, concerns, and expectations may be when seeking gynecological advice.

A common presentation of patients with fibroids may be a gradual change in the heaviness of menses. This may not necessarily affect the patient in any way, but she may have concerns as to the underlying cause of this change. More often than not, a simple ultrasound may point to a definitive diagnosis and no further action is needed once her concerns have been addressed. Annual follow-up with an ultrasound scan may be offered in order to review any changes in fibroid dimensions and any symptomatology, should the woman request this.

Shrinkage of fibroids is usually anticipated with the commencement of the menopause. On the other hand, if the patient is experiencing symptoms that greatly impinge on her quality of life, medical or surgical therapy can be offered. Menstrual flooding, for example, may be devastating for some women and the impact of this on their life should not be underestimated. It may result in days of isolation at home, affecting professional, financial, social, and interpersonal relationships.

Commonly, patients may present with menorrhagia secondary to fibroids and symptoms associated with anemia. These may include shortness of breath on exertion, or lethargy. In such cases, a full blood examination (FBE) and film may reveal a long-standing microcytic anemia caused by depleted iron reserves. In general, medical strategies may be adopted in order to reduce the blood loss. These involve either hormonal or nonhormonal options with the concomitant supplementation of iron. Tranexamic acid has been shown to reduce blood loss by approximately 50%. Combined

Fibroids, First Edition. Edited by James H. Segars.

hormonal oral contraceptives (COCP) have not been shown to be associated with hormone-driven enlargement of fibroids. It has been demonstrated that a decrease in blood loss of the order of 50% has been associated with the use of COCP and they may be used to regulate cycle control in perimenopausal patients. This may also be advantageous as a perimenopausal patient may require concomitant contraception.

Prior to commencement of the COCP, the relative and absolute contraindications should be considered. By definition, women over the age of 40 can be advised that no contraceptive method is contraindicated by age alone. Combined hormonal oral contraception use in perimenopausal women may help in maintaining bone mineral density (Lopez et al., 2009). Reduction in menstrual blood flow and menopausal symptoms has been documented. Protective effects against development of ovarian, endometrial ,and colorectal cancer, as well as benign breast disease, are associated with the use of COCP. With regard to breast cancer, there is no clear evidence as to the risk associated with the use of these drugs. Several large studies have attributed a small increase in the risk of breast cancer on the background of increasing risk with age (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Kahlenborn et al., 2006). Women with a family history of breast cancer are not put at any increased risk of developing the disease themselves by using the COCP. On the other hand, carriers of BRCA1 or BRCA2 gene mutations are inherently at an increased risk of developing breast cancer, and as such the COCP may impose an increased risk. Discretion under these circumstances may be exercised by the clinician after consultation with an oncologist and involvement with the family practitioner. Although a blanket policy is not appropriate, the author's recommendation would be to adopt a conservative approach as the risks may outweigh the benefits.

EVIDENCE AT A GLANCE

Current or previous history of ischemic heart disease	Absolute contraindication
Current or previous history venous thromboembolism	Absolute contraindication
History of stroke including transient ischemic attacks	Absolute contraindication
Controlled hypertension	Risks outweigh benefits
Systolic BP >140–159 mmHg or diastolic 90–94 mmHg	Risks outweigh benefits
Systolic BP ≥160 mmHg or diastolic ≥95 mmHg	Absolute contraindication
Vascular disease	Absolute contraindication
Smoking in women over the age 35	Risks outweigh benefits
Stroke, migraine with aura	Absolute contraindication

BP, blood pressure.

When prescribing COCP to women over the age of 40, the clinician may wish to consider a pill containing under 30 μg ethinylestradiol. Blood pressure should be taken prior to commencement of treatment and again at 6 months following initiation of treatment and yearly thereafter. In general, women over the age of 35 who smoke should be advised that the risks of combined hormonal contraception outweigh the benefits as there is a small rise in the risk of ischemic stroke. In addition, other medical strategies may prove especially beneficial in the older woman with menorrhagia due to fibroids; for example, the levonorgestrel intrauterine system (IUS) may reduce bleeding without dramatic alterations of peripheral hormone levels (see Chapter 6).

The authors would encourage clinicians to adopt local evidence based best practice guidelines when prescribing hormonal contraception, as variations in practice do occur.

Acute presentation with shock

Older women may occasionally present acutely to the emergency department with very heavy bleeding (flooding) and evidence of circulatory compromise due to hypovolemic shock. This is a rare presentation of a complication associated with fibroids. Rapid assessment of the patient and commencement of local resuscitation protocols should be initiated. In such cases, a thorough examination is vital in order to determine not only the exact nature of the hemorrhage but also the origin of the bleeding. Under these circumstances, a speculum examination should be complemented with a rectal examination.

In most cases, if the presentation is due to an acute bleeding event, fluid resuscitation in conjunction with intravenous tranexamic acid will suffice. Transfusions of packed red cells for severe anemia with platelets and fresh frozen plasma may be necessary if the patient is actively bleeding with evidence of hemodynamic compromise despite the initial measures described above being taken. Under these extreme circumstances, consultation with hematologists and senior gynecological advice should be sought. Precipitating events that may have been attributed to this acute presentation should be determined in order to establish whether reversible measures can be instituted. Factors that may influence blood dyscrasias should be investigated. Warfarin is increasingly prescribed with advancing age. This drug, or drug interactions associated with warfarin, may result in prolonged clotting times that may precipitate large bleeds. Stopping medications or reversing the actions of warfarin should only be done after appropriate consultation with an experienced physician. Hepatic disease of any cause may result in clotting abnormalities and this should be investigated appropriately.

In extreme cases, should medical interventions fail and bleeding continue, additional measures should be considered. Depending on local facilities, the patient's medical stability in conjunction with platelet count and clotting study results, radiological interventions by means of uterine artery embolization may be considered (see Chapter 7). Complications in terms of hematomas at the femoral puncture site, ischemic uterine pain, and sepsis may present and as such informed consent is vital. Emergency surgical intervention may be considered, with the option of a hysterectomy reserved *in extremis*.

Once the patient is stabilized, it is important to monitor with regular observations, keeping strict fluids balance charts and measuring blood loss by means of weighing blood-soaked pads and hourly urine output. High-dependency observation charts are strongly recommended in these cases.

Fibroid associated with perimenopausal bleeding

An important consideration is whether the abnormal bleeding is a result of the fibroid or due to other underlying serious pathology such as endometrial cancer. The cause, nature, and precipitating factors associated with the bleeding need to be clearly established. The patient may also have concurrent menopausal symptoms that may need to be addressed. A thorough examination may reveal the underlying cause of bleeding. For example, as shown in Plate 5.1, speculum examination may reveal a pedunculated submucosal fibroid causing bleeding.

☆ TIPS & TRICKS #1

Hysteroscopy should be conducted in a case such as shown in Plate 5.1 prior to attempting avulsion, in order to determine the nature of the attachment point of the fibroid base to the uterine wall. This will also allow concurrent inspection of the uterine cavity in order to determine the presence of any additional fibroids or polyps that may be contributing to the bleeding.

At hysteroscopy, the base of a pedunculated fibroid (or polyp) should be assessed. A thick base would imply extensive vascular supply and the surgeon should therefore consider electrocautery to disrupt vessels. Conversely, a thin base may be removed by a continuous twisting motion until the fibroid is separated from the wall. As with all cases when biopsies or tissues are removed, these samples must always be sent to histopathology in order to determine the exact nature of the sample. Hysteroscopy may be conducted with either a flexible or rigid instrument. The advantage of the former is that it obviates the need for a general anesthetic and postoperative recovery time. In experienced hands, a compliant patient and selected cases, electrocautery can be safely used and is generally very well tolerated with preoperative analgesia and infiltration of the cervix with local anesthetic. Alternatively, hysteroscopy may be performed under a general anesthetic.

The perimenopausal patient with fibroid-associated pain

For this patient, the type of pain needs to be clarified. The clinician needs to establish whether the pain is related to pressure symptoms from the fibroid, related to period discomfort or due to nongynecological causes. If the pain is not thought to be due

to the fibroid/s then these may not need to be treated. However, the fibroids should be watched for growth using ultrasound at yearly intervals until the patient progresses through the menopause. Fibroids grow slowly but growth spurts can occur at menopause due to the derangements and rapid fluctuations of hormone concentrations with very high highs in estradiol (E2) concentrations and very low lows. While these growth spurts are common, they are short-lived with changes diluted over longer time intervals.

One question that the patient always wants reassurance about is "Do fibroids become malignant if not removed?." There is now overwhelming evidence that this is not the case.

Patient in mid forties with a large fibroid uterus wishing to conceive

As with all patients seeking advice regarding their fertility, a comprehensive history and investigations should be carried out on both partners. Previous pregnancies, duration of infertility, contraception usage, and previous gynecological, medical, and surgical histories should be determined. Specific histories regarding the nature, duration, and commencement of the periods should be established. Symptoms relating to thyroid disease and pituitary pathologies (visual disturbances, galactorrhea) should be explored. Whilst the consultation should be conducted sensitively, it is imperative that the couple are given realistic information with regard to their expectations and chances of conception.

Investigations including hormonal profiling should be performed and include early-phase follicular follicle-stimulating hormone, luteinizing hormone, E2, and thyroid-stimulating hormone. A prolactin level should measured if suspicion is raised, as discussed above. An ultrasound scan in order to establish the morphology of the uterus is crucial if planning intervention. Magnetic resonance imaging (MRI) studies will provide further information as to the precise number, size, and locations of fibroids. A hysterosalpingogram will not only provide corroborative information as to encroachment of fibroids into the uterine cavity but also information regarding tubal patency. Should hydrosalpinges be present on ultrasound and fill and spill not demonstrated on hysterosalpingogram, if surgical intervention is chosen, these can be occluded at the time of a myomectomy in order to increase the chances of conception at assisted reproduction, possibly using donor oocytes. In the more mature patient wishing to conceive, the hormonal studies described above can be used in conjunction with serum antimullerian hormone (AMH) concentrations in order to give the patient a realistic idea of her chances of conceiving either spontaneously or by assisted reproductive technologies.

Myomectomy is generally the treatment of choice for women with fibroids wishing to preserve their fertility or their uterus, and this remains true for the older patient (Plate 5.2). Retrospective studies have reported symptomatic relief from menorrhagia in the order of 80% in patients undergoing this procedure. Recurrence is common and is in the order of 25% of patients 10 years after myomectomy. Some studies have further alluded to a decrease in implantation and pregnancy rate in women with fibroids, particularly those with a submucosal component. There are therefore some very valid reasons as to why, in selected cases, a surgeon may opt to perform a myomectomy. However, this needs to be balanced by the complications associated with this procedure and the patient's expectations.

Surgical complications of myomectomy can be divided into early and late. As with all procedures involving major abdominal surgery, bleeding is a potential major complication. Bleeding may, on occasion, require additional surgical procedures, and rarely hysterectomy. It is strongly recommended that women who require a myomectomy and who are anemic secondary to menorrhagia have their hemoglobin concentration optimized preoperatively. This will not only be of benefit to both the surgeon and anaesthetist intraoperatively, but recovery may be accelerated and it will substantially reduce the need for blood transfusion. This may be achieved by supplementing the patient with iron, and reducing the bleeding can be achieved hormonally, primarily by the use of gonadotropin-releasing hormone (GnRH) agonists. The latter will have the added benefit of shrinking the fibroids preoperatively and therefore potentially making the procedure easier, though this has been questioned by some authors. On occasion, preoperative GnRH agonist therapy will cause sufficient shrinkage of a very large uterus to allow access via a Pfannenstiel

incision, thus avoiding a midline laparotomy. It should, however, be remembered that the measures outlined above may require 3 months to achieve maximal benefit, although more rapid shrinkage (2 weeks) has been reported in patients treated with GnRH antagonists. For cases where time is short, GnRH antagonists may be especially beneficial.

Fertility decreases with increasing age and in some circumstances the patient and the clinician may feel that the privilege of waiting several months in order to optimize conditions is simply not an acceptable option. Anemia, therefore, can be rapidly and transiently corrected with a blood transfusion, and a midline laparotomy does in fact allow for easier surgical access, at the expense of cosmesis and a more protracted postoperative recovery course. Intraoperative measures that may be used to reduce blood loss include the use of vasopressin, tourniquets, and occlusive clamps. Meticulous closure of the uterus in layers is imperative in order to ensure subsequent haemostasis.

☆ TIPS & TRICKS #2

A false sense of security can be gained when occlusive techniques are adopted intraoperatively, with significant bleeding noted once these measures are removed. The authors also recommend that should these occlusive measures be adopted, the surgery should be conducted in a fast and safe fashion, thus minimizing the time of vascular depletion to the uterus. A large-bore drain should be placed intra-abdominally postoperatively in order to recognize and quantify any postoperative bleeding. As with all drains placed within the abdominal cavity, the use of vacuum drains is not encouraged as these can potentially be occluded by omentum or bowel loops, therefore concealing any active bleeding, but also have the potential of causing injury by means of direct negative pressure on these structures.

Intramural fibroids up to 6 cm or less can safely be removed laparoscopically in the older woman. For skilled laparoscopic surgeons, this size barrier may not be an issue. It should, however, be considered that the rates of uterine rupture are higher in subsequent pregnancies. Pedunculated subserosal fibroids may be easily removed by diathermy to the base and cutting the stalk (Plate 5.3).

☆ TIPS & TRICKS #3

During laparoscopic myomectomy it is advisable that a length of the stalk is maintained for two main reasons. First, this will allow the surgeon additional length to tackle any subsequent bleeding and second, vessels have the potential of retracting back into the body of the uterus. Should this be the case and the vessels start bleeding, the surgery can become increasingly complicated.

Other complications associated with the type of surgery are the risk of thromboembolism and therefore anticoagulation is recommended in such cases. Infections should be minimized by the appropriate antibiotic prophylaxis. Late postoperative complications of myomectomies can include recurrence of the fibroids (see Chapter 10). This typically takes years to develop and the hope is that women approaching the age of menopause may be spared this complication. Should women conceive post myomectomy, a significant increase in the rates of uterine rupture have widely been documented. It is therefore imperative that the patient is made aware of this preoperatively as subsequent deliveries may need to be conducted as planned elective cesarean sections. As fibroids can sometimes rapidly grow during pregnancy, these cesarean sections may be very challenging as incision through the uterus should avoid the fibroids.

Postoperative pain associated with adhesion formation following myomectomy may interfere with the patient's quality of life, years after an operation. Indeed, patients may have transitioned into menopause, with subsequent shrinkage of remaining fibroids but symptoms associated with adhesions may be crippling to the patient. In Plate 5.4, extensive adhesions are demonstrated. The bladder of the patient is adherent to the anterior uterine wall. Urogynecological symptoms may result from a bladder that is not fully compliant. Extensive thick adhesions of the uterus to the pelvic side wal may result in dyspareunia. At the bottom of this image, bowel is extensively adherent to uterus resulting in gastrointestinal symptoms. In experienced surgical hands, these adhesions can be divided laparoscopically with the aim of alleviating symptomatology of the adhesions.

Some older women may want to preserve their uterus, although there are no plans for childbirth or reproduction. In such cases, myomectomy may be performed to reduce symptoms, if needed, provided the patient is counseled regarding the risks noted above and is an appropriate surgical candidate. Two other options for treatment of the perimenopausal woman who wants to retain her uterus are uterine artery embolization (UAE) and magnetic resonance (MR)-guided focused ultrasound. These options are discussed in detail in Chapter 7 and Chapter 8, respectively.

Fibroids in the postmenopausal woman

Occasionally the presence of fibroids in postmenopausal women may present with vaginal bleeding. Under these circumstances and as with all patients with postmenopausal bleeding (PMB), rapid access should be available in order to determine the precise cause of this bleeding with the prime aim of diagnosis and expedient treatment of endometrial cancer.

A thorough history of the presenting complaint should include the duration and number of such episodes and nature of the bleeding, and precipitating factors such as trauma should be sensitively explored. Past medical history and drug history should be determined. A specific note of body mass index, diabetes, and medications, including the use of hormone replacement therapy (HRT), may shed further light on the underlying cause of the bleeding. It is also important to determine if there is a known history of fibroids. Examination should be comprehensive, looking for any cause of bleeding such as pathologies of the vulva, cervix or rectum. Hysteroscopy (Plate 5.5) and a guided biopsy or resection should be the initial line of management if the endometrial lining is thicker than 4 mm on ultrasound studies. This should be coupled with MRI imagery if concerns arise as to the nature of the fibroid. It is important to remember that the presence of a fibroid does not exclude a concurrent underlying endometrial carcinoma and as such, guided biopsies from the endometrium should be taken of any areas which arouse suspicion.

In general, if the fibroid is not causing any symptoms and underlying pathology has been excluded, a policy of watchful waiting could be adopted with yearly follow-up reviews. This is with the proviso of early presentation should any further bouts of bleeding occur. If on the other hand symptoms recur, or the patient has concerns or is distressed by PMB and wishes definitive management, a submucosal or partial intramural fibroid may be formally resected. Complications associated with hysteroscopy and the use of the resectoscope are well established and include fluid overload, uterine perforation, hemorrhage, and infection.

CAUTION #1

Measures should be taken to minimize risks associated with hysteroscopy, particularly in the older woman. In all cases the surgeon should adhere to the following rules.

1. Fully functioning and serviced surgical equipment
2. Use of appropriate distension media
3. Safe operating – aiming to keep operating time to a safe minimum
4. Meticulous note of hysteroscopic fluid balance – abandon if glycine deficit exceeds 1 L and safe to do so
5. Aim to keep fluid pressure as low as possible whilst maintaining adequate views

While newer hysteroscopic instruments using cautery have been developed that are compatible with normal saline distension media, glycine is the commonly used distension medium. Fluid overload at hysteroscopy may result in nausea and hyponatremia. Excessive overload with glycine can produce elevated serum ammonia concentrations that may result in encephalopathy and death. Hyponatremia should be treated with diuretics and hypertonic saline, with regular serum electrolyte monitoring. Encephalopathy may require hemodialysis to be performed.

CAUTION #2

Remember that glycine and its by-products (primarily ammonia) are toxic. Glycine acts as a neuroinhibitory transmitter within the central nervous system. When used primarily in hysteroscopic surgery, in rare events its use has been associated with transient visual disturbances or complete transient visual loss. Glycine, being a nonessential amino acid, normally undergoes hepatic and renal oxidative deamination resulting in the formation of glycolytic acid and ammonia.

On rare occasions, clearance of ammonia may be faulty, resulting in elevated serum concentrations of ammonia. L-arginine is necessary for the breakdown of ammonia via the ornithine cycle and in some instances patients may be deficient in this. Prior administration of L-arginine prevents increase in blood ammonia concentrations.

Perforation can be minimized by always introducing the hysteroscope under direct vision, after gentle dilation. Forcing instruments into the uterine cavity should always be avoided. If difficulty or resistance is encountered, one should suspect that this may be due to distortion of the cavity secondary to a fibroid. Gentle manipulation of a sound will in most cases guide a path into the cavity. A simple perforation is rarely associated with any complications. It is advised that a laparoscope be inserted abdominally in order to exclude any active bleeding. Regular observations and the use of broad-spectrum antibiotics should be initiated. Complicated perforations associated with electrosurgery or laser or operative instrumentation may involve other organs and as such a laparoscopy should be conducted in order to recognize and treat any occult injury. In cases when complicated hysteroscopies are performed, simultaneous visualization of the uterus via a laparoscope is advised.

Menopausal women with fibroids requesting hormone replacement therapy

The question arises as to how to treat a menopausal woman with fibroids who requests HRT. Randomized trials have primarily been conducted based on the use of either continuous combined preparations or tibolone in menopausal women with pre-existing fibroids in established menopause. Fifty micrograms of transdermal estradiol in combination with 5 mg medroxyprogesterone acetate (MPA) has been shown to result in significant uterine enlargement when compared to 0.625 µg conjugated equine estrogens (CEE) in combination with 2.5 mg MPA. Symptomatic responses and bleeding patterns were the same in both arms. CEE 0.625 µg in combination with 5 mg MPA when compared to tibolone caused less amenorrhea and more irregular bleeding but neither caused uterine enlargement. Overall, tibolone may be the treatment of choice in postmenopausal women with fibroids (Farquhar et al., 2001), although this therapy is not available in the US.

Conclusion

The older woman with uterine fibroids demands special consideration. In the perimenopausal state, a conservative approach is generally adopted in women who are mildly symptomatic with fibroids. Because of the patient's age, one might anticipate shrinkage of fibroids and resolution of symptoms during the transition into menopause. If excess bleeding is the only symptom and given that menopause is approaching, symptomatic relief of the bleeding using medical therapy, such as tranexamic acid with iron sulfate, may work well, thus obviating the need for invasive surgical interventions. Another option for the patient in whom bleeding is the only symptom is the levonorgestrel IUS. Pain and bulk symptoms may respond to UAE or MR-guided focused ultrasound. As with the menopausal patient described above, other diagnoses should be excluded.

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6

Medical Management of Women with Symptomatic Uterine Fibroids

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Introduction

In this chapter, we will evaluate the role of current medical treatments for women with uterine fibroids based on a literature review with a focus on evidence from randomized, controlled clinical studies and treatment guidelines. Exploratory studies with investigational drugs will be reviewed, as well. Unfortunately, evidence in peer-reviewed literature regarding medical treatment of uterine fibroids is limited and, to date only a few randomized, controlled studies have been published. Some of these studies only evaluated reductions in fibroid volume without addressing symptoms such as heavy uterine bleeding or those related to fibroid size. In the US, only two drugs are currently Food and Drug Administration (FDA) approved for the treatment of women with uterine fibroids: the gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate for preoperative hematological improvement of patients with anemia caused by uterine fibroids, and the oral antifibrinolytic agent tranexamic acid for the management of heavy menstrual bleeding in women with or without uterine fibroids. All other treatments reviewed below must be recognized as off-label for temporary relief of symptoms.

Medical management of symptomatic uterine fibroids (not followed by surgery)

Uterine fibroids (leiomyomata), the most frequent neoplasm in women, occur with a cumulative incidence of nearly 70% among Caucasian women and >80% in African-American women by age 50. Although most often asymptomatic, fibroids may cause symptoms severe enough to warrant therapy in 20–50% of women. Symptoms associated with fibroids most commonly include heavy or prolonged menstrual bleeding, pelvic pressure and pelvic organ compression, back pain, and adverse reproductive outcomes. Heavy menstrual bleeding (menorrhagia), which is inconvenient and may lead to iron-deficiency anemia, is the key symptom of uterine fibroids and the leading cause of surgical interventions that may include hysterectomy. Other symptoms, in particular pressure symptoms, are largely dependent on the size, number, and location of the tumors.

Uterine fibroids are highly heterogeneous tumors with variable growth rates and symptomatology. Therefore, the choice of treatment should be based on individual symptoms, patient preference, and desire to preserve fertility or the uterus. Historically, hysterectomy or myomectomy was the preferred treatment option for women with symptomatic uterine fibroids. As more and more women delay maternity into their 30s and 40s, there is a growing need for alternatives to surgical treatments, especially hysterectomy. To meet this demand, during the past two decades, many new uterus-sparing therapies have been proposed and studied. These new therapies include semi-invasive procedures, as well as nonsurgical, medical treatments (discussed in Chapters 7 and 8).

Fibroids, First Edition. Edited by James H. Segars.

Although the pathogenesis has yet to be fully elucidated, the growth of uterine fibroids is known to be highly dependent on both estrogen and progesterone. This dependence on ovarian hormones is evidenced by the spontaneous reduction in fibroid size commonly observed after menopause, a natural anovulatory and hypoestrogenic state. On this basis, most medical treatments for women with symptomatic uterine fibroids are aimed at either hormone-blocking or hormone-modulating strategies.

The ideal medical treatment for symptomatic uterine fibroids, as an alternative to surgical interventions, should be able to control heavy menstrual bleeding, reduce fibroid and uterine volume, improve quality of life, and be safe and tolerable as a chronic therapy. Unfortunately, currently available medical options either provide only short-term improvement of symptoms or their side-effects limit their long-term use. A safe and effective chronic medical therapy for symptomatic uterine fibroids, as an alternative to hysterectomy, has not yet been developed.

Heavy menstrual bleeding (menorrhagia) is a common symptom of uterine fibroids and is the major reason why patients seek medical treatment. Heavy menstrual bleeding is defined as either excessive uterine bleeding that occurs at regular intervals or prolonged uterine bleeding that lasts more than 7 days. It may also involve both heavy and prolonged bleeding. The classic definition of heavy menstrual bleeding (i.e. greater than 80 mL of blood loss per menstrual cycle) is rarely used clinically, since assessment of actual blood volume lost is exceedingly difficult. There are several medical options for the management of heavy menstrual bleeding associated with uterine fibroids that include tranexamic acid, combined oral contraceptives, levonorgestrel intrauterine system (LNG-IUS), high-dose progestins, androgens (danazol), progesterone receptor modulators (PRMs), GnRH agonists, and GnRH antagonists (Tables 6.1, 6.2). All of these treatments are variously effective in reducing heavy menstrual bleeding, but only a few (GnRH agonists, androgens, aromatase inhibitors) also reduce fibroid and uterine volume.

The American College of Obstetricians and Gynecologists (ACOG) recommends testing for von Willebrand disease in adolescents with severe heavy menstrual bleeding, in adult women with heavy menstrual bleeding, and in women undergoing hysterectomy for the sole indication of heavy menstrual bleeding.

SCIENCE REVISITED #1

The mechanism(s) of heavy menstrual bleeding, in association with uterine fibroids, remains unclear and seems to be more complex than previously anticipated. Historically, heavy menstrual bleeding in women with uterine fibroids was linked to an anatomical distortion of the uterine cavity by a fibroid; however, bleeding abnormalities are common in women with small intramural fibroids that do not distort the uterine cavity. This suggests that fibroids may indirectly affect endometrial function via secretion of growth and angiogenesis factors.

Heavy menstrual bleeding can be controlled via various mechanisms. Recently, it has been demonstrated that the endometrium of women who experience menorrhagia has higher levels of plasminogen activator than that of women with normal flow. Plasminogen activators are a group of enzymes that trigger fibrinolysis by catalyzing the conversion of fibrin-bound plasminogen to plasmin (fibrinolysin), an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid is a synthetic lysine derivative that exerts its effect by blocking lysine-binding sites on plasminogen, thus preventing fibrin degradation.

The GnRH agonists induce amenorrhea by completely suppressing the hypothalamo-pituitary-ovarian axis. High-dose progestins inhibit ovulation and induce decidualization of the endometrium. Combination oral contraceptives inhibit ovulation and also provide continuous exposure of the endometrium to a progestin, thus preventing cyclic endometrial changes that occur during normal ovarian cycles. The LNG-IUS directly targets the endometrium by inducing decidualization and leads eventually to endometrial atrophy. PRMs generally inhibit ovulation, but do not fully suppress ovarian estrogen secretion. Asoprisnil has been shown to induce amenorrhea via an endometrial effect.

Table 6.1 Medical management of symptomatic uterine fibroids: available options

Treatments	Mechanism of action	Efficacy		Limitations and potential issues	Comments
		Bleeding control	Volume reduction		
Combination OCs	Anovulation	√	–	Short-term effects	Off-label
Progestins	Anovulation, decidualization of the endometrium, decrease in estrogen receptors	√	–	Side-effects	Off-label
LNG-IUS	Decidualization of the endometrium	√	–	Increased risk of uterine perforation in the presence of fibroids	
Tranexamic acid	Inhibition of fibrinolysis	√	–	Frequent dosing (three tablets three times a day)	Approved for the treatment of heavy menstrual bleeding in women with or without uterine fibroids Lower efficacy compared to GnRH agonists
GnRH agonists Injectable GnRH antagonists	Complete suppression of ovarian estrogen and progesterone production	√	√	Hypoestrogenic side-effects (bone loss, vasomotor symptoms, etc.)	Approved for 3-month use (with iron); no approved add-back therapy available

GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel intrauterine system; OC, oral contraceptive.

Table 6.2 Medical management of symptomatic uterine fibroids: investigational drugs (not approved)

Treatments	Mechanism of action	Efficacy		Limitations and potential issues	Comments
		Bleeding control	Volume reduction		
PRMs: Mifepristone Asoprisnil Ulipristal acetate Telapristone acetate	Antiproliferative and proapoptotic effects in leiomyoma cells. Inhibition of bleeding via a direct endometrial effect	√	√	Cystic endometrial changes with unknown long-term significance	Ulipristal acetate is under development in the EU for preoperative (3-month) treatment
Letrozole	Aromatase inhibitor	?	√	Hypoestrogenic side-effects; potential ovarian stimulation and cyst formation	Chronic use unlikely without add-back therapy; may require a combination with progestin or oral COCP
Pirfenidone	Antifibrotic	?	?	High incidence of side-effects (nausea, dizziness, fatigue, and photosensitive rush) in patients with idiopathic pulmonary fibrosis	Clinical trials in patients with uterine fibroids are still lacking

COCP, continuous oral contraceptive; PRM, progesterone receptor modulator.

CAUTION #1

Since heavy menstrual bleeding may be a symptom associated with coagulopathies or endometrial pathology, a thorough endometrial assessment is mandatory prior to initiation of any medical therapy regardless of whether fibroids are present.

Heavy menstrual bleeding, and other bleeding irregularity, may be caused by endometrial pathology, including endometrial cancer and endometrial polyps. Therefore, ACOG recommends an endometrial assessment using endometrial biopsy and saline infusion sonohysteroscopy (SIS) prior to initiation of any medical therapy for heavy menstrual bleeding. The detection rate of an endometrial cancer using endometrial biopsy is approximately 91%, with a 2% false-positive rate in premenopausal women, making it an accurate diagnostic test for women with heavy uterine bleeding. Greater sensitivity (97%) and negative predictive value (94%) can be achieved by combining endometrial biopsy with SIS.

When a woman over the age of 35 years presents with a complaint of heavy menstrual bleeding, regardless of whether or not the presence of uterine fibroids is suspected or documented, an endometrial assessment should be undertaken. The presence of endometrial pathology (hyperplasia, polyps or malignancy) requires therapy directed at that pathology regardless of whether or not fibroids are present. In the absence of evidence of endometrial pathology, as well as blood disorders, therapy can then be directed at the fibroids as a potential cause of the heavy menstrual bleeding.

Antifibrinolytic drugs

The antifibrinolytic drug, tranexamic acid, has been widely used for more than two decades outside the US for the management of heavy menstrual bleeding. It recently became available as an FDA-approved medication for the management of heavy menstrual bleeding in women with or without uterine fibroids. It is only used during the menstrual phase of the menstrual cycle (1300 mg [two 650 mg tablets] three times a day [3900 mg/day] for a maximum of 5 days). This treatment has been documented to reduce menstrual blood loss by up to 50%, as measured by the objective alkaline hematin method (Figure 6.1). One report in the literature, based on a retrospective clinicopathological study, suggested that tranexamic acid treatment may be associated with necrosis and early infarction of uterine fibroids. The risk of venous thromboembolism, or other thrombotic events associated with the use of tranexamic acid, seems to be similar to that associated with other drugs used to manage heavy menstrual bleeding. It should be noted that concurrent use of tranexamic acid and combination oral contraceptives may be associated with an increased risk of thrombotic events.

CAUTION #2

Combination oral contraceptives are known to increase the risk of venous, as well as arterial thromboembolism and may cause stroke and myocardial infarction.

Because tranexamic acid is antifibrinolytic, the concomitant use of hormonal contraception and tranexamic acid may further exacerbate the increased risk of venous and arterial thrombosis observed in women, especially those over 35 years of age. Women using hormonal contraception should use tranexamic acid only if there is a strong medical need and if the benefits of treatment outweigh the potential increased risks of a thrombotic event.

Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. As a result, women taking this drug should be told to report any visual symptoms promptly.

Combination oral contraceptives

Although combination oral contraceptives (OCs) are widely used for the treatment of women complaining of anovulatory bleeding, there are to date no high-quality comparative studies supporting their use in heavy menstrual bleeding associated with uterine fibroids. Nevertheless, combined oral contraceptives are frequently used for the temporary management of heavy menstrual bleeding. Epidemiological studies indicate that combination

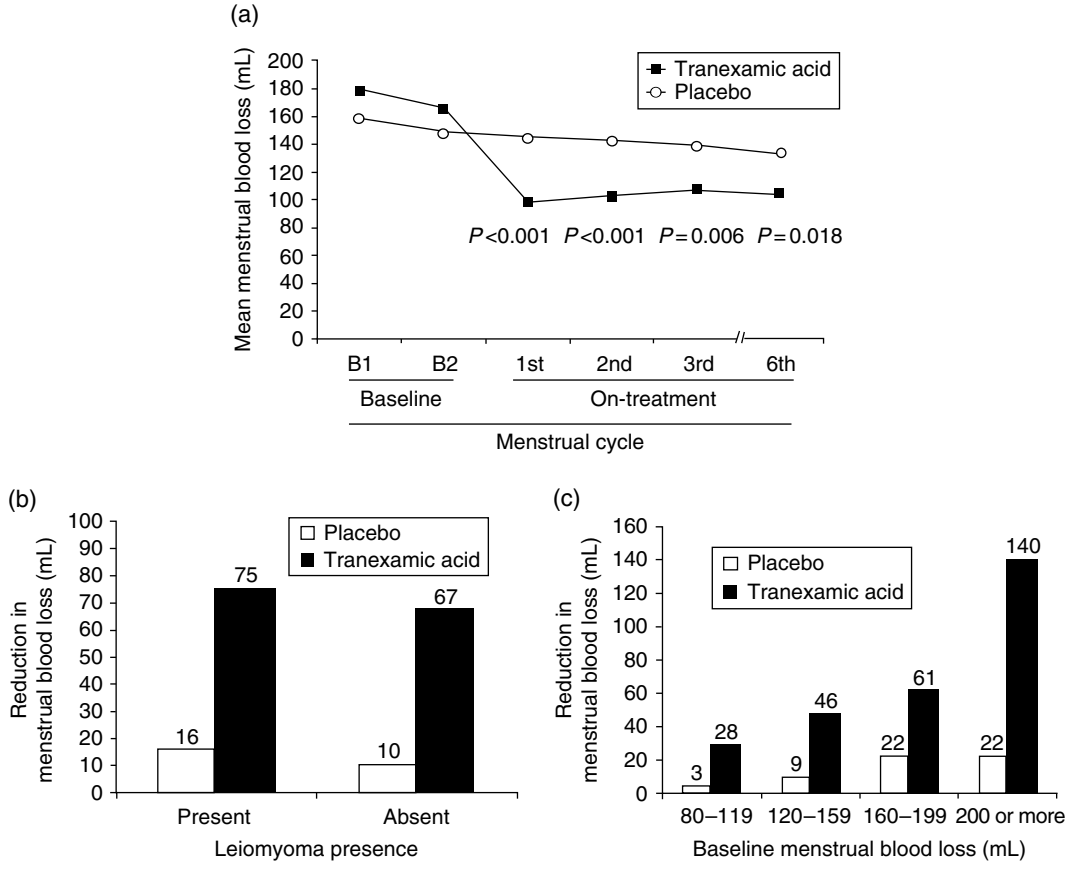

Figure 6.1 The effects of tranexamic acid on monthly menstrual blood loss (MBL) in women with heavy menstrual bleeding (HMB). (a) MBL change over study course. Effects of tranexamic acid ($n = 115$) and placebo ($n = 72$) use on MBL as measured by the alkaline hematin method are illustrated over the time course of the study. p values are for the comparison between tranexamic acid and placebo. (b,c) Reduction in menstrual blood loss from baseline stratified by presence of uterine fibroids (b) and by baseline menstrual blood loss (c). For all comparisons between tranexamic acid and placebo, $p < 0.05$. Reproduced from Lukes et al. (2010) with permission from Lippincott Williams and Wilkins.

OCs are neutral in terms of their effects on fibroid growth or prevalence.

Levonorgestrel intrauterine system

The levonorgestrel intrauterine system **(**LNG-IUS) was originally developed for long-term contraception, and has been used globally for two decades. The initial release rate of levonorgestrel from the LNG-IUS is 20 μg per day; this rate is reduced by about 50% after 5 years. The LNG-IUS should, therefore, be replaced after 5 years. Long-term studies with the LNG-IUS have demonstrated that this treatment is associated with a significant reduction in blood loss, secondary to reductions in endometrial thickness within 3–6 months of insertion, and is more effective than an oral progestin treatment (Figure 6.2). Based on this finding, and additional studies in women with heavy menstrual bleeding, the FDA approved the LNG-IUS in 2009 for the management of heavy menstrual bleeding in women who use intrauterine contraception as their method of pregnancy prevention. The LNG-IUS reduces bleeding by causing decidualization of the endometrium, and eventually its atrophy. Most women develop amenorrhea within 6 months after

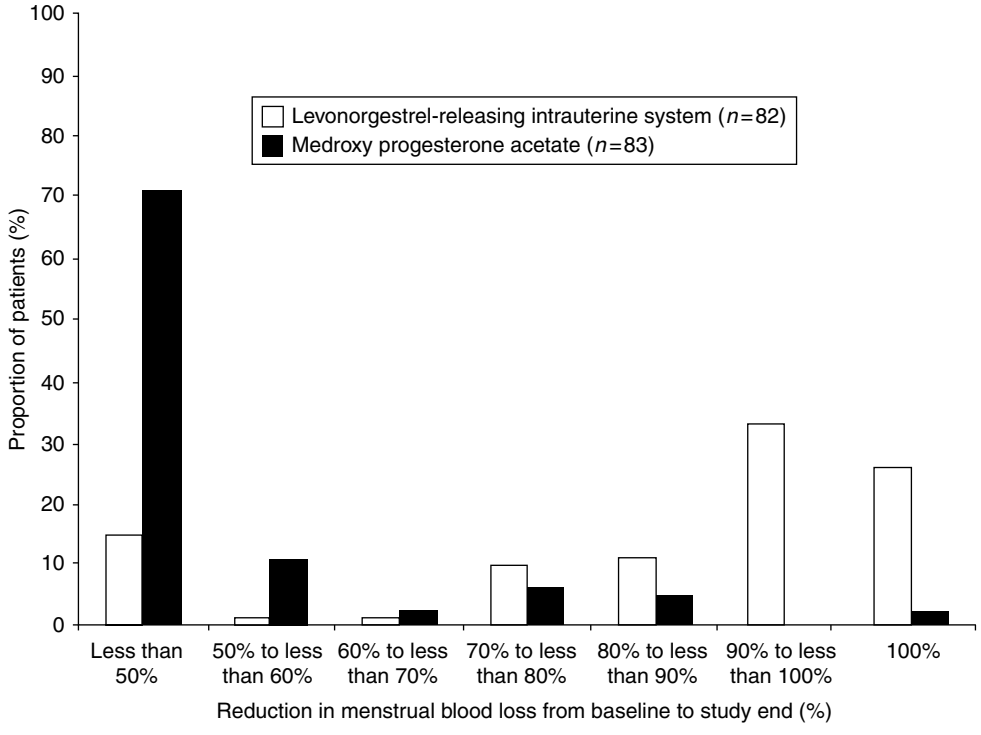

Figure 6.2 The effects of the LNG-IUS and medroxyprogesterone acetate in women with heavy menstrual bleeding over the period of 12 weeks. Percentage reduction in menstrual blood loss from baseline to study end experienced by the participants in the two treatment groups. Women with uterine fibroids that did not distort the uterine cavity or cervical canal were included in this study. Reproduced from Kaunitz et al. (2010) with permission from Lippincott Williams and Wilkins.

insertion of the LNG-IUS. The LNG-IUS also reduces dysmenorrhea, likely the result of the endometrial atrophy as well as alterations in prostaglandin production in the endometrium. It is important to note that the LNG-IUS should only be used in women who have no distortion of the uterine cavity.

While the LNG-IUS may provide a considerable reduction in uterine bleeding and dysmenorrhea (if present), it typically does not reduce the size or number of uterine fibroids. There are studies in the literature that report less uterine surgery and less incidence of hysterectomy, as well as lower growth rates of uterine fibroids after 5 years of LNG-IUS use compared to similar periods of use of a copper intrauterine device (IUD). Importantly, there are also reports in the literature of fibroid enlargement following use of the LNG-IUS in some women.

CAUTION #3

The LNG-IUS may be unsuitable for use in women with an irregular uterus or a significantly increased uterine cavity. The effectiveness of the LNG-IUS, both as a contraceptive and for control of heavy uterine bleeding in women with a fibroid uterus in which the endometrial cavity is grossly distorted, remains unknown. Caution is needed during placement of an LNG-IUS in the presence of uterine fibroids that distort the cervical canal or submucosal fibroids, since these conditions may increase the risk of uterine perforation during insertion.

The LNG-IUS is contraindicated in the presence of known or suspected pelvic inflammatory disease (PID) or in women with a history of PID unless there has been

a subsequent intrauterine pregnancy. Use of all forms of intrauterine devices has been associated with an increased risk of PID.

Progestins

Oral high-dose progestins are the most commonly prescribed therapy for short-term management of heavy menstrual bleeding, not associated with uterine fibroids. There is, however, little evidence to support the use of progestins in the presence of uterine fibroids. In fact, high-dose progestin may stimulate fibroid growth when used continuously as a monotherapy, or in conjunction with a GnRH agonist as add-back therapy. In addition, continuous use of progestins may actually increase uterine bleeding via negative effects on normal endometrial angiogenesis. For these reasons, high-dose progestins are not suitable as add-back therapy in combination with GnRH agonists in women with symptomatic uterine fibroids.

SCIENCE REVISITED #2

Although the factors that initiate, as well as those that influence the early steps in the pathogenesis of uterine fibroids are still unclear, their development is highly dependent on ovarian steroid hormones. Traditionally, uterine fibroids were viewed as an estrogen-dependent condition. There is increasing evidence, however, from biochemical, histological, clinical, and pharmacological studies indicating that progesterone and progesterone receptors (PR) play a key role in uterine fibroid development and growth. Several investigators have shown an increased concentration of both PR isoforms (PR-A and PR-B) in uterine fibroid tissue, and elevated mitotic activity in fibroid tissue relative to the adjacent, normal myometrial tissue during the luteal phase of the ovarian cycle. In addition, studies *in vitro* show that progesterone suppresses apoptosis and stimulates proliferation of leiomyoma cells. Similar observations were made in clinical studies with progestins and PRMs. The synthetic progestins, medroxyprogesterone acetate and norethindrone, when used as add-back therapy in combination with GnRH agonists, attenuate or reverse the inhibitory effects of the GnRH agonists on leiomyoma size; in contrast, the PRMs (e.g. mifepristone, asoprisnil, ulipristal acetate) reduce fibroid volume.

Progesterone receptor modulators

The term progesterone receptor modulators (PRMs) is usually used for compounds that modulate the function of PR and includes PR antagonists (e.g. mifepristone) and selective progesterone receptor modulators (SPRMs) (e.g. asoprisnil), which are mixed agonists/antagonists. Several PRMs, including mifepristone, asoprisnil, ulipristal acetate (CDB 2914), and telapristone acetate (CDB-4124), have been evaluated in women with uterine fibroids. None of these compounds, however, has been approved for the treatment of symptomatic uterine fibroids to date. Ulipristal acetate is currently under development for short-term preoperative treatment of women with symptomatic uterine fibroids.

Mifepristone has been shown to reduce bleeding substantially and to decrease fibroid volume by approximately 30% within 3 months of the commencement of treatment. These effects are dose dependent. Similar effects have been reported during treatment with asoprisnil (Figure 6.3) and ulipristal acetate. Studies with asoprisnil also showed a concomitant reduction in pressure symptoms and an improvement in quality of life measures. Although most women develop amenorrhea during treatment with PRMs, these drugs do not cause hypoestrogenemia and the associated side-effects, such as bone mineral density loss and hot flashes. *In vitro* studies with leiomyoma cells in culture indicate that PRMs decrease leiomyoma cell proliferation, increase rates of apoptosis, and reduce formation of the extracellular matrix (ECM). These findings highlight the role of PR in the pathogenesis of uterine fibroids. Asoprisnil has been shown to induce amenorrhea via an endometrial effect.

Prolonged treatment with PRMs, however, is associated with unusual endometrial changes not seen previously with any other drugs. Although these changes are most likely compound specific, the most common effects were formation of cystically dilated endometrial glands (which were different from cystic endometrial hyperplasia) with low mitotic activity and no atypia, and variable

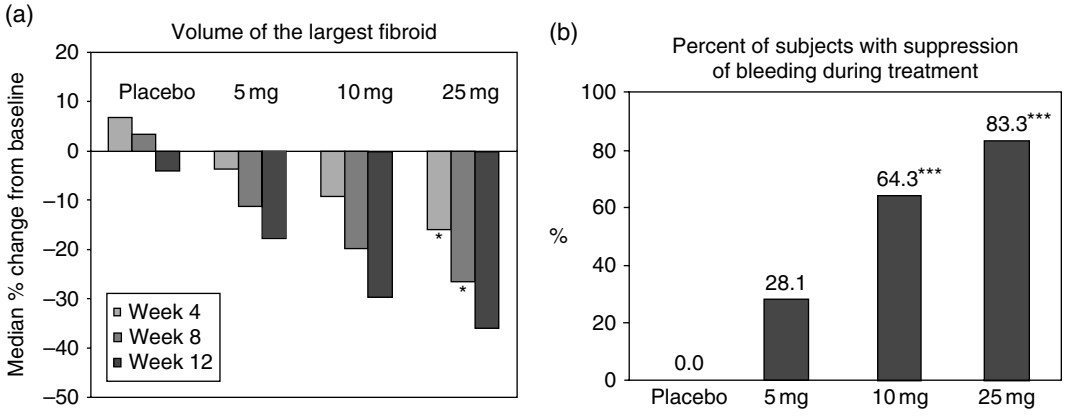

Figure 6.3 The effects of the progesterone receptor modulator asoprisnil on fibroid volume and uterine bleeding in a randomized, placebo-controlled trial. (a) Effects of asoprisnil on the volume of the largest fibroid during 12 weeks of treatment. Leiomyoma volume was assessed at baseline as well as during treatment at weeks 4, 8, and 12 using transvaginal or abdominal ultrasound. The results are presented as median percentage changes from baseline (*p<0.05 compared with placebo). (b) Suppression of uterine bleeding during treatment with asoprisnil. Suppression of uterine bleeding was defined as having no light, medium, and heavy bleeding from the end of baseline menses through the end of dosing (**p<0.01 and ***p<0.001). Reproduced from Chwalisz et al. (2010) with permission from Elsevier.

effects on endometrial stroma. These endometrial changes that mimicked endometrial hyperplasia on ultrasound images resulted in the cessation of development of these drugs as a chronic treatment for symptomatic uterine fibroids, because of potential difficulties in safety monitoring.

SCIENCE REVISITED #3

Physiologically, GnRH is released from the hypothalamus in a pulsatile manner, which differentially regulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the pituitary gland. When a GnRH agonist is administered continuously at a high dose, after a short (7–14 days) stimulatory phase ("flare effect"), it downregulates GnRH receptors in the pituitary gland, which leads to a profound suppression of gonadotropin production and complete cessation of ovarian sex steroid production. The resulting hypoestrogenism and anovulation lead to amenorrhea. Since fibroids require the presence of estrogen and progesterone to maintain growth, the hypoestrogenic state (and perhaps the lack of progesterone) is associated with a decrease in fibroid size. This is the presumed cause of the gradual shrinkage of fibroids post menopause.

GnRH antagonists, which competitively inhibit GnRH receptors in the pituitary gland, induce immediate suppression of the hypothalamo-pituitary-ovarian axis with no initial hormonal stimulation.

The mechanism(s) of uterine and fibroid volume reduction during treatment with GnRH agonists or GnRH antagonists involve a complex set of events, and include a reduction in blood perfusion of the fibroids and the uterus that induces subsequent fibroid degeneration; a decrease in leiomyoma cell proliferation due to the absence of mitotic activity stimulated by estrogen and progesterone; a downregulation of PR and estrogen receptors (ER) in leiomyoma and normal myometrial cells; a reduction in extracellular matrix production; and a decreased expression of growth factors, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). These

growth factors have been implicated in fibroid growth and the formation of new blood vessels requisite for fibroid development. Importantly, treatment with GnRH agonists and antagonists also leads to the reduction of nonfibroid volume, i.e., normal myometrial tissue.

Gonadotropin-releasing hormone agonists and antagonists

The GnRH agonists and antagonists result in a variety of beneficial effects, when administered to women with symptomatic uterine fibroids, and these agents have been studied extensively in this population. Only one GnRH agonist (leuprolide acetate 1-month and 3-month depot injections) is currently approved by the FDA as a short-term pre-operative treatment for women with symptomatic uterine fibroids, as discussed below.

Multiple studies confirm reduction in fibroid volumes ranging from 35% to 65% within 3 months of starting treatment with GnRH agonists, as a result of reduction in cell volume rather than a reduction in fibroid cell number (Figure 6.4). This treatment is also associated with a concomitant reduction in

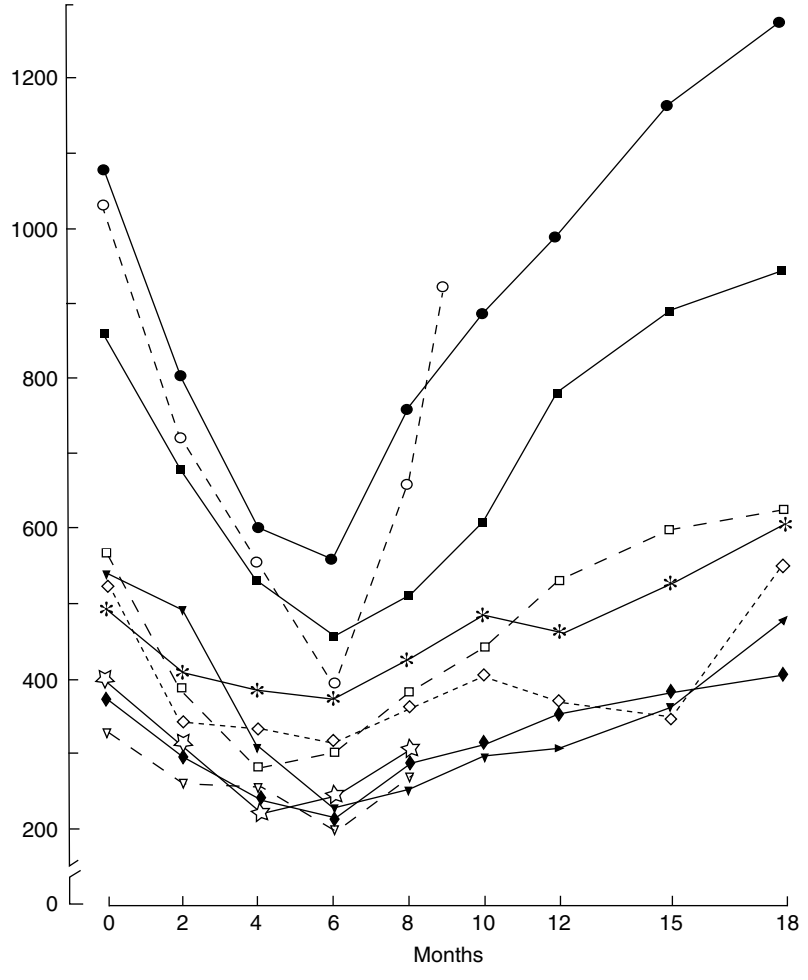

Figure 6.4 Total uterine volume (cm^3) changes in 10 patients with uterine fibroid, during and after treatment with intranasal buserelin (GnRH agonist). The patients were treated for 6 months. Note a progressive decrease in uterine volume during the treatment period and gradual increase in uterine volume after stopping treatment. Reproduced from Matta et al. (1989) with permission from Elsevier.

pressure symptoms. The symptoms of pelvic pain and dysmenorrhea that some women with uterine fibroids present are also improved during treatment with GnRH agonists. It should be noted that the effects of GnRH agonists on fibroid and uterine volume are temporary, with gradual, recurrent growth to the original size, after stopping treatment ("rebound effect") (see Figure 6.4).

SCIENCE REVISITED #4

The overall effects of injectable, peptidergic GnRH antagonists are similar to those of GnRH agonists in women with symptomatic uterine fibroids. Because GnRH antagonists inhibit the pituitary gland directly, the amenorrhea state and the reduction in uterine and fibroid volume are expected to occur earlier during treatment with GnRH antagonists, due to the absence of the hormonal flare. More recently, oral, nonpeptide, GnRH antagonists (e.g. elagolix and TAK 385) have been discovered and are currently being developed for the treatment of hormone-dependent diseases, including symptomatic uterine fibroids. Oral, short-acting GnRH antagonists have the ability to modulate the hypothalamo-pituitary-ovarian axis in a dose-dependent manner.

Because of their mechanism of action, treatment with a GnRH agonist or injectable GnRH antagonist is associated with potentially severe hypoestrogenic side-effects, including a progressive bone loss and vasomotor symptoms, as well as vaginal and urethral atrophy. Vasomotor symptoms, which may be severe, occur in the vast majority of women who are treated with GnRH agonists and antagonists. The bone loss effects limit their use beyond 6 months of therapy unless a bone-sparing add-back therapy is used concomitantly.

Concerns about bone loss and poor tolerability of GnRH agonist monotherapy led to a number of studies on potential add-back therapies. In contrast to the management of endometriosis, there are no FDA-approved add-back therapies for use with GnRH agonists for women with uterine fibroids. Early trials focused on progestin-only add-back therapies, including medroxyprogesterone acetate (15–20 mg/day orally) or norethindrone (10 mg/day orally). With the addition of progestin-only add-back therapy, there was a reduction of hot flashes but the reduction in uterine or uterine fibroid volume was significantly limited (Figure 6.5). The effect of progestin-only add-back therapy on uterine bleeding was not reported in these studies, although treatment with high-dose progestins is known to be associated with breakthrough bleeding and spotting.

There are isolated reports in the literature suggesting that both low-dose estrogen/progestin postmenopausal hormone therapy (EP therapy) and tibolone can be used as add-back therapy with GnRH agonists without negatively influencing their effectiveness in terms of bleeding control and volume reduction. Tibolone, a steroidal compound which forms estrogenic, progestogenic, and androgenic metabolites, is widely used outside of the US for postmenopausal hormone therapy. It has been demonstrated that women, who initially take high-dose EP therapy concomitantly with GnRH agonists at the beginning of treatment with the GnRH agonist in an attempt to reduce fibroid and uterine volume fail to experience any reduction in fibroid volume. Thus, if high-dose EP therapy is to be used with GnRH agonists, it is best to wait to commence treatment with EP therapy for 3 months after the initiation of GnRH agonist therapy to allow for a reduction in fibroid volume before the EP therapy is started.

Aromatase inhibitors and selective estrogen receptor modulators

Uterine fibroids were shown to express aromatase, the enzyme that converts androgens to estrogens, which suggests that estrogen may be produced locally to stimulate fibroid growth. Interestingly, leiomyoma tissue from African-American women has been shown to contain the highest levels of aromatase expression when compared to levels observed in tissues obtained from Caucasian and Japanese women. Increased aromatase expression may result in elevated tissue concentrations of estrogen and thus may account for the higher prevalence and earlier incidence of uterine fibroids in the African-American population.

These findings provide the scientific rationale for the treatment of women with symptomatic uterine fibroids with aromatase inhibitors. Currently, there is limited evidence from clinical studies to support their use for the chronic treatment of women with

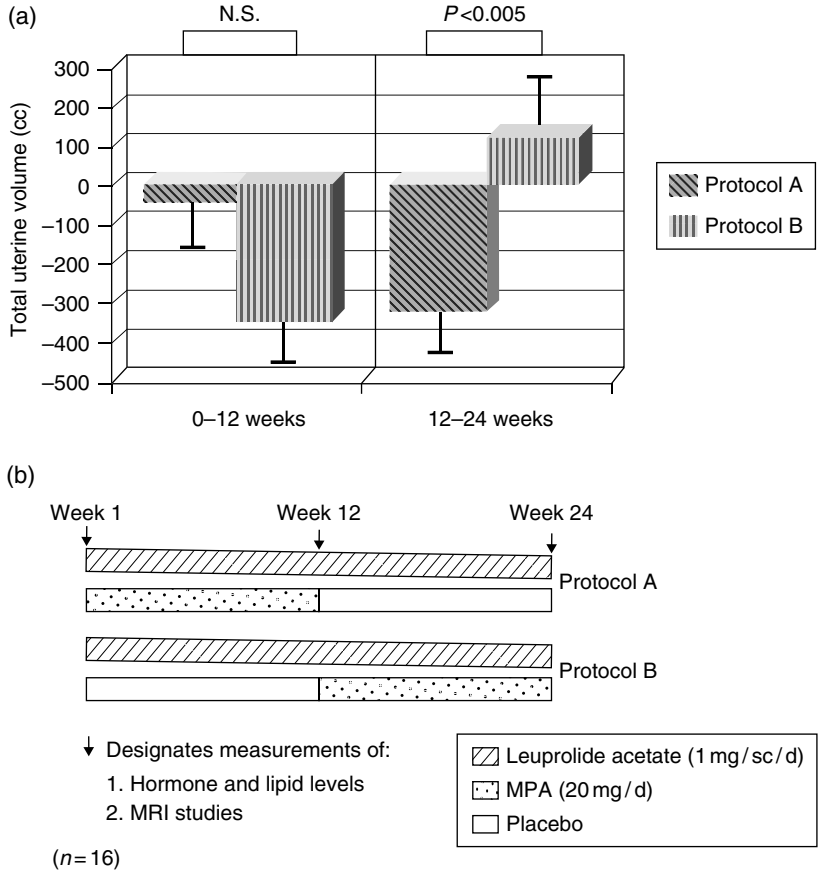

Figure 6.5 The effects of a GnRH agonist (leuprolide acetate) and medroxyprogesterone acetate on the total uterine volume. Results from a prospective, randomized, double-blind, placebo-controlled, cross-over trial. (a) The effects on the uterine volume as measured by magnetic resonance imaging (MRI). Comparisons were made between volume responses occurring 0–12 weeks (where 0 = baseline measurements) and from 12–24 weeks (where 0 = 12-week measurement). (b) Cross-over design of this study. Reproduced from Carr et al. (1993) with permission from the Endocrine Society.

symptomatic uterine fibroids. To date, only one randomized controlled study of letrozole (5 mg) versus a GnRH agonist in women with uterine fibroids has been published. This study showed a similar reduction in fibroid volume at week 12 in both treatment groups. The effects of letrozole on symptoms associated with uterine fibroids were not evaluated in this study. Clearly, more studies are needed to evaluate the effects of this class of drugs in women with symptomatic uterine fibroids. Based on the experience of the use of aromatase inhibitors in women with endometriosis, the addition of a progestin may be needed to prevent ovarian cyst formation. It remains unclear if aromatase inhibitors may be used long term in premenopausal women without inducing unacceptable bone loss.

Pure antiestrogens and selective estrogen receptor modulators (SERMs) were shown to be effective in the rat model of uterine fibroids (ERKO rat). There is, however, no evidence to support the use of SERMs in women with symptomatic uterine fibroids. Most studies published to date showed little, if any, effect of SERMs on uterine fibroid volume or associated symptoms.

Other medical treatments

Although nonsteroidal anti-inflammatory drugs (NSAIDs) can be useful in reducing heavy menstrual

bleeding that is not associated with uterine fibroids, there is no evidence to support their use in women with symptomatic uterine fibroids.

Historically, androgenic compounds, such as danazol or gestrinone, were used for the management of heavy uterine bleeding, but the androgenic side effects preclude their use as a chronic treatment. There are reports in the literature of fibroid volume reduction during treatment with both danazol and gestrinone, a finding consistent with the antiproliferative effects of androgens on various uterine tissues.

In Asia, alternative therapies, e.g., traditional Chinese herbal preparation with multiple ingredients (Kui-chin-fu-ling-wang), are frequently used for the treatment of heavy menstrual bleeding and other symptoms of uterine fibroids with apparently very good results. It must be stated, however, that the reports in the literature are limited to uncontrolled studies or case reports that are difficult to interpret.

Emerging medical therapies

More recently, there has been growing interest in drugs that specifically target fibrosis or the production of extracellular matrix, including the antifibrotic drug pirfenidone that is used for the treatment of pulmonary fibrosis. Although pirfenidone showed promising effects in cultured myometrial cells, clinical data from women with symptomatic uterine fibroids are still missing.

Treatment with pirfenidone is associated with a high incidence of side effects (nausea, dizziness, fatigue, and photosensitive rash) in patients with idiopathic pulmonary fibrosis, which may limit its use in women with symptomatic uterine fibroids. Other potential antifibrotic or antiproliferative treatments, such as halofuginone (collagen type 1 inhibitor and matrix metalloproteinase 2 expression with antitumor properties, which is approved for the treatment of scleroderma) and all-trans retinoic acid (ATRA), showed promising effects in studies using cultured leiomyoma cells, but clinical studies in women with symptomatic uterine fibroids are still lacking. Exposure of leiomyoma cells to ATRA downregulated cell proliferation, ECM formation, retinoic acid metabolism and transforming growth factor (TGF)-beta regulation, which suggests that retinoic acid exposure can alter the leiomyoma cell phenotype to one that more closely approximates normal myometrium. Although these potential new treatments may be effective in reducing fibrosis in the uterus, it is still unclear if this effect will be associated with a reduction in uterine bleeding.

Preoperative medical treatment of uterine fibroids

Gonadotropin-releasing hormone agonists induce a profound suppression of hormonal activity of the ovary and consequently produce amenorrhea in most women, and a 35–65% reduction in fibroid volume within 3 months of starting treatment. In view of these effects, multiple randomized, controlled studies have been conducted to evaluate the role of GnRH agonists as a preoperative treatment prior to either myomectomy or hysterectomy. These studies were the subject of a Cochrane review, which evaluated both the pre-, intra-, and postoperative outcomes of this treatment (Box 6.1). In the US, leuprolide acetate, in combination with iron, is approved by the FDA for the preoperative

BOX 6.1 Benefits and limitations of the preoperative use of GNRH agonists in women with symptomatic uterine fibroids

Established benefits

- Reduction in uterine volume and fibroid size (30–50% in 3 months)
- Correction of preoperative iron-deficiency anemia
- Reduction of intraoperative blood loss
- Avoidance of a midline incision
- Vaginal hysterectomy is more likely possible
- Laparoscopic myomectomy more likely possible
- Hysteroscopic procedure becomes technically easier

Limitations and potential issues

- Vasomotor symptoms
- Surgical issues with myomectomy (?)
- Change in fibroid consistency, too much shrinkage (?)
- Increased recurrence of fibroids after myomectomy (?)
- Smaller fibroids may become unpalpable and thus be missed at surgery

hematological improvement of patients with anemia caused by uterine fibroids. The recommended treatment duration is 3 months.

The major side effects of preoperative GnRHa therapy are hypoestrogenic symptoms, including hot flashes, headaches, sleep disturbances, and vaginal dryness.

Preoperative outcomes

Hematological parameters, such as hemoglobin and hematocrit, are significantly increased during treatment with leuprolide acetate for 2–4 months. According to the Cochrane meta-analysis, the weighted mean increase during a 3–4-month course of therapy is 1.3 g/dL for hemoglobin concentration and 3.1% for hematocrit, which may be of clinical significance in some women with anemia. Importantly, both uterine and fibroid volumes are significantly reduced during this treatment. The weighted mean difference, when data from different studies are combined, represents an average reduction in uterine volume by 159 mL, and in fibroid volume by an average of 12.5 mL. According to some studies, even greater reductions were seen with large uteri. Pressure symptoms are reduced in some women, as well.

Intraoperative and postoperative outcomes

Combined data from different studies indicate that intraoperative blood loss is reduced during both hysterectomy and myomectomy, compared to placebo or no treatment, but these reductions are associated with relatively small improvements in postoperative hematological outcomes. Pretreatment with a GnRH agonist was shown to have a profoundly positive impact on the choice of surgical approach, e.g., vaginal versus abdominal hysterectomy, the type of incision (midline versus transverse) during hysterectomy or myomectomy, and the type of myomectomy (abdominal versus laparoscopic).

According to the Cochrane meta-analysis, blood loss during hysterectomy of women pretreated with a GnRH agonist was reduced by an average of 60 mL, the duration of surgery was shortened by an average of 6 minutes, and the hospital stay was reduced by 1 day. The rate of blood transfusions was not reduced by GnRH agonist treatment, but fewer operations were assessed as difficult by the surgeon. Importantly, for the abdominal hysterectomy or myomectomy patients, the vertical versus transverse incisions were reduced by at least two-thirds in women treated with a GnRH agonist prior to surgery. In addition, those women were eight times more likely to have a vaginal versus abdominal hysterectomy.

There is still uncertainty whether preoperative treatment with GnRH agonists is beneficial prior to myomectomy, other than that which is performed hysteroscopically. Some studies suggest an increased risk of fibroid recurrence, presumably because small fibroids may not be seen or palpable at surgery due to volume reduction. In addition, some case report studies indicated technical difficulties in defining the fibroid pseudocapsule during myomectomy after pretreatment with a GnRH agonist. Randomized studies to address these potential issues of preoperative GnRH agonist therapy are still missing. A second unanswered question is whether GnRH agonists improve fertility outcomes in women with uterine fibroids.

In summary, the preoperative use of GnRH agonists appears to offer some benefit from preoperative improvement in hematological parameters and reduction in uterine and fibroid volume. The latter allows women to gain access to other types of surgical approaches and has benefits of shorter surgery time with less blood loss and shorter recovery time. These benefits should be weighed against the side effects of this treatment, mostly vasomotor symptoms.

Conclusion

Heavy menstrual bleeding is the key symptom of uterine fibroids and is the major reason why patients seek medical treatment. Current evidence indicates that both estrogen and progesterone are involved in the pathogenesis of uterine fibroids. Therefore, most treatments for women with symptomatic uterine fibroids are aimed at either hormone-blocking/suppressing or hormone-modulating strategies. The current options for medical treatment of women with symptomatic uterine fibroids are limited and include tranexamic acid, combined oral contraceptives, levonorgestrel-intrauterine system, and GnRH agonists. All these treatments reduce heavy menstrual bleeding associated with uterine fibroids, but only GnRH agonists reduce both fibroid and uterine

volumes and thereby improve pressure-related symptoms. However, the use of GnRH agonists is limited to preoperative treatment, due to side effects of long-term estrogen deprivation and the lack of add-back therapy. The antifibrinolytic agent tranexamic acid has recently been approved by the FDA for the management of heavy menstrual bleeding in women with or without uterine fibroids. A chronic medical treatment for symptomatic uterine fibroids is not yet available. Emerging medical treatments include PRMs and orally active GnRH antagonists. These treatments are currently under evaluation in clinical trials.

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7

Nonsurgical Option for Fibroid Treatment: Uterine Fibroid Embolization

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Introduction

Uterine fibroid embolization (UFE) is a minimally invasive therapy for symptomatic fibroids that was first reported in 1995. Since the first reported use of UFE in the United States in 1997, the technique has become an accepted and widely used minimally invasive therapy for the treatment of symptomatic uterine fibroids. Several randomized comparative trials have shown that UFE is an acceptable alternative to conventional surgical interventions with similar clinical outcomes. This growing body of data on UFE has lead to its recognition by the American College of Obstetricians and Gynecologists as having level A evidence to support its safety and efficacy in the treatment of fibroids for appropriately selected women.

Uterine fibroid embolization is a suitable therapy for most women with symptomatic fibroids and should be considered when discussing all available treatment options with a patient. UFE is ideal for women with menorrhagia and/or bulk symptoms as a result of their fibroids who wish to preserve their uterus, and for patients who are not good surgical candidates. In this review, we summarize what a gynecologist needs to know about UFE, including patient selection, indications and contraindications, periprocedural care, complications, and important studies on the efficacy of UFE.

Patient selection

Most patients with symptomatic fibroids are suitable candidates for embolization. There are both patient factors and anatomical considerations that might guide the gynecologist in advising patients concerning their options.

The important patient factors are age, prior fibroid and surgical history, interest in future fertility, interest in uterine preservation, and preferences in terms of recovery and tolerance of fibroid recurrence. While women of any reproductive age may be good candidates for embolization, UFE is most common in women in their 40s. Younger women are candidates but the decision is more complex as there must be consideration of the patient's interest in future child bearing. Based on current evidence, those with a strong interest in having a child in the future are likely better served by myomectomy. Women can become pregnant after UFE but the pregnancy and delivery rates appear to be lower than with myomectomy. However, in those with fibroids too extensive for myomectomy, for those who have had a prior myomectomy or those who are poor surgical candidates, UFE may be the best alternative to surgery. The question of UFE and future fertility is discussed in greater detail in a later section.

Another important consideration is whether the patient wishes to retain her uterus. Despite having completed child bearing, many women do not want to lose their uterus. In this case, uterine embolization is an excellent choice. Myomectomy is a consideration but current clinical outcomes from myomectomy and embolization are very similar and the recovery from embolization is much faster.

Fibroids, First Edition. Edited by James H. Segars.

Any of the uterine-sparing therapies has the potential to allow growth of new fibroids until the patient reaches menopause. Recurrence rates for both myomectomy and embolization are in the range of 20–25% by 5 years after treatment. Hysterectomy is the only definitive therapy for uterine fibroids. Thus, a key step in advising each patient is to ascertain her preferences. For those who do not wish to have the potential of recurrence and who do not mind losing their uterus, hysterectomy may be the best choice. For those who wish to retain their uterus and avoid surgery, UFE is often the most effective choice.

There are some anatomical factors to consider with any fibroid therapy. The uterine size, number of fibroids, size of the largest fibroids, and the location of key fibroids are all important to consider when recommending therapies. For small intracavitary fibroids, hysteroscopic resection is preferred, provided they are resectable. For very large pedunculated serosal fibroids, particularly if they are attached by a narrow base, surgical resection may be preferred.

Given those exceptions, most patients with either single or multiple fibroids are anatomically good candidates for embolization. There are some factors that are associated with better outcomes. For example, those with menorrhagia as a primary presenting symptom have greater improvement compared to those with pain or pressure only. Also, greater shrinkage is seen in those with smaller fibroids compared to larger fibroids and multiple small fibroids do better when compared to uteri with single large fibroids. While all these groups typically can be treated with good outcomes, these groups are most likely to be improved. Some anatomical exceptions do exist and are discussed in the section on contraindications.

Indications

In general, UFE is indicated for patients of reproductive age with symptomatic fibroids who wish to avoid surgery or for whom surgery is contraindicated.

Heavy menstrual bleeding is the most common symptom among women seeking UFE. Heavy menstrual bleeding due to fibroids can present as menorrhagia, metrorrhagia, or menometrorrhagia. Fibroids usually present with menorrhagia without interperiod bleeding, though submucosal fibroids can present with both menorrhagia and metrorrhagia. Pelvic pressure, bloating, and pelvic pain are also effectively treated with UFE. These symptoms are typically worse during the perimenstrual period, as fibroids tend to exacerbate normal perimenstrual bloating and discomfort. Pelvic pain due to symptomatic fibroids is typically low grade and a dull ache, often described as discomfort more than pain. Moderate pain can occur but severe pain is atypical and other causes, such as endometriosis, should be considered.

Urinary symptoms can also be effectively treated with uterine embolization, particularly if the symptoms are urgency, frequency or retention. Incontinence is less reliably improved after UFE. Hydronephrosis from the enlarged uterus can be relieved by embolization as the compression usually resolves as the uterus shrinks.

☆ TIPS & TRICKS

All patients presenting with heavy menstrual bleeding should be further evaluated if the bleeding pattern suggests a cause other than fibroids. An irregular pattern not typical of fibroids is any bleeding that occurs more frequent than every 21 days or lasts for longer than 10 days. Endometrial polyps, hyperplasia, and neoplasm can all cause interperiod bleeding and these will not be treated by embolization. Postmenopausal bleeding is rarely due to fibroids and should be further evaluated with an endometrial biopsy to rule out malignancy. Patients with heavy bleeding also commonly present with progressive dysmenorrhea and this also responds well to UFE.

Contraindications

There are relatively few absolute contraindications to UFE. Pregnancy is one and patients must be tested for current pregnancy on the day of the procedure. Known or suspected uterine and adnexal malignancy should be evaluated before treatment. Active uterine or adnexal infections are also contraindications as these may predispose to fibroid infection. Embolization is safe after the infection resolves with appropriate therapy. An allergy to the intravenous contrast used under fluoroscopy during UFE is

a relative contraindication, although this may be minimized with preprocedural administration of corticosteroids. In patients with severe contrast allergy, the procedure may best be completed with anesthesia support to ensure appropriate airway support.

Renal insufficiency is a relative contraindication that requires preprocedure hydration and on occasion the use of acetylcysteine. With care and limitation of contrast, the procedure can be completed safely without further impairment. Anticoagulation and coagulopathy also must be treated with caution but can be managed with proper preprocedural stabilization of a patient's coagulation status as well as the use of arterial closure devices to reduce the risk of postprocedural bleeding from the puncture site.

Another consideration when determining the appropriateness of UFE is the size and location of a fibroid. Some studies suggest that very large fibroids (uterine sizes greater than 22 weeks' gestation) may not be best suited for UFE since these patients tend to see less of an improvement in their symptoms. Broad ligament and cervical fibroids are less likely to respond to uterine embolization, as they have collateral sources of blood supply that make complete treatment difficult.

Finally, as implied by the earlier discussion on fertility after UFE, infertility presumed secondary to fibroids is a relative contraindication for treatment and myomectomy is the preferred approach.

Preprocedural evaluation

Optimal management of a patient undergoing UFE requires the collaboration of her gynecologist and interventional radiologist at each step of the way. A patient should first visit both her gynecologist and an interventional radiologist to discuss the appropriateness of UFE. Prior to consideration of UFE, she should see her gynecologist for an exam to confirm the diagnosis of fibroids and rule out any other existing gynecological pathology. Patients should have a current negative Papanicolaou smear. Women with either an atypical bleeding pattern or imaging findings suggesting an endometrial abnormality should undergo an endometrial biopsy prior to UFE.

A complete blood count and metabolic panel should be performed before the procedure. Ideally, UFE should be performed within the first 2 weeks of a patient's menstrual cycle but in any case a patient needs to have a negative pregnancy test on the day of the procedure. If a patient is currently on a gonadotropin-releasing hormone (GnRH) agonist or antagonist for medical management of fibroids, it is best to allow the effect of these medications to dissipate prior to UFE. These medications may affect the caliber of uterine arteries, which increases the technical difficulty of uterine artery catheterization and embolization. This may diminish the effectiveness of the procedure.

Imaging is essential in both the initial evaluation and follow-up after UFE. Imaging confirms the diagnosis of fibroids and characterizes fibroid size, location, and morphology. The two most commonly used imaging modalities are transvaginal ultrasound and magnetic resonance imaging (MRI). Ultrasound has a long history of use in gynecology and its benefits include low cost and availability. However, it lacks the spatial resolution of more advanced imaging modalities and features an inconsistent sensitivity and specificity for the diagnosis of fibroids and other uterine abnormalities such as adenomyosis. In contrast, MRI has high sensitivity and specificity in diagnosing fibroids of all sizes, shapes, and locations and has the added benefit of revealing the vascularity of fibroids when gadolinium-based contrast is used. MRI with contrast is also beneficial in assessing the reduction of fibroid perfusion and size following UFE, both of which have been correlated with treatment success (Figure 7.1a).

Preprocedure care

Patients are asked to ingest nothing by mouth for the 6–8 hours prior to the procedure except for any scheduled medications that should be taken with only sips of water. Antibiotics are often given intravenously as prophylaxis, although the frequency of infections after UFE is very low and the efficacy of antimicrobial prophylaxis in preventing them is unknown. Intravenous hydration is given along with an intravenous antiemetic and anti-inflammatory for postprocedural comfort. In anticipation of moderate postprocedural pain, patient-controlled analgesia (PCA) with narcotics is commonly ready at the bedside once the procedure has ended. A Foley catheter is often placed for postprocedural comfort and to

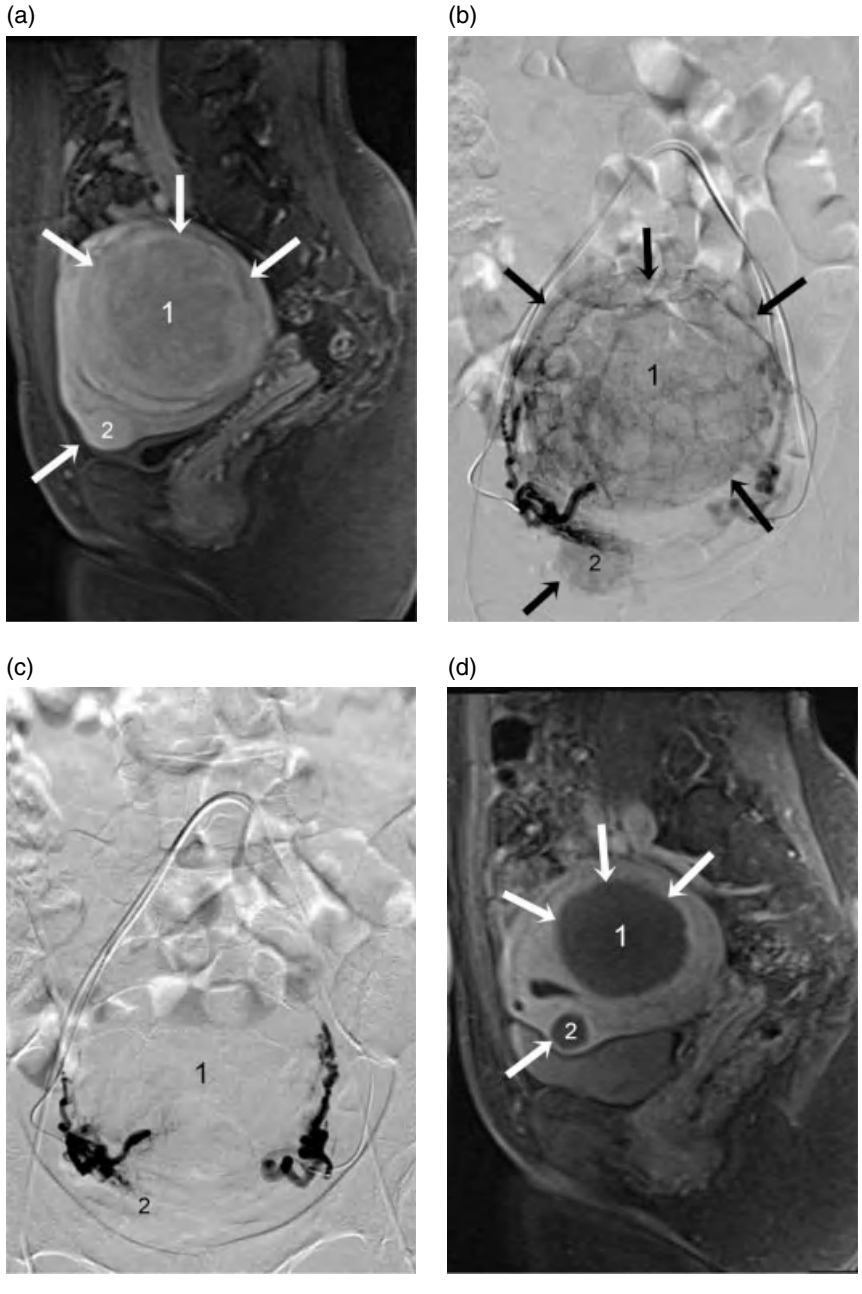

Figure 7.1 The patient is a 42-year-old woman with heavy menstrual bleeding and dysmenorrhea secondary to fibroids. (a) Sagittal view, T1-weighted contrast-enhanced MRI image showing one large fibroid (*arrows indicating margins of fibroid marked 1*) and one small fibroid anteriorly (*arrow indicating fibroid marked 2*). Both fibroids enhance with contrast as the fibroids are white, similar in intensity to the surrounding myometrium. (b) Initial angiographic frontal view image before embolization with bilateral simultaneous uterine artery injection, with arrows indicating the vessels and parenchymal blush of the fibroids. (c) Angiographic image of uterine arteries after embolization showing the main uterine arteries remaining patent but the fibroid branches occluded and the fibroid parenchymal blush gone. (d) Sagittal view, T1-weighted contrast-enhanced MRI image 3 months after uterine embolization. The fibroid residual tissue is now dark, the myometrium is normally enhancing and the fibroid tissue is significantly diminished in diameter. The patient's symptoms had completely resolved at the time of this follow-up visit.

minimize any field of view obstruction of the uterus during the procedure.

Technique

Uterine fibroid embolization is typically performed in a angiographic suite in a hospital setting. With the patient under moderate sedation, arterial access is gained from the patient's common femoral artery. Under fluoroscopic guidance, the catheter is advanced across the aortic bifurcation and into the contralateral internal iliac artery from which the uterine artery normally arises. The uterine artery is usually catheterized using a microcatheter and microwire. Once the catheter is in place in the uterine artery, arteriography is completed to visualize the arterial supply to the fibroid (Figure 7.1b). Embolic particles are then injected and are carried by the arterial flow to the fibroid vessels. The fibroid vessels are typically large and have high flow and the embolic is carried preferentially to those vessels. The embolization is completed once the blood flow in the uterine artery becomes sluggish, indicating distal occlusion of the fibroid blood supply. The uterine artery is not completely occluded (Figure 7.1c). This process is then repeated on the contralateral common femoral artery to obtain bilateral embolization. In nearly all cases, the fibroids receive blood supply from both uterine arteries. The entire procedure takes approximately 1.5–2 hours to complete.

SCIENCE REVISITED

The majority of the blood supply to the pelvis and inner aspects of the thighs is supplied by the internal iliac arteries, which then bifurcate to an anterior and posterior branch in most of the population. In approximately 51% of the population, the uterine artery is the first or second branch off the anterior division of the internal iliac artery. In 40% of the population, the uterine artery is a division that arises from a trifurcation of the internal iliac. Fibroids are fed almost exclusively by the uterine artery but may feature some collaterals that arise from ovarian arteries. In approximately 1% of the population, the uterine artery is absent and the major blood supply to the uterus is via the ipsilateral ovarian artery.

Postprocedure care

Moderate pelvic pain is the most common complaint immediately following the procedure, but pain can become severe without proper pain control. To avoid severe pain, a combination of intravenous ketorolac and narcotics is used. The narcotics are usually administered by a PCA pump. Pain typically lasts between 2 and 6 hours after the procedure and can be accompanied by nausea. Oral, rectal or intravenous antiemetics are administered as needed. Many patients will have relief of these symptoms by the evening of the procedure and may be considered for same-day discharge. If the procedure is performed with a goal of same-day discharge, it is imperative that pain be well controlled prior to discharge. In most centers, the patient is kept for an overnight 23-hour admission, during which pain and short-term complications can be better managed.

On the morning after a UFE procedure, the patient's pain is typically resolved or minimal and intravenous nonsteroidal anti-inflammatories and intravenous narcotics are replaced with their oral counterparts. Patients will likely have recurring mild-to-moderate cramping for 2–3 days. Fatigue and malaise for several days are common. Low-grade fever occurs in about a third of patients. Because there is inflammation in the fibroids, the patient should limit activity for several days to avoid cramping. Typically patients are given prescription nonsteroidal anti-inflammatories for 4–5 days. Oral narcotics are provided in the event of pain not being controlled by the anti-inflammatories. In addition to moderate cramping, constipation from decreased activity and diet and from the medications is common and either stool softeners or mild laxatives may be needed. A patient should expect to return to their normal daily activities within 7–10 days of the procedure.

Many patients can expect light vaginal bleeding or discharge for several days or weeks following the procedure. Occasionally, menstrual bleeding may be irregular for 2–3 cycles, but typically normalizes by the third cycle. Patients may also have vasomotor symptoms for some days to weeks after the procedure, but these usually resolve spontaneously. Patients can expect their fibroid symptoms to progressively improve over several months after the procedure, with 85–90% of patients experiencing symptom relief by the third month. On MRI, the fibroids become avascular and shrink (Figure 7.1d),

with a typical reduction of 40–50% in volume by 3 months after the procedure. Complete infarction of all the fibroids occurs in the large majority of cases and this correlates with an excellent clinical outcome long term.

Outcomes

Several large cohort and randomized trial studies have demonstrated the efficacy and safety of UFE. The EMMY (Embolization versus Hysterectomy) trial was a multicenter randomized controlled trial conducted in The Netherlands that compared outcomes between UFE and hysterectomy for the treatment of symptomatic fibroids. Symptom control and satisfaction with outcomes over the 2-year follow-up period were comparable between groups. Both groups featured at least 90% of participants who reported being moderately satisfied with their outcome (92% in UFE and 90% in hysterectomy), but the percentage of participants who reported being very satisfied with their outcome was higher in the hysterectomy group. Average hospital stay was significantly shorter for the UFE group compared to the hysterectomy group, with a mean stay of 2.5 days and 5.1 days respectively.

The REST (Randomized Trial of Embolization versus Surgical Treatment for Fibroids) trial was another multicenter randomized study conducted in the United Kingdom that placed participants in either a UFE group or a surgical group (hysterectomy or myomectomy, with 80% having hysterectomy). This study reported similar outcomes to the EMMY trial with both groups having comparable quality of life improvement and satisfaction with treatment outcomes. Symptom improvement was somewhat better with the surgery group, but the embolization patients had fewer major complications.

Recurrence of fibroids after embolization is possible and reintervention for any reason is more common after embolization than it is for hysterectomy. Reintervention was needed in 28% of patients in the EMMY trial by 5 years after therapy and the cumulative reintervention rate was 32% for UFE in the REST trial. Somewhat lower intervention rates have been reported in larger single-center studies, with 20–25% needing further interventions for recurrent symptoms due to either failure to completely treat all the fibroids at the first intervention or the development of new fibroids.

Complications

Several postprocedural symptoms, including mild-to-moderate pain, malaise, and low-grade fever, are common in the several days after UFE and should not be considered complications. This constellation of symptoms is sometimes referred to as postembolization syndrome and can be managed with analgesics and antipyretics. Patients presenting with more severe manifestations of postembolization syndrome may require a longer hospitalization following the procedure, and should be carefully evaluated for another explanation for their symptoms, including infection.

The Fibroid Registry, the largest study to have looked at adverse events following UFE, noted that the rates of major complications during the inpatient stay and first 30 days following the procedure were 0.66% and 4.8% respectively. The most common complication was severe pain requiring additional hospitalization. The mortality rate following UFE is practically zero with only a few case reports describing such an event.

Another more common complication following UFE is the passage or sloughing of an embolized fibroid into the uterine cavity, which occurs in approximately 2.2–7% of patients. Frequently the fibroid that is being passed is a large intracavitary fibroid or a large fibroid with a significant submucosal component. Fibroid passage commonly occurs between 3 weeks and 6 months after embolization and can present with pelvic pain, menstrual cramping with heavy bleeding, discharge, and actual passage of the fibroid. Fibroid passage is diagnosed when either a vaginal exam demonstrates tissue within the vagina and a dilated cervix or when MRI of the pelvis demonstrates necrotic fibroid tissue descending in the uterine cavity.

Based on case reports of mortalities, pulmonary embolism is the most common potentially fatal complication following UFE, with an incidence of 1 in 400 patients. The cause of pulmonary embolism in these rare cases is likely hypercoaguability induced by the embolization procedure, as the immobilization during hospitalization is only for a few hours. Prophylaxis for deep venous thrombosis and pulmonary embolism in patients who have undergone UFE includes the use of pneumatic leg compression devices and may include periprocedural prophylaxis with low molecular weight

CAUTION

A chronically sloughed fibroid that has not actually passed from the uterine cavity can cause increased chronic discharge that is a clear or watery mucus. Without intervention, a sloughed fibroid can become infected. If an impending fibroid passage is diagnosed and the fibroid fails to pass spontaneously from the uterine cavity in a reasonable amount of time or the patient shows signs of a superinfection of the fibroid, additional interventions may be necessary, including surgical extraction and antibiotic therapy. When the fibroid cannot be extracted, hysterectomy may eventually be required. This is the most common reason for hysterectomy for a complication after UFE and occurs in about 1 in 100 patients.

heparin in patients with a significant risk or history of thrombosis. Most pulmonary emboli after this procedure are small, but there have been anecdotal reports of several deaths due to pulmonary embolus, with the rate estimated to be 1 in 8000–10,000 patients.

Misembolization of nontarget organs, including superficial muscle and skin, bladder or other pelvic organs, is a very rare complication that may occur if proper technique is not followed. Misembolization typically occurs as a result of refluxed flow of embolization particles out of the uterine artery or via collaterals between uterine artery branches and the arteries of another organ. Misembolization can also occur to the ovaries, although this cannot easily be avoided. The tubal branches communicate between the uterine and ovarian arteries in many women and can allow passage of embolic material to the ovarian branches, disrupting blood flow to the ovaries. This can lead to a reduction in ovarian reserve and either transient or permanent amenorrhea. Transient amenorrhea is seen in up to 10% of women who undergo UFE, while permanent amenorrhea occurs in less than 5% of all women. However, the vast majority of women who experience permanent amenorrhea are perimenopausal and most studies have not demonstrated an impact on ovarian reserve in women under 40.

Uterine fibroid embolization and fertility

One important question that remains to be answered is whether uterine embolization will have an impact (good or bad) on a woman's ability to become pregnant and carry a pregnancy to term. There are few quality studies illustrating the effects of UFE on postprocedural fertility but the evidence to date suggests that myomectomy may be the preferred intervention when compared to uterine embolization for women planning on becoming pregnant.

One of the strongest studies to examine the effects of UFE on fertility is by Mara et al. (2008) who compared UFE with myomectomy in a randomized trial in 121 women wishing to preserve fertility during a 2-year period. The results of their study demonstrated that myomectomy is associated with a higher rate of pregnancy and successful delivery. Patients who were randomized to receive UFE had a higher risk of failing to become pregnant, not delivering, and having a spontaneous abortion. In the 2 years following their procedures, 78% of patients who had undergone myomectomy were able to become pregnant compared to 50% of patients who had undergone UFE. This study showed that UFE was associated with a greater risk of not becoming pregnant (relative risk (RR) = 2.22), not delivering (RR = 1.54), and spontaneous abortion (RR = 2.79) in the short term. Long-term data (>2 years) are not currently available.

Besides a concern for diminished pregnancy rates and increased miscarriage rate, there is concern that UFE can increase the risk of certain complications in future pregnancies. One retrospective study by Goldberg et al. (2004) compared 53 pregnancies after UFE with 139 pregnancies after myomectomy and demonstrated a higher risk of preterm delivery, malpresentation at delivery, and cesarean section in the UFE group. These results are not definitive, however, as these women were among the first treated with uterine embolization, had an average age of over 40 and most had had prior fibroid surgeries or cesarean sections. All these factors likely increased the risk of subsequent pregnancy.

The most likely cause or causes of decreased fertility following UFE have not been clarified, but several explanations have been given. One of the possible causes of decreased fertility following UFE is a

decrease in ovarian reserve. Decreases in follicle-stimulating hormone and antimullerian hormone following UFE indicate an average decrease in ovarian reserve, although the large majority of the data is in women in their mid to later 40s. Studies in women under age 40 have not shown such a change, although the literature is less extensive in this younger cohort. In addition, endometrial atrophy may rarely result following UFE and impair normal implantation and placental development. This uncommon secondary effect may be due to overembolization.

Conclusion

Based on current data, UFE is generally not recommended in women who wish to become pregnant. Women seeking treatment for their symptomatic fibroids who foresee a desire to become pregnant in the future should either attempt pregnancy prior to any interventions or have their fibroids removed via myomectomy. Patients who are not surgical candidates due to comorbidities or who have had prior myomectomy may be considered for embolization. The reproductive outcomes after repeated myomectomy are not good and UFE may be an appropriate substitute. It is clear that women can become pregnant after embolization and those who wish to undergo UFE despite their intentions of having future pregnancies should be informed of the uncertainty regarding pregnancy after UFE.

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8

Magnetic Resonance-Guided Focused Ultrasound Surgery Treatment for Uterine Fibroids

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Image-guided therapy

Image-guided thermal therapy, which encompasses the use of various tumor ablation techniques and imaging guidance, is one of the most rapidly expanding areas in the field of medicine. Tissue ablation usually occurs when a rapid thermal change is induced. Imaging is used to target the lesion for ablation and subsequently to assess treatment response. The ideal imaging technique should provide anatomical information about the target and surrounding tissues, and temperature feedback regarding the temperature reached within the target tissue. It should also confirm nonablative temperatures in surrounding tissue. Magnetic resonance-guided high focused ultrasound surgery (MRgFUS) is such an ideal tool. The currently used ExAblate 2000 (Insightec Inc., Haifa, Israel) is the first MRgFUS device, which received Food and Drug Administration (FDA) clearance for treatment of uterine fibroids in 2004. Since then, over 8000 patients have been treated worldwide for fibroid disease with this device.

Fundamental principles of magnetic resonance-guided high focused ultrasound surgery

Magnetic resonance (MR) imaging offers anatomical, functional, and thermal guidance during delivery of the focused ultrasound beam. The excellent anatomical resolution provided by MR imaging offers continuous imaging of the fibroid and adjacent structures (such as bowel, bladder, sacral nerves) during the treatment. Another big advantage of MR imaging is that it offers MR thermometry, in that MR imaging has the ability to measure the temperature elevations in tissue. This is because an increase in tissue temperature leads to an increase in Brownian motion of water molecules, which leads to a change in signal intensity in certain imaging sequences, which can then be measured. This temperature imaging occurs before, during, and after each sonication, to monitor the tissue temperature elevations within the targeted tissue. It also checks for inadvertent temperature deposition in surrounding nontargeted tissue.

The energy for treatment originates from multiple ultrasound transducer elements (phased arrays) arising from a spherically curved ultrasound transducer. The system focuses to a specific point within the body, with ultrasound waves being emitted in phase at the focal point of convergence, where there is substantial temperature increase (55–90°C). As a result, well-defined areas of protein denaturation, irreversible cell damage, and coagulative necrosis are produced, while overlying and surrounding tissues are spared.

As shown in Figure 8.1, the ultrasound transducer assembly is held within a sealed deionized water

Fibroids, First Edition. Edited by James H. Segars.

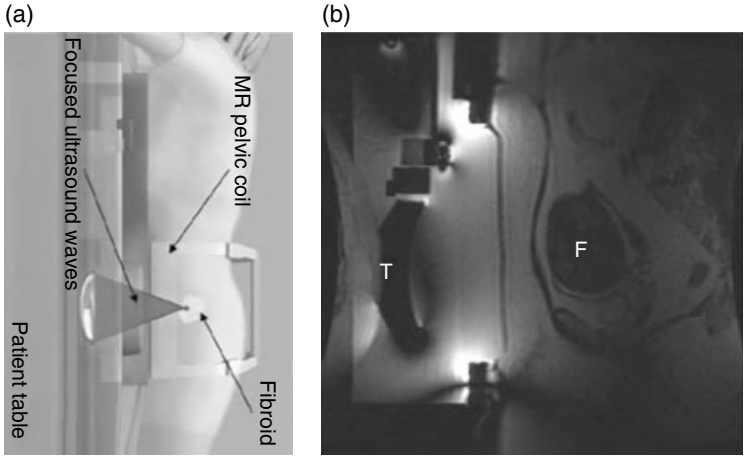

Figure 8.1 Overview of ExAblate 2000 device (Insightec Inc., Haifa, Israel). (a) Treatment diagram of MRgFUS. The patient lies in a prone position on the treatment table that contains the transducer. The transducer is contained within a sealed deionized water bath. A gel pad is placed between the window in the water bath and the skin of the anterior abdominal wall, to allow for acoustic coupling. The table is docked to the MR scanner. (b) Sagittal MR T2-weighted image before treatment. T, transducer; F, fibroid. Reproduced from Shen et al. (2009) with permission from Elsevier.

bath, which is housed within a specialized MR table that locks into position. A gel pad is placed on top of the sealed water bath, on top of which degassed water is poured. The patient then lies in the prone position over the gel pad, and acoustic coupling between the skin of the anterior abdominal wall and the transducer is obtained.

Patient selection for treatment

Patients with symptomatic fibroids referred for MRgFUS treatment undergo a screening evaluation in order to ensure their suitability for the procedure. Women in good general health and with clinically symptomatic uterine fibroids are eligible for screening. The goals of the screening are to select suitable candidates who can be safely and effectively treated with MRgFUS. Patients are screened through a full history, physical examination, and fibroid symptom review. Fibroid symptomatology is usually assessed through use of a previously validated questionnaire such as the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire. This is a useful, relatively objective tool for assessing the extent of fibroid symptoms and is important for establishing a baseline symptom level before the procedure, and for postprocedure monitoring of response to therapy.

On physical exam, particular attention is paid to the skin of the anterior abdominal/pelvic wall to evaluate for scar tissue. Patients with severe health problems, severe claustrophobia, pregnant patients, those who are unable to lie prone on the MR table for about 3 hours or those who do not have the ability to communicate during the procedure should not be treated. Candidates need to be screened for MR contraindications, such as berry aneurysm clips or a cardiac pacemaker.

As part of the screening process, a pelvic MRI is subsequently scheduled. This imaging is obtained with the patient in the prone position, if possible, to allow her to experience the position she will be in on the day of treatment. If at all feasible, it is also helpful for the patient to be screened in the magnet (or a similar magnet) in which she will be treated, as magnets have different bores (widths) and different lengths. Other than the prone positioning of the patient, the preprocedure MRI follows a routine pelvic MR protocol: multiplanar T2-weighted imaging (WI) and T1-WI before and after contrast (gadolinium chelate) administration. The MR

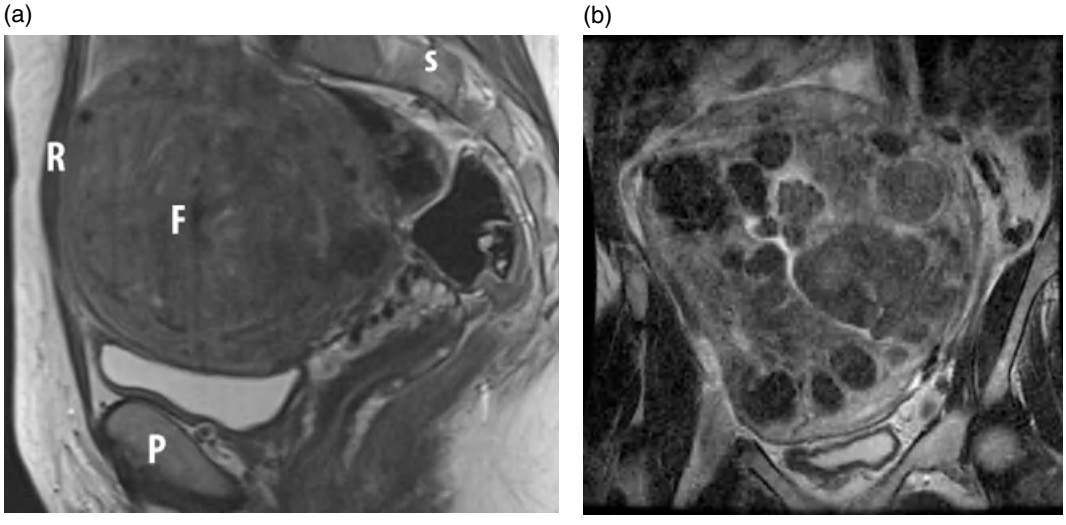

Figure 8.2 Ideal candidate for MRgFUS (a) and example of a candidate who is not ideal for MRgFUS (b). (a) Sagittal T2-weighted MR image demonstrating a fibroid (F) of moderate size, and of intermediate to low signal intensity. The uterus lies just posterior to the anterior abdominal wall. F, fibroid; S, spine; P, pubic bone; R, rectus abdominis muscle. (b) Coronal T2-weighted MR image demonstrating innumerable fibroids (well-defined areas of low signal (dark) and intermediate signal) of varying sizes throughout the uterus. It is difficult to determine which fibroid is most symptomatic to target, and not possible to target all in one treatment sitting.

images confirm the diagnosis of uterine fibroids and exclude other causes for the patient's symptoms (such as adenomyosis). The number, size, location, signal intensity, and enhancement characteristics of the fibroids are recorded. Other than fibroid evaluation, the screening MR allows for evaluation of anterior abdominal wall scarring and the location of this scarring relative to the position of underlying fibroids. It also allows for evaluation of the position of uterus relative to coursing anterior bowel loops, and evaluates how close a fibroid lies to the sacrum and exiting nerve roots. MR also evaluates the thickness of subcutaneous tissue of the anterior abdominal wall and distance from the skin to the uterine fibroid being targeted. Intrauterine devices should be identified and removed prior to treatment, to prevent heating.

An ideal candidate for MRgFUS has up to three fibroids, moderate in size (4–6 cm), of low signal intensity on T2-WI, which can be safely accessed with the ultrasound beam (Figure 8.2). A single dominant fibroid of 10 cm or less can also be treated in one sitting. Fibroids that are located anteriorly in the uterus are usually easier to treat compared to fibroids located within the posterior uterus. This is because there are system limitations regarding the maximal distance that the beam can travel, such that very posterior fibroids may not be reached or may be only partially treatable. If the distance from the skin of the anterior abdominal wall to the center of the fibroid is greater than 12 cm, the fibroid is considered too posterior. There should be no coursing anterior bowel loops, and no overlying scar tissue within the skin of the anterior abdominal wall. It is possible to treat through a fluid-filled bladder but any gas pockets within the bladder (from instrumentation) must be carefully examined for, as must the position of the Foley catheter within the bladder, and avoided by the beam path to prevent heat build-up within the bladder wall.

Challenging candidates

There are many factors that can limit the amount of treatment of uterine fibroids, and these are outlined in Table 8.1, as are some possible solutions.

Patients with numerous small (<3 cm) fibroids may not be suitable for treatment, due to the

Table 8.1 Limiting factors for fibroid treatment with MRgFUS, and possible solutions

Factor	Limitation	Possible solution
Fibroid size		
Too big	If >10 cm, will result in small nonperfused volume and poor outcome	Pretreat with GnRH agonist
Too small/multiple	Cannot treat all in one session	More than one treatment session
Fibroid location		
Too posterior	Fibroid tissue >12 cm from skin of anterior abdominal wall cannot be reached	Use of thinner gel pad
	≤4 cm from sacrum, may result in heating and nerve injury	Change in beam path such that exiting beam is >4 cm from bone
Fibroid characteristics		
Calcified fibroid	Calcifications interfere with beam propagation	None
High signal on T2-WI	Due to high cellular content it is difficult to obtain high treatment temperatures	Possible role for GnRH agonist
Degenerated fibroid	Areas of nonperfusion pre-treatment; poor effect with MRgFUS	None
Poor acoustic window		
Intervening bowel loops	Small acoustic window to avoid visceral damage	Use of gel pad to push bowel loops superiorly; change beam pathway
Anterior abdominal wall scarring	Interferes with beam propagation; may result in skin burn	Change beam pathway

difficulty in planning and targeting multiple ablations to innumerable fibroids (see Figure 8.2), which would be more conclusively treated with other fibroid treatment options, such as uterine artery embolization. In patients with large uterine fibroids (>10 cm or thereabouts), we advise pretreatment with a gonadotropin-releasing hormone (GnRH) agonist. By interference with the hypothalamo-pituitary-ovarian axis, a GnRH agonist will result in a reduction in size of the fibroid, allowing for a more manageable treatment within a defined period of time. In addition, because GnRH agonists decrease the vascularity of fibroids, it has been found that the response to individual sonications post treatment with GnRH agonist is in fact greater, with an average of 50% larger area of tissue destruction per unit of energy applied. Because GnRH agonists potentiate the effects of MRgFUS, we also consider pretreatment of patients with fibroids that are bright on T2-WI on MR imaging (indicative of highly cellular fibroids, which are usually difficult to treat).

☆ TIPS & TRICKS #1

Treatment of large fibroids

In cases of patients with large (>10 cm) fibroids, pretreatment with a GnRH agonist is recommended. A GnRH agonist pretreatment shortens treatment times and increases treatment efficiency. Pretreatment with GnRH agonists causes a reduction in size of the fibroid, allowing for a more manageable treatment within a defined period of treatment time. GnRH agonists also decrease the vascularity of fibroids. Subsequently, response to individual sonications post treatment with GnRH agonist is greater, with an average of 50% larger area of tissue destruction per unit of energy applied. The GnRH agonist is given at day 1–2 of the menstrual cycle, and is repeated at monthly intervals (for 3 times in total). MRgFUS is then performed close to a month after the third injection, in order to get the maximal shrinkage effect before MRgFUS treatment.

Patients with predominantly submucosal or predominantly subserosal, pedunculated fibroids with a narrow stalk of attachment are not suitable for MRgFUS treatment, due to the risk of subsequent sloughing into the uterine cavity or detachment from the uterine wall. Because of system limitations of targeting tissue greater than 12 cm from the skin of the anterior abdominal wall, obese patients may be problematic. The use of a thinner gel pad may help in some situations.

Magnetic resonance-guided focused ultrasound procedure

Preprocedure preparation

The night before the procedure, patients are instructed to shave any hair from the skin of the lower anterior abdominal wall to the pubic symphysis, and are asked not to use any creams or oil on the skin after showering. These are all precautionary measures to prevent heat build-up in the skin at treatment. Patients are also asked to fast from midnight, as they will receive intravenous conscious sedation (IVCS). After obtaining an informed consent for both IVCS and the treatment procedure, a negative urine pregnancy test is confirmed. A Foley catheter is placed to drain the urinary bladder to prevent uterine motion due to bladder filling. Before the procedure begins, the patient's lower abdominal wall skin is carefully examined for scars. If present, these must be noted on the treatment planning MR images.

CAUTION #1

Contrast-enhanced MR imaging necessary prior to deciding on treatment

An MR imaging study is necessary firstly to confirm the presence of uterine fibroids but also to confirm the presence of enhancement within the fibroids (autoinfarcted/nonperfused fibroids will not benefit from MRgFUS ablation), and to confirm absence of calcification (which will deflect the ultrasound beam and cause heat build-up in nontargeted areas). The signal intensity on T2-WIs is also important to consider: those that are of low signal intensity are usually treatable, whereas those that are of high signal intensity on T2-WIs (indicative of highly cellular fibroids) are often difficult to obtain sufficiently high therapeutic temperatures in. Consider pretreating with GnRH agonist.

The patient is then brought to the MR suite and is positioned on the MR table in a prone position, such that the skin overlying the lower anterior abdominal wall overlies the gel pad (see Figure 8.1). Monitoring leads for oxygen saturation and heart rate are attached to the patient, and titrated doses of fentanyl and midazolam are used to reduce patient positional discomfort, procedure-related pain and anxiety, and to minimize motion during the procedure. The patient does, however, need to remain responsive throughout the procedure.

Treatment planning

Localizing images are first obtained to check that the patient is positioned correctly, such that the fibroid to be treated is accessible by the ultrasound transducer. The patient is repositioned accordingly until in a satisfactory position. T2-WIs (which give best anatomical detail) are obtained in coronal, axial, and sagittal planes. These images are used to outline the uterus, fibroid(s), adjacent bowel loops, bladder, and spine. It is important that the patient does not change her position once the planning T2-WIs have been obtained.

CAUTION #2

Always check for abdominal wall scarring!

Laparotomy or visible laparoscopic scars should always be looked for on the patient's skin, and also on MR imaging prior to starting treatment. Scar tissue absolutely needs to be avoided. Do not rely on patient feedback regarding lack of pain in regions of scar tissue as these areas may be denervated. Check thermal maps that cover the skin area regularly throughout the treatment to look for inadvertent heat build-up.

The treatment volume is selected based on these images and is manually outlined by the treating physician on coronal imaging, and displayed on sagittal and axial imaging also. Software in the system places sonication spots within the outlined treatment area, and the ultrasound beam pathway to the targeted fibroid is displayed. The beam pathways are carefully examined to ensure no bowel loops are traversed. The low-energy exiting beam

pathway is also examined to ensure it is within a safe margin of the sacral nerve roots. Should any beam pathways involve bowel loops or scar tissue, or exit too close to adjacent spine such that they would have an undesirable effect on energy deposition, the sonication spots can be moved or deleted. Or if necessary, the transducer can be angled such that the sonication beam enters through a different pathway but converges on the same point (Figure 8.3). To avoid treating bowel loops, an alternative pathway for the beam is selected. Where this is not possible, an attempt can be made to push the bowel loops in a superior direction and out of the beam path, using a thicker gel pad (see Figure 8.3).

☆ TIPS & TRICKS #2

Coursing bowel loops anterior to the uterus

If bowel loops are seen to course anterior to the uterus on the MR screening study, the distance from the anterior abdominal wall to the uterus should be taken into consideration when trying to decide if the bowel loops are negotiable. For example, if the uterus is posteriorly positioned within the pelvis, with multiple loops coursing anterior to it, the patient is not a good candidate for MRgFUS. However, if the uterus is in close proximity to or abutting the anterior abdominal wall, with a short section of bowel abutting part of the anterior surface of the uterus, the patient is likely treatable. On treatment day, the patient should be scanned with short localizer sequences to determine where bowel is. A thicker gel pad may be used to displace bowel loops superiorly (although keep in mind that this adds to the distance necessary for the beam to travel through, so may not be possible in obese patients), or the angle of ultrasound beam may be tilted to avoid the bowel loops entirely. Distension of the urinary bladder is another option to displace bowel loops superiorly, out of the beam path.

An initial low-energy test pulse (50–100 W) is delivered to a spot within the target volume before commencing the therapeutic sonications. The non-therapeutic slight temperature increase induced by this low-energy test pulse can be detected with MR imaging (using a fast spoiled gradient echo sequence). The location of the tissue temperature increase is then used to precisely align the MR images and the ultrasound beam co-ordinates. Once this is confirmed, treatment can begin.

Magnetic resonance-guided focused ultrasound treatment

The power of the sonications is gradually increased until a therapeutic thermal dose is achieved to coagulate the entire volume of tissue at temperatures over 60°C. In between each sonication, adequate cooling time is allowed to avoid thermal build-up. The temperature-sensitive images and dose distribution maps are displayed within seconds of completion of each sonication. The thermal maps are constantly reviewed to confirm adequate temperature elevation in the targeted area, and to determine if additional sonication spots need to be placed to complete dose coverage of the targeted volume.

Throughout the treatment, the patient is encouraged to make the treating physician aware of any heating or burning sensations she may feel in the anterior abdominal wall, buttocks or perineal region, or of any shooting pains down the legs. While this is important in all patients, it is particularly important in those who have scarring of the anterior abdominal wall, which may cause the ultrasound beam to become unfocused. Should this occur, the sonication beam pathway can be altered and/or the sonication power can be adjusted accordingly.

☆ TIPS & TRICKS #3

Patient comfort during treatment

Adequate analgesia is very important, while at the same time allowing for patient feedback regarding any heating or burning sensations. It is necessary to ensure that the patient has the "stop sonication" button in her hand during the treatment, to allow her have some control and terminate a painful sonication. A medical staff member (usually a nurse) should either stay in the MR suite with the patient or enter the treatment room every 10 minutes to ensure the patient is comfortable.

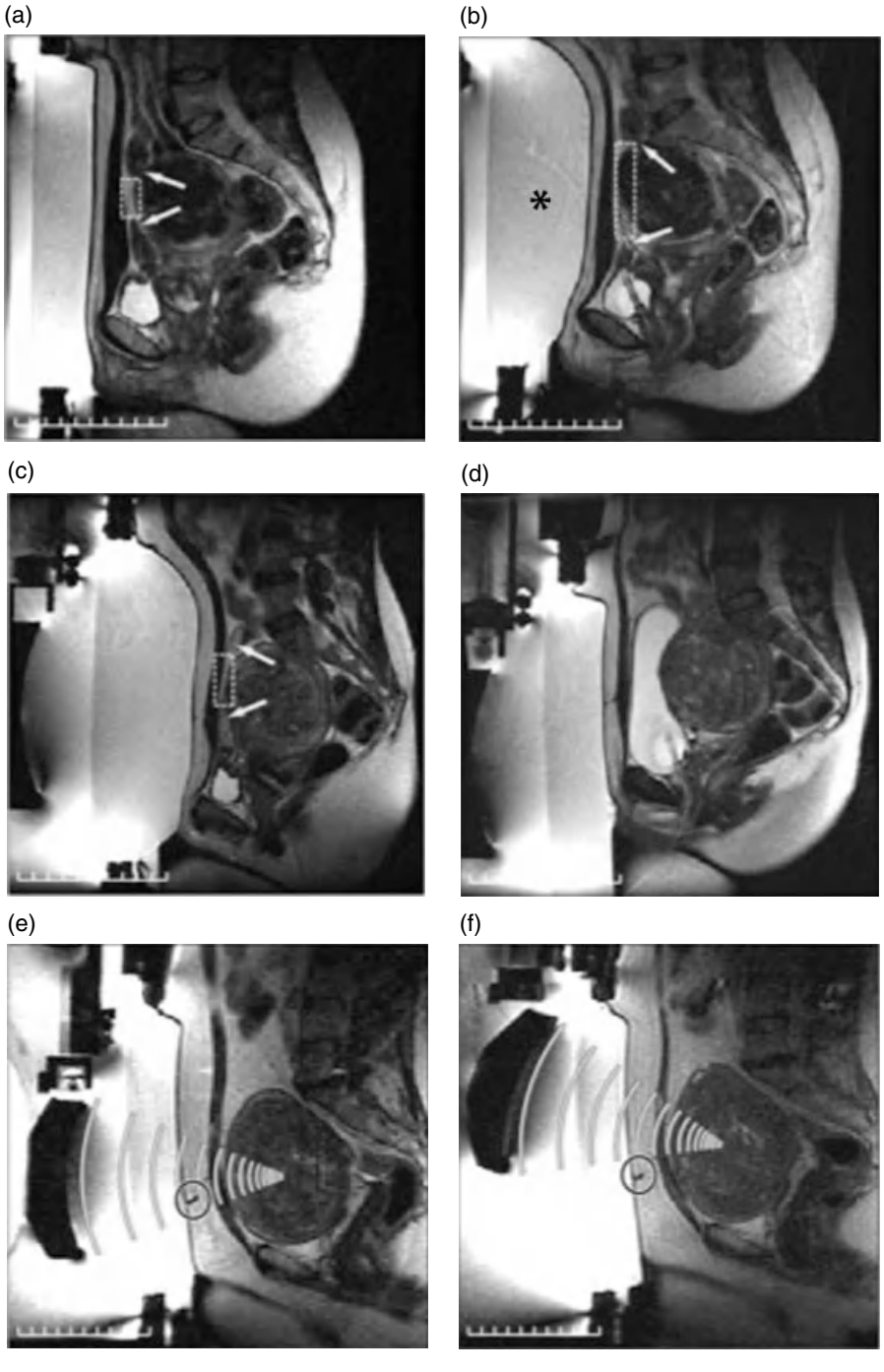

Figure 8.3 Challenging treatment planning scenarios. (a) In this patient, bowel loops in front of the fibroid (*arrows*) initially reduce the acoustic window (*box*). (b) To move these loops aside, a larger gel pad is placed below the abdomen (*), increasing the acoustic window, and allowing most of the fibroid to be accessible. (c) In another patient, even with this larger gel pad, bowel loops in front of the fibroid (*arrows*) still severely limit the acoustic window (*box*). (d) Normal saline is instilled into the urinary bladder via a Foley catheter, which displaces the bowel loops and creates a much larger acoustic window. (e) The third patient has a scar directly in front of the fibroid (*circle*). (f) By tilting the ultrasound beam, the scar can be avoided. Reproduced from Shen et al. (2009) with permission from Elsevier.

Throughout the procedure, patient motion should be constantly monitored for, and the patient should be reminded not to move. If motion is suspected, MR imaging co-ordinates on the current images can be compared to the planning T2-WIs to determine if sufficient motion has occurred to necessitate sonication pathway replanning.

The goal of the treatment is to achieve maximal tissue coagulation within the fibroids, using sufficient thermal dose, without causing patient discomfort. Typically, the entire treatment takes 3 hours (room time) depending on fibroid size, location, number, and patient co-operation. The procedure may be terminated prematurely due to targeting difficulties, patient motion or complaints of intractable pain.

At the end of the treatment, post-treatment T1-WIs are acquired after administration of intravenous gadolinium chelate, to assess the treatment effect. The area of tissue necrosis within the fibroid appears as an area of nonenhancement (Figure 8.4). In cases of remaining significant volume of untreated tissue, a second MRgFUS treatment can be scheduled in a 2–4-weeks interval following the first treatment. Patients are observed for 1–2 hours after treatment. Before discharge, the skin of the lower anterior abdominal wall is examined, to evaluate for any possible heat-induced changes. Patients can resume their routine activities within 24 hours of treatment.

There have been recent technical improvements to reduce treatment time and simultaneously increase treatment volume. One such improvement is "interleave mode" whereby the order of the sonications is predetermined to minimize any overlap between individual sonications, thereby preventing build-up of heat in the sonication pathway. The cooling time between sonications can therefore be reduced, and subsequently treatment time is reduced. Another improvement is "enhanced sonications" whereby high-power bursts of energy are used, which generate microbubbles that result in greater energy absorption at the spot location. This is compared to the continuous power transmission that was used in the MRgFUS clinical trials, where a focal spot is gradually heated over 20 seconds. As the energy absorption is greater with enhanced sonications, the volume of tissue ablated per sonication is much greater, thus reducing treatment time.

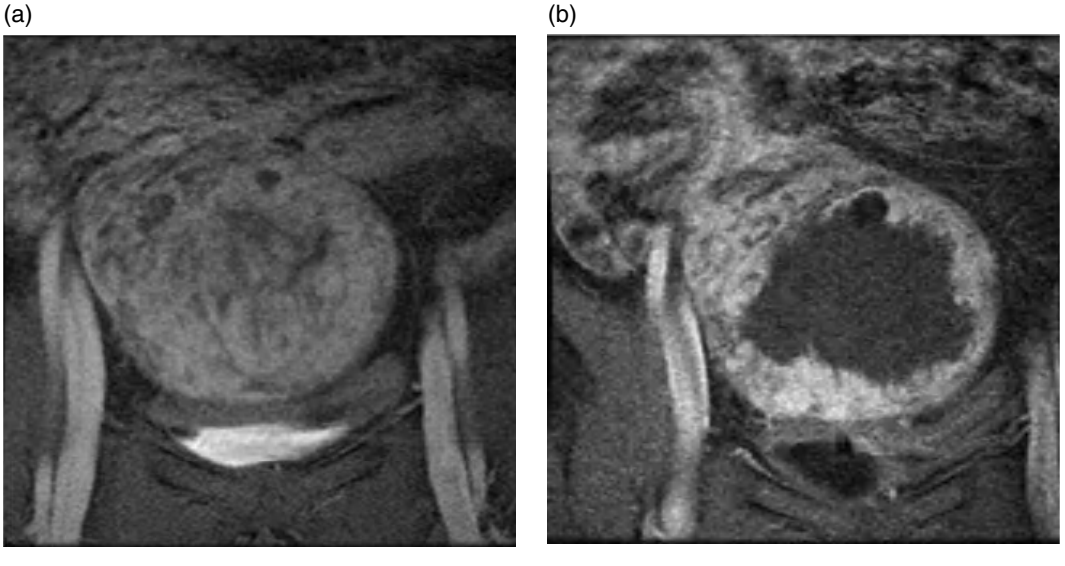

Figure 8.4 Magnetic resonance images of a uterine fibroid before (a) and after (b) MRgFUS treatment. (a) Coronal image post IV contrast with gadolinium chelate at screening demonstrates diffuse enhancement of the uterine fibroid. (b) Coronal image post IV contrast with gadolinium chelate immediately after MRgFUS treatment demonstrating a large area of nonenhancement in the region of thermal ablation.

Side-effects of treatment

The rate of side-effects with MRgFUS fibroid treatment is low. The most common side-effects seen are transient abdominal pain related to sonications and position-related discomfort within the magnet. Other possible transient side-effects include urinary discomfort (usually secondary to the catheter insertion) and nausea (usually secondary to IVCS). There has been a case of sciatic nerve palsy that resolved of its own accord, thought to be due to absorption of energy by bone in the far field, and subsequent transfer of heat to the adjacent nerve. Measures have been taken subsequently to prevent such an event, such that fibroid tissue lying within 4 cm of the anterior spine cannot be treated. Other superficial skin burns in addition to a case of a full-thickness abdominal skin burn were reported early in the learning curve process of this technology, underscoring the need for careful examination of the skin of the anterior abdominal wall and avoidance of scar tissue.

Symptom improvement

Relief of fibroid-associated symptoms is usually apparent by 3 months post therapy. Initial results of the phase I/II trial of the ExAblate 2000 device were published in 2003 and showed the device to be feasible and safe, through pathological correction with hysterectomy specimens. Subsequent to this, results of a multicenter phase III clinical trial published in 2007 evaluated patients who were treated with restrictive and less restrictive protocols, and found that those treated with a less restrictive protocol had a greater area of nonenhancement immediately after treatment (25.8% nonenhancement as a percentage of total fibroid load, versus 16.7% in those treated with the more restrictive protocol), with 91% of those treated with the less restrictive protocol reaching a significant decrease in symptomology, versus 73% of the original group. The importance of obtaining as large an area of nonperfusion as possible after treatment has been echoed in many subsequent studies, as a large area of nonperfusion is necessary for sustained symptom relief, and has been shown to be associated with a much lower chance of needing additional fibroid therapy.

Magnetic resonance-guided focused ultrasound and fertility

The FDA labeling of the ExAblate 2000 is for fibroid treatment in women "who should have completed child bearing." However, there have been many reports of anecdotal pregnancies, including a report of 54 pregnancies with a high rate of delivered pregnancies. While a role for MRgFUS in treating uterine fibroids in women with unexplained infertility has yet to be determined, it is reassuring that term pregnancies can be achieved in a substantial percentage of women conceiving after MRgFUS treatment of uterine fibroids.

Conclusion

Although feasibility studies and multicenter clinical trials have shown MRgFUS to be an effective treatment option for symptomatic uterine fibroids that produces long-term relief, MRgFUS must be deemed as beneficial as established alternatives to be widely accepted. There have been no randomized controlled trials to date comparing MRgFUS to alternative options. MRgFUS needs to be evaluated with respect to patient preferences for treatment and outcome of treatment with regard to quality of life, offset against the cost of treatment, both to the individual and healthcare system/society as a whole. Cost–utility analysis is an integral part of this new technology assessment. It has been shown that fibroid utility values increase after MRgFUS treatment, and that perceived patient morbidity for the noninvasive MRgFUS treatment option is far less than that for hysterectomy, indicating a patient preference for MRgFUS. In addition, retrospective decision analysis modeling has been performed to compare MRgFUS to hysterectomy, myomectomy, and uterine artery embolization treatment options; these studies have concluded that a treatment strategy starting with MRgFUS for fibroid treatment is likely to be cost-effective.

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9

Minimally Invasive Treatment Options for Uterine Fibroids

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Introduction

Minimally invasive gynecological surgery (MIGS) broadens the clinician's therapeutic options for the treatment of fibroids. It is easily adaptable to different situations and creative use can provide individualized treatment. Advantages of minimally invasive surgery for treatment of fibroids are avoidance of hospitalization, rapid recovery, and reduction in some complications, such as formation of adhesions following surgery. For some minimally invasive approaches, such as hysteroscopic and laparoscopic resection of fibroids, sufficient data and experience suggest outcomes are equal to or surpass standard surgical approaches for treatment of uterine fibroids. In this chapter, we review evidence regarding minimally invasive approaches, especially as it relates to treatment of uterine fibroids. In addition, we review some important procedural considerations for the application of minimally invasive approaches relevant to the surgical treatment of women with uterine fibroids.

Hysteroscopy

Hysteroscopy was first used in 1869 by Panteleoni using a urethroscope (Batra et al., 2004). Today hysteroscopy is an integral part of both diagnosis and treatment. The hysteroscope is easily adaptable to both the office and the operating room. An office set-up can consist of either a flexible or rigid scope. An endometrial biopsy can be done concurrently to provide pathological diagnosis. An ultrasound may be used before, during or after an office hysteroscopy to provide critical information regarding fibroid size, type, and location, thus aiding in further surgical planning as needed. Ideally, women should be days 6–11 of their menstrual cycle, or on a hormonal contraceptive, which will also help to minimize endometrial thickness.

Rigid hysteroscopes

Rigid hysteroscopes range in size from 3.5 mm mini-hysteroscopes (outer sheath diameter), 4 or 5 mm Bettocchi hysteroscopes, to large operative hysteroscopes at 8–10 mm diameter or 24–31 French (Fr). French measurement corresponds to the circumference in millimeters. Conversion between diameter and circumference is done by multiplying the diameter by π (3.14). Three different optics are routinely used: 0°, 12°, and 30°. A 30° degree hysteroscope is best used for evaluation of the cavity because the entire cavity can be assessed with minimal torque on the cervix. This is accomplished by using the light cord to rotate the operating lens. To maintain orientation, the view of the lens is opposite the light cord (i.e. when the light cord is pointing down, the view is toward the anterior aspect of the uterus).

Flexible hysteroscopes

Flexible hysteroscopes are considered ideal for office hysteroscopy due to their small size (3 mm) and the flexibility of visualizing irregular cavities, as

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the visualization angle ranges up to 120–160°. The smaller diameter allows for easier navigation through the cervix, especially with significantly anteflexed or retroflexed uteri. Flexible hysteroscopes are limited in that they do not have instrument ports for treatment options. Furthermore, the fiberoptics provide inferior image quality compared to rigid hysteroscopes.

☆ TIPS & TRICKS #1

Hysteroscopy basics

- Patient selection and expectation
- Bimanual exam
- No blind entry > hysteroscopic visualization of the cervical canal and internal os
- Use of cervical ripening agents
- Visualize all intracavitary landmarks
- Use 30° optics
- Fluid status
- Preoperative Na^+

Office hysteroscopy

Traditionally, office hysteroscopy was confined to diagnostic procedures. With the development of smaller caliber rigid hysteroscopes that accommodate instruments, there has a move to performing more procedures in the office. Additionally, the development of a bipolar electrosurgery system (Gynecare VersaPoint®) that can navigate through the 5 Fr operating channel has increased the number of pathological conditions that can be treated in the office (Di Spiezio Sardo et al., 2010). The operative and pathological diagnosis of uterine fibroids using office-based procedures has been shown to be equal to that of outpatient operating room procedures.

☆ TIPS & TRICKS #2

Office hysteroscopy

- Use normal saline if possible
- 500 cc or 1 L bag elevated or as a pressure bag
- Limited inflow
- Consider preoperative misoprostol (200–400 μg vaginally 10–12 hours preoperatively)

Numerous studies have shown significant advantages of office procedures in terms of reduced anesthesia risks, improved cost-effectiveness, faster recovery, and shorter convalescence (Di Spiezio Sardo et al., 2010). Despite this, many providers hesitate to perform office procedures because of procedural discomfort and concern about access to complex care facilities in the event of a serious complication. With proper patient selection and appropriate pain management, however, office-based operative hysteroscopy may be provided. In general, patients with chronic pelvic pain, anxiety or previous cesarean section, or postmenopausal women have an increased incidence of procedural pain (Cicinelli, 2010). Appropriate preprocedural discussion with the patient is essential.

Bettocchi et al. (2002) advocate operative office hysteroscopy on fibroids that are less than 2 cm if entirely intracavitary (type 0) or less than 1.5 cm if an intramural component exists (type 1), using a decreased current setting. It is best to begin with patients at low risk for pain, treating small type 0 submucosal fibroids. With increased experience of the surgeon and support staff, the size and difficulty can be increased.

Procedure

The vaginoscopic approach to the uterus has been shown to provide the least painful access. This technique involves introducing a 30° hysteroscope into the vagina without the use of a speculum or a tenaculum. The hysteroscope is introduced with the distending media flowing to fill the proximal vagina and cervix. Utilizing the hysteroscopic optics, the cervical os is located and navigated to gain access into the uterus. This simple technique is easily learned in the operating room and can then be introduced into the office setting. This approach may not be appropriate with severe uterine ante- or retroflexion.

In addition to a vaginoscopic approach, preprocedural analgesia has been shown to be effective in outpatient endometrial ablations (Marsh et al., 2005). Ibuprofen 600 mg is started the night before the procedure, repeated 1 hour prior to the procedure and again 4 hours after the procedure. Provided there are no contraindications to non-steroidal anti-inflammatory drugs (NSAIDs), this approach provides satisfactory analgesia for most office procedures.

The paracervical block has been the gynecologist's mainstay for local anesthesia. While this does provide anesthesia for cervical manipulation, the actual injection is the most painful part of the procedure (Chudnoff et al., 2010), so some surgeons reserve the method for patients with increased risk of pain (cervical stenosis, etc.). The recommended technique is injection of 5 cc of 1% lidocaine at both the 4 and 8 o'clock positions at the cervical–vaginal interface and confirming with aspiration that injection is not intravascular. To further ensure that lidocaine has not been injected intravascularly, verbally confirm with the patient that she is not experiencing ringing in the ears or a metallic taste. If so, stop the injection, monitor her pulse and then once the symptoms have passed, the lidocaine injection can proceed. Utilizing 1 mL of 1% lidocaine on the anterior lip of the cervix has also been shown to decrease the pain associated with tenaculum placement. Along with preoperative ibuprofen and moderate saline flow, the majority of patients can be accessed with minimal discomfort without the use of a paracervical block. The use of 2% lidocaine jelly has not been shown to decrease the pain of diagnostic hysteroscopy.

Preoperative preparation

Fifty percent of hysteroscopic complications occur with cervical entry and include cervical tears, false tracks, and uterine perforation. The use of a preoperative cervical ripening agent may reduce hysteroscopic complications. Traditionally laminaria have been used but are contraindicated in women with shellfish allergies, can be difficult to insert with cervical stenosis, and require that the patient be seen in the office for administration.

Cytotec or misoprostol is a synthetic prostaglandin E1 analog that has been used in gynecology. Pharmacokinetics demonstrate that vaginally administered misoprostol peaks in approximately 1 hour. The vaginally administered drug persists for at least 6 hours at substantially higher levels than the oral or sublingually administered drug. In nonpregnant women, 200–400 μg given vaginally 10–12 hours preoperatively has been found to be an effective regimen. Doses higher than 400 μg were not shown to have any significant improvement in cervical dilation and the longer preoperative interval between misoprostol administration and surgery was found to improve effectiveness (Choksuchat, 2010). The use of misoprostol in postmenopausal women has not shown the same benefit as in premenopausal women. Since there is also decreased response to misoprostol in women receiving gonadotropin-releasing hormone (GnRH) analogs, it is theorized that the estrogen receptors in the cervix are important to the prostaglandin response of the cervix to misoprostol. Side-effects of nausea, vaginal bleeding, and diarrhea are common. Because of these side-effects, routine use of preoperative misoprostol is not recommended, but women with a history of cervical stenosis, nulliparity, or cesarean section may be good candidates.

EVIDENCE AT A GLANCE #1

Hysteroscopic fibroid classification system

- Type 0 (pedunculated)
- Type 1 (<50% submucosal)
- Type 2 (>50% submucosal)

Hysteroscopic myomectomy

Submucosal fibroids are most amenable to a hysteroscopic surgical approach (Plate 9.1). Although the initial impulse is to separate the fibroid by incising the attachment, this should be avoided as the retrieval and removal of the fibroid can then become quite challenging. Submucosal fibroids can have a significant amount of intracavitary volume. Standard surgical principles apply with visualization being of utmost importance. Debulking the fibroid initially using a resectoloop or an ablation bar, if saline is used, can aid in the resection. The advantage of the ablation bar is the lack of chip debris. The rigidity of the bar also helps to locate and delineate the margin of the fibroid. Intravasation can be minimized if the intracavitary fluid pressure is less than or equal to the mean arterial pressure (MAP). Pressures greater than 70 mmHg will cause fluid to leak into the peritoneal cavity since this pressure exceeds the tubal pressure.

☆ TIPS & TRICKS #3

Intracervical vasopressin for deep fibroid resection

- 20 U vasopressin in 100 cc injectable saline
- Deep stromal injection at 4 and 8 o'clock positions
- Avoid intravascular injection (blood flashback at injection)
- Observe for bradycardia, hypertension

With type 2 and some large type 1 fibroids, concurrent use of transabdominal ultrasound can help delineate fibroid planes and confirm the complete removal of the fibroid. When resecting large type 1 and 2 submucosal fibroids, intracervical injection of vasopressin prior to removing the embedded portion of fibroid and then every 30–45 minutes can help decrease intravasation. This technique involves injecting dilute vasopressin with a 20 gauge spinal needle at the 4 and 8 o'clock positions deeply into the stroma. Care must be taken to avoid vascular injection and to inform the anesthesiologist prior to injection. Once the margin between the uterus and the fibroid has been developed and portions of the fibroid resected, the planes may become less clear. By removing all instruments and distending media and waiting approximately 10 minutes, the uterus will often help extrude the fibroid and continued resection will be possible. Patient expectation is important. When approaching large fibroids, it is important to make sure that patients know that multiple surgeries may be required. Ideally, this should occur after the next menstrual cycle or if on contraception, within a month.

CAUTION #1

1. Maximal fluid deficit at hysteroscopy
   - 2 L saline
   - L hypo-osmolar fluid
2. Do not use laminaria in women with a seafood allergy

In situations where there has been extensive resection, it is important to consider the possible postoperative development of intrauterine synechiae. This can be addressed by performing an office hysteroscopy within a week or two of surgery. The fluid will often break down any filmy adhesions that may have developed. Other approaches are to use postoperative estrogen followed by progesterone, the insertion of a pediatric Foley (7 Fr) or an intrauterine device (IUD). Multiple hormone regimens exist but none has been studied for superiority. In general, the use of 2.5 mg conjugated equine estrogen daily for 30 days with the addition of 10 mg medroxyprogesterone acetate concurrently for the last 10 days is a common regimen. The surgeon must bear in mind the risk of deep vein thrombosis and pulmonary embolus, as well as gastrointestinal symptoms, when using hormone therapy. Studies evaluating the use of an IUD have recommended a loop IUD over the copper T-shaped IUD due to its greater surface area and lack of inflammatory changes. The progesterone IUD is not recommended because of the atrophic changes it produces. A pediatric Foley or Cook balloon uterine stent placed in the uterus and removed in 3–10 days may also be used. No randomized trials comparing these options have been done. Small nonrandomized studies suggest hormone therapy is as effective as the IUD and that fewer recurrent adhesions occurred when a pediatric Foley was used compared with the IUD. Newer approaches are the use of hyaluronic acid (Seprafilm) which has shown promise although further studies are needed (Deans and Abbott, 2010).

CAUTION #2

Symptoms of hyponatremia

- Disorientation, twitching, shortness of breath (Na 130–135 mmol/L)
- Pulmonary edema (125–130 mmol/L)
- Hypotension, bradycardia (120–125 mmol/L)
- Lethargy, confusion (<120 mmol/L)
- Brainstem herniation (<115 mmol/L)

Endometrial ablation for fibroid disease

The treatment of menorrhagia in a fibroid uterus with global endometrial ablation technologies is less well defined. Retrospective studies by Glasser et al. (2009) using a hydrothermal ablation system showed that the failure rate with submucous fibroids compared with a normal cavity was 23.2% versus 3.7%, respectively. Use of judicious biopsy of submucosal myomas, polyps or other intracavitary pathology is recommended to rule out an occult malignancy. In women who are poor surgical candidates, perimenopausal or need only temporary amelioration of their menorrhagia, the use of global endometrial ablation may provide the results needed to improve the patient's quality of life.

CASE REPORT #1

A 43-year-old woman presented with complaints of menometrorrhagia and increasing pelvic pressure. On exam, the uterus was smooth but 10 weeks size and nontender. A scanning ultrasound showed a large intracavitary lesion consistent with a fibroid, approximately 5 cm in diameter. The patient was adamant that she wanted to keep her uterus. A saline infusion sonogram (sonohysterogram) revealed a type 1 fibroid with wide posterior attachment. Treatment options discussed with the patient were:

- a hysteroscopic myomectomy. Discussion of advantages included minimal convalescence and missed work; however, the possible need for office hysteroscopy postoperatively to lyse uterine synechiae was discussed
- hysteroscopic myomectomy with global endometrial ablation. Even though complete resection may not occur, advantages include only one outpatient hysteroscopic procedure, possibly followed by intermittent assessment of menometrorrhagia and pressure symptoms
- laparoscopic myomectomy with removal of the fibroid.

The patient opted for hysteroscopic resection. Eighty percent of the fibroid was removed but there was a problem with the fluid management system and the deficit was 2300 mL of normal saline. The anesthesiologist was informed of the intravasation and IV fluid infusion was minimized. A preoperative sodium was normal. Ten mg of Lasix was given in the operating room and a Foley inserted. The patient was monitored in the recovery room for 4 hours. A postoperative sodium was normal and she remained asymptomatic. The patient was discharged to home and not hospitalized overnight. She was seen at her postoperative visit in 2 weeks at which time an office hysteroscopy was performed, and some filmy adhesions were removed.

Laparoscopic myomectomy

Laparoscopic myomectomy was first performed by Semm in 1979 but did not become mainstream until the early 1990s. With advancing technology, this procedure is now commonly performed (Plate 5.3 shows laparoscopic resection of a fibroid). Traditionally, myomectomy was reserved for those women desiring future child bearing. Today many women desire uterine preservation regardless of their future plans for procreation. Candidates for myomectomy are women who desire future fertility, those with bulk and bleeding symptoms whose fibroids are not submucosal, or if submucosal are not amenable to hysteroscopic resection. Regardless of the chosen approach to myomectomy (i.e. open, laparoscopic or robotic), the steps to perform a myomectomy are the same: hysterotomy, enucleation, closure of defect, and removal of fibroids. The goal is to choose the approach that provides the best patient outcome.

The tactile sensation of laparoscopic surgery is inferior to abdominal (open) surgery. Knowledge of fibroid location is paramount prior to commencing with surgery since fibroid location will determine approach and highlight potential challenges. Transvaginal ultrasound is appropriate for initial screening to document fibroids but has clear limitations. The sensitivity of transvaginal ultrasound for fibroid number is approximately 60%, with the sensitivity decreasing with increasing fibroid number. The use of saline infusion sonogram improves the sensitivity of fibroid location, especially for submucosal fibroids (see diagnosis of fibroids, Chapter 2). Magnetic resonance imaging (MRI) shows fibroid location and size in a three-dimensional (3D) view. Furthermore, MRI can differentiate fibroids from adenomyosis and demonstrate aberrant vascular patterns.

Bleeding is one of the great challenges of all myomectomies with reported transfusion rates as high as 20%. Methods that statistically decrease intraoperative bleeding include preoperative vaginal misoprostol, tourniquet, and injection of vasopressin and bupivacaine with epinephrine (reviewed in Chapter 10). Misoprostol given vaginally is documented to provide longer lasting blood levels than oral or sublingual administration. The mechanism of action is via uterine contraction and direct uterine artery constriction. Similar to abdominal myomectomy, clinical studies utilizing vaginal misoprostol prior to laparoscopic myomectomy have supported

its beneficial effect on blood loss. The benefit was not observed with rectal use of misoprostol (Kalogiannidis et al., 2011).

☆ TIPS & TRICKS #4

Hemostatic options at laparoscopy include

- Vaginal misoprostol
- Vicryl tourniquet
- Uterine artery ligation
- Vasopressin

Tourniquets were as effective as preoperative misoprostol in decreasing operative blood loss. Despite this, there was no change in transfusion rates due to continued postoperative bleeding. The use of a pericervical Roeder knot using 0 Vicryl suture and left in place has been described and is quite amenable to a laparoscopic approach. Opening the broad ligament anteriorly, placing the suture around the lower uterine segment at the inner os, and using an extracorporeal Roeder knot is a straightforward approach unless large posterior or broad ligament fibroids are present. In these cases, uterine artery ligation/occlusion should be considered. Occlusion of the uterine artery utilizing laparoscopic vascular clamps can address some of the issues associated with placement of the pericervical tourniquet. Use of these clamps also can be very helpful when bleeding is encountered by decreasing the pulse pressure so that the bleeding source can be identified and rendered hemostatic. Of course, the use of vascular clamps does not address postoperative bleeding.

CAUTION #3

Caution must be exercised because of significant risks associated with vasoconstrictive agents. Bupivacaine is associated with seizures and cardiotoxic effects. Vasopressin has been associated with bradycardia, pulmonary edema, and cardiac arrest. It causes increased vagal tone through baroreflex-mediated neurogenic regulation of blood pressure while sympathetic tone and coronary flow are decreased. Vasopression also causes increased pulmonary capillary hydrostatic pressure, decreased pulmonary capillary oncotic pressure, and increased capillary permeability. Recommended doses for vasopressin are 0.05–0.3 U/mL (i.e. 20 U diluted in either 60–400 mL injectable saline). Cardiac arrest has been noted with as little as 11 units vasopressin total. These vasoconstrictive agents are contraindicated in patients with known cardiac or renal disease.

A cell-saver can also be used in laparoscopic cases. This can be helpful when there is anticipated difficulty in securing the blood supply to the uterus and when the patient would allow autotransfusion. Some Jehovah's Witness patients will accept a transfusion from a cell-saver since it does not leave the operating room and is considered a closed system. A second laparoscopic suction is set up that is attached to the cell-saver tubing. A Kelly clamp can be used to titrate the amount of suction during use to preserve the pneumoperitoneum.

Procedure

The hysterotomy (uterine) incision should be made thoughtfully to avoid incising near the corneal regions or major blood vessels and to allow for easy closure. The incision can be made vertically or horizontally depending on which ports are to be used for suturing. The instrument used to make the hysterotomy incision is important. In the past, monopolar cautery was used for both incision and hemostasis. Monopolar cautery results in the highest tissue temperatures, the greatest amount of lateral spread and the greatest thermal damage. Temperatures above 42°C (the temperature associated with damage to the cell membrane) were found up to 1 cm away. Thermal damage contributes to tissue death, necrosis, and impaired wound healing (Sutton et al., 2010). Use of other modalities (bipolar, Ligasure, harmonic scalpel) did not demonstrate significant lateral spread, but the temperature at the tips remained elevated for up to 15 seconds, so caution should be exercised with use of these tools to avoid inadvertent injury.

CAUTION #4

Laparoscopic electrocautery

- Tips stay hot >42°
- Monopolar – 55 sec
- Bipolar – 25 sec
- Harmonic scalpel and Ligasure – 15 sec

Removal of the fibroid should be accomplished with classic surgical techniques of traction and countertraction through an adequate incision. Use of a laparoscopic tenaculum, laparoscopic corkscrew or suture through the fibroid can help with enucleation. Perforating vessels should be addressed during the enucleation. The use of dissecting agents, such as Mesna, or morcellating the fibroid *in situ* have not been shown to be of significant benefit. Once the fibroid has been removed, it is best to "store" it either in the upper quadrant if it is large enough to be easily visualized or in the posterior cul de sac. A suture placed through the fibroid allows for easy retrieval by bringing the suture out through the port site separate from the trocar. Parasitic fibroids have been documented and it is important to make sure that all fibroids are removed as well as chip particles.

☆ TIPS & TRICKS #5

Laparoscopic closure of uterine muscle

- Don't push when using the laparoscopic needle drivers. Set the needle perpendicular and rotate the wrist, letting the needle glide through the tissue. The depth is determined by the needle size
- A CT 1 needle can fit through a 10–12 mm port and is the best size to use when closing deep myometrial defects
- Use a multilayer closure
- Avoid excessive electrocautery

Closure of the hysterotomy defect needs to follow the standard open technique of multilayer closure, described as approximately two deep layers and one layer to reapproximate the serosal surface. This traditional multilayer closure and obliteration of the dead space has been followed in open myomectomy with a uterine rupture rate of approximately 0.2%. Einarsson et al. (2010) reviewed cases of uterine rupture following laparoscopic myomectomies that occurred over the last 18 years. Of the 19 ruptures reviewed, only three occurred in multilayer closures. In addition, electrocautery was also used in 16 of the 19 cases. In three cases, rupture occurred over areas where pedunculated fibroids were removed without suturing the defect and where electrocautery was used for hemostasis. Based on these evaluations, it was concluded that failure to adequately close the uterine defect, as well as the excessive use of electrocautery, might contribute to the higher incidence of rupture that has been found in laparoscopic myomectomies.

The inherent learning curve of laparoscopic suturing has probably contributed to the deviation from the standard multilayer hysterotomy closure. Closure of thick myometrial defects can be accomplished with heavy-duty laparoscopic needle drivers and attention to the physics of laparoscopic suturing. Because the laparoscopic needle drivers have a weaker grip than open needle drivers, it is important that the needle be positioned perpendicular to the incision and to use a wrist rotation motion to follow the curve of the needle. It is imperative to avoid the push-rotation technique used in open suturing, otherwise the needle will twist in the laparoscopic needle driver. Intracorporeal knots or Lapra-Ty® can be used to secure the suture. It is important to maintain tension and approximation of the two edges. Use of barbed suture can overcome many of the difficulties of laparoscopic suturing. Because of the barbed nature, one size higher suture size should be used. The barbs self-anchor every 1 mm to maintain consistent tension and do not require knots (Leung, 2004). Studies have shown that the tensile strength of the barbed suture is equal to, or superior to, open closure. Further studies evaluating long-term and pregnancy outcomes will need to be performed.

Removal of the fibroids is usually performed with a morcellator. If the fibroid is quite large, it may not be safe to use a commercial morcellator because of decreased visualization. In these cases, a mini-lap incision and hand morcellation with a scalpel may be better. The mini-incision for hand morcellation can be done via the umbilical port or the suprapubic port. Of note, lateral ports may cause increased postoperative pain and scaring because of injury to rectus muscles. It is also possible to remove the fibroids via a vaginal colpotomy incision depending on the vaginal and fibroid size. Importantly, morcellation should be avoided in cases of atypical (cellular) fibroids because of reports of intraperitoneal seeding of tumors.

CAUTION #5

Use of the morcellator may lead to seeding of the peritoneal cavity with fibroid cells and potentially to the patient presenting with

leimoyomatosis at a later time, if the fibroid removed was cellular or atypical. For that reason, until additional information becomes available, morcellation should be avoided for removal of cellular or atypical fibroids.

Uterine artery ligation

Uterine artery ligation (UAL) is a technique that can address both operative and perioperative hemorrhage. It involves opening the anterior leaf of the broad ligament and gaining entrance to the retroperitoneal space. The ureter is found on the medial leaf of the broad ligament, and it can be followed until the uterine artery crosses it. It is important to clearly identify the uterine artery branching off the internal iliac artery and the continuation of the superior vesical artery. The ureter should be protected medially and the uterine artery ligated with a small pedicle from its origin. This has been done with suture, hemaclips, with or without transection, bipolar electrocautery, harmonic scalpel, or other methods.

Uterine artery ligation not only affects the perioperative circumstances but may have long-term effects. Both open and laparoscopic studies have shown a significant decrease in fibroid recurrence when simultaneous uterine artery ligation was performed at the time of myomectomy. The longest study at 42.5 months showed a 5.8% recurrence when a UAL was performed compared with 36.7% recurrence without concurrent UAL. Other studies support this with recurrence at 11 months (2% versus 13%) and at 24 months (6.2% versus 20.75%) for UAL compared to control.

Pregnancy after laparoscopic myomectomy

Concern has been raised regarding pregnancy following myomectomy with uterine artery ligation. Based on perfusion studies, there is no compromise on uterine blood flow. There is only one head-to-head study evaluating pregnancy rates following laparoscopic myomectomy with or without uterine artery ligation which showed a 35% pregnancy rate in both groups with a similar livebirth rate (Alborzi et al., 2009). More studies with outcome data are needed before evidence-based recommendations can be made.

Future fecundity is often the reason for performing a laparoscopic myomectomy over hysterectomy. Once a laparoscopic myomectomy has been performed, the timing of pregnancy, the inherent risks of the pregnancy, and delivery options must all be addressed in order to ensure safety for both mother and child. The pregnancy rate following laparoscopic myomectomy ranges from 11% to 64% depending on the study. Most patients studied conceived between 12 and 36 months after surgery. In general, the consensus is to wait 4–6 months to conceive, but this is not evidence based. Transvaginal ultrasound studies suggest myomectomy wound healing is complete by 3 months post procedure (Darwish et al., 2005). Uterine rupture rates following laparoscopic myomectomy based on studies from Parker et al. (2010) are approximately 1% but as discussed, this may be skewed based on surgical technique, use of electrocautery, and other factors. There does not appear to be an association between the number, size or location of fibroids and uterine rupture. Spontaneous abortion rates seem to be higher than that of the general population (26% versus 15%), with the majority occurring in the first trimester.

The American College of Obstetricians and Gynecologists (2008) recommends cesarean section when extensive transfundal surgery has occurred. This has been interpreted to include myomectomy. However, studies done in Japan evaluating vaginal birth after laparoscopic myomectomy have not shown an increased uterine rupture rate. The largest study with 221 pregnancies had a vaginal delivery rate of 79.7%. There was a higher percentage of failed vaginal deliveries in those pregnancies where the endometrial cavity had been entered (Kumakiri et al., 2008). There are no recommendations regarding timing of delivery in relation to myomectomy.

CASE REPORT #2

A 32-year-old G1P1001 presented with complaints of pressure, heavy bleeding, and desire for pregnancy. Her first pregnancy 12 years ago was spontaneous. She has been practicing unprotected timed intercourse for over a year. Abdominal exam revealed a lower abdominal mass above the symphysis. This was confirmed on pelvic exam. A transvaginal ultrasound revealed a large 8 cm subserosal fibroid. MRI was obtained which confirmed the 8 cm subserosal fibroid, but additionally revealed an anterior 4 cm submucosal type 2

fibroid. The patient opted for a laparoscopic myomectomy. Preoperatively, a Zumi™ uterine manipulator was inserted. Methylene blue was used to document tubal patency and to stain the endometrium. A harmonic scalpel was used. The subserosal fibroid had a wide base and was removed distal to the base. The pedicle was sutured in two layers with an initial layer using a barbed 1 on a CT 1 needle in an imbricating manner. The serosal layer was sutured as a baseball stitch with a 2-0 PDS with intracorporeal knots. The submucosal type 2 fibroid was not grossly visible. The MRI was reviewed in the operating room and an incision was made with the harmonic scalpel to reveal the fibroid. A 0 Vicryl suture was deeply placed in the exposed fibroid and used for traction, while the harmonic scalpel was used to lysis the attachments bluntly and with energy. An assistant retracted the myometrium. Once the fibroid was removed, it was noticed that the endometrium had been entered. A 2-0 PDS was used to close the endometrium in running, imbricating layers. The myometrium was approximated with two layers of a #1 double-armed barbed suture and the serosal layer was closed with 2-0 PDS. Intra-abdominal pressure was reduced to assess for bleeding. Interceed® was applied to minimize the risk of adhesions. The patient was discharged home that day. Two weeks later, an office hysteroscopy under low pressure was performed and no intrauterine adhesions were noted. At her 6-week postoperative visit, the patient was counseled regarding the need for a cesarean section. She was to utilize contraception for 6 months.

Laparoscopic hysterectomy

Laparoscopic hysterectomy can be the definitive treatment for fibroids. Although women choose to remove the uterus because of years of pain, bleeding, and pressure, some experience significant grief surrounding their hysterectomy. Using a minimally invasive approach with the benefits of decreased postoperative pain, faster recovery, and decreased blood loss may provide some consolation.

Once the decision to proceed with a laparoscopic hysterectomy is made, the choice of a laparoscopic supracervical hysterectomy (LSH) or total laparoscopic hysterectomy (TLH) needs to be determined. A LSH may give some women the comfort of retaining a portion of their uterus. If a LSH is performed, the uterus needs to be removed at or below the level of the internal os (ACOG, 2007). However, there is no reported benefit of cervical retention in terms of perioperative morbidity, pelvic support or sexual and urinary function (Kho and Magrina, 2011). Notably, recent comparative studies of LSH versus TLH demonstrated that patients undergoing LSH returned to daily activities 5 days earlier than patients undergoing TLH, and had some short-term postoperative quality of life parameters that were significantly better. In addition, a large retrospective analysis demonstrated small but significant increased risk of urinary tract injuries in TLH cases (2.2%) compared with LSH cases (0.5%) (Harmanli et al., 2009). Postoperative cyclic spotting is one of the most significant disadvantages of LSH compared with TLH, occurring in up to 25% of patients. The average reported incidence ranges between 5% and 10% after a LSH.

Procedure

The initial trocar insertion causes a significant proportion of laparoscopic surgical complications. The options for entry are either an open (Hasson) approach or a closed entry approach. The closed approach utilizes either the Veress needle or a direct entry via optical access, or radially expanding trocars. Based on current studies, one approach has not been shown to be superior to the other. However, some surgical practices may decrease the risks associated with the initial laparoscopic entrance. In extremely thin or obese patients, and those with known abdominal adhesions, the umbilical entry approach has increased risk of injury. Previous surgery increases the risk of umbilical or anterior abdominal wall adhesions.

☆ TIPS & TRICKS #6

Palmer's point

Location is 3 cm below the left subcostal border in the midclavicular line. **Avoid** Palmer's point insertion if there is:

- history of splenic or gastric surgery
- hepatosplenomegaly
- portal hypertension
- gastropancreatic mass

In these cases the placement of a left upper quadrant port (Palmer's point) should be considered. It is prudent to have the anesthesiologist insert a nasogastric or orogastric tube since the stomach can become inflated during intubation. Very thin patients have only a 1–2 cm distance from the umbilicus to the bifurcation of the aorta and vena cava. Use of towel clamps to invert the umbilicus and elevate the abdomen is the only method that provides significant elevation of the peritoneum (6.8 cm) from the great vessels. If utilizing this technique, place the Veress needle no deeper than 1–2 cm, with an opening pressure of less than 10 mmHg. The abdomen should continue to be elevated during insufflation. Set the intra-abdominal pressure to 24–25 mmHg temporarily, as this provides the countertraction necessary for trocar insertion by preventing compression of the abdominal wall. Once insertion is made, decreasing the pressure to 12–15 mmHg is imperative to decrease the risks of subcutaneous emphysema, impaired venous return, and hypercarbia leading to respiratory acidosis and arrhythmia. Although use of a visual entry cannula is helpful, there are no studies to indicate benefit. When operating on large uteri, it is helpful to lift the uterus out of the pelvis during the exam under anesthesia to determine the telescope trocar site, which should be approximately 8–10 cm above the elevated fundus. This ensures an optimal view of the pelvis. In cases where the abdomen is short, consider Palmer's point.

☆ TIPS & TRICKS #7

Insufflation pressures at laparoscopy

- Entering pressure >24–25 mmHg
- Maintain pressure at 12–15 mmHg

Once entrance into the abdomen is made, adhesiolysis should first be done to approximate normal pelvic anatomy, if necessary. A critical step of any laparoscopic hysterectomy is the ability to lift the uterus out of the pelvis (Plate 9.2). The use of a uterine manipulator is helpful. In addition, a midline 5 mm suprapubic port can be valuable to help lift the uterus and push it away from the lateral sidewall. The round ligament should be ligated and half of the bladder flap created. Only two main sources of blood flow to the uterus exist: the uterine vessels and the utero-ovarian vessels. Once these are ligated, the risk of bleeding is minimal. In order to reliably control these vessels, the anterior broad ligament should be opened parallel to the external iliac vessels with entrance into the retroperitoneal space, allowing visualization of the ureter. If the anatomy is unclear, then the uterine artery can be ligated at the level of the internal os, although more bleeding may be encountered due to collateral flow. With large lower uterine segment fibroids, the lateral retroperitoneal approach can provide the easiest and safest way to control blood loss. A window can then be made in the broad ligament which can be bluntly stretched parallel to the infundibular pelvic (IP) ligament. The IP can be ligated either proximal or distal from the ovary depending on whether a salpingo-oophorectomy is planned. Notably, the Nurse's Health Study showed that removal of the ovaries in women younger than 45 years caused a significantly increased risk of coronary heart disease and the recommendation is ovarian retention in these women.

When the major vessels and peritoneal attachments have been ligated, the anterior colpotomy can be done. It is important to make sure that the bladder has been retracted adequately. Fill the bladder with sterile milk to assess for leaks, if there is concern regarding a bladder injury. For suspected ureteral injury, the anesthesiologist can administer indigo carmine. The two different fluids will allow easy differentiation of the injury source. It is important to make the anterior colpotomy incision low enough to clear the cervix.

If a noncupped uterine manipulator has been used, a sponge on a stick can be placed in the vagina and the anterior vagina tented upward towards the abdomen to clearly delineate the vagina. The uterus should be firmly grasped with a tenaculum or other secure grasper. The uterus must be held up out of the pelvis. If the uterus is large, the lower lateral side of the uterus should be grasped so that it is clearly visible. Once the pneumoperitoneum is compromised, placement of a sponge in a glove can be used to maintain the pneumoperitoneum. The uterus can then be separated from the vagina. This can be challenging if the uterus is not maintained on tension.

With the uterus detached from the vagina, a single toothed tenaculum can be placed vaginally over the sponge in a glove (to prevent loss of the pneumoperitoneum) and under direct visualization,

the cervix can be grasped by the vaginal tenaculum while the laparoscopic assistant stabilizes the uterus. The uterus is then removed via the vagina. If the uterus is too large to be removed vaginally, two approaches may be done. The uterus can be morcellated within the abdomen or it can be morcellated via the vagina. Even large uteri can be morcellated vaginally. It is important to use a long weighted Steiner speculum to protect the vagina posteriorly. A Deaver retractor is used anteriorly. The uterus is held securely with a tenaculum (similarly as in a vaginal hysterectomy) and utilizing a scalpel, the uterus is rotated side to side to debulk it. Once the uterus is removed, the vaginal cuff is closed and secured to the uterosacroal ligaments either vaginally or laparoscopically.

CAUTION #6

TLH cuff closure considerations to avoid dehiscence

- Delayed coitus
- Monofilament, delayed absorbable suture
- Energy source
- Consider transvaginal closure

Total laparoscopic hysterectomy has been associated with a significantly increased incidence of vaginal cuff dehiscence when the cuff is closed laparoscopically. Compared with a transvaginal closure, there is a three-fold greater risk of dehiscence with laparoscopic closure of a TLH. Vaginal cuff dehiscence is a gynecological emergency requiring prompt surgical management with the risk of bowel perforation, peritonitis, and sepsis. Factors associated with vaginal cuff dehiscence are early coitus and cuff infection (Uccella et al., 2011). Potential risk factors may involve the type of energy source used as well as different techniques for vaginal cuff closure. The harmonic scalpel creates the least amount of tissue damage, bipolar the most. A large observational cohort study of more than 7000 TLH surgeries over a 10-year period showed that there was a 4.9-fold increased risk of dehiscence compared to laparoscopically assisted vaginal hysterectomy, a nine-fold increased risk compared with a total abdominal hysterectomy and a 17-fold greater risk compared to a total vaginal hysterectomy. In addition, this study noted a decreased incidence of dehiscence when the suture was changed to a monofilament, delayed absorbable suture. The surgeon should treat for preoperative vaginal infections, use delayed absorbable monofilament suture, and be cognizant of the type of energy used for the colpotomy incision. The laparoscope magnifies the surgical field, so maintaining deep "bites" during the cuff closure is imperative. If there is concern regarding the closure, a transvaginal approach should be considered. Adhesion barrier should be placed over the vaginal cuff.

EVIDENCE AT A GLANCE #2

Risk of abdominal adhesions with previous surgery

- Laparoscopy 0–15%
- Pfannenstiel 20–28%
- Vertical 50–60%

Robotic surgery

Use of the robot is becoming more common, as both physician and consumer interest in robotic surgery has increased. The suggested advantages of robotic surgery include improved dexterity, 3D visual optics, decreased physician fatigue, and removal of any tremor (Chen and Falcone, 2009). The most significant challenge of minimally invasive surgery is the modest conversion from laparotomy to laparoscopy despite the known patient advantages. In contrast, the DaVinci® robot has had quick acceptance and utilization. By April 2011, more hysterectomies were being done robotically than vaginally or laparoscopically (Lenihan, 2011), and uterine fibroids were a frequent indication. Laparoscopic surgery requires movements to be the mirror image of the desired action and the rigid instruments provide only 4˚ of movement. The robot mimics movements used in open cases and the wristed instruments provide 7˚ of movement. However, robotic surgery has a distinct learning curve. Most studies show that set-up and docking times stabilize after approximately 20 cases.

Clinical assessments of gynecological robotic cases compared to laparoscopy have been primarily retrospective in nature. Currently, there are no compelling, evidence-based studies demonstrating superiority of robotic surgery over standard laparoscopic methods

for resection of uterine fibroids. Nonetheless, the robotic platform has inconsistently trended towards fewer conversions to laparotomy, less blood loss, and shorter hospital stays. Use of the robot in obese patients may also provide some advantages to laparoscopy.

Limitations of the robot include the lack of haptics, bulkiness of the instrument, limited energy sources, and cost. Haptics are the ability to obtain information or feedback through touch. This lack of haptics is challenging and the use of excessive pressure can be hazardous. Side docking is paramount for the gynecological surgeon in order to provide vaginal access. Currently the only available energy sources are monopolar and bipolar. In the future more options will be available but the operator must remain cognizant of the specific risks associated with these energy sources, which as noted above may be suboptimal for fibroid resection. Another issue is the cost of robotic surgery. The initial purchase price for a robot unit is approximately $1.5 million (2010). The robotic instruments can be reused a limited number of times and cost $2000 per instrument. In one study evaluating comparative costs (albeit not for fibroid surgery), the authors concluded that the robot was more cost-effective than laparotomy but more expensive than laparoscopy, when factoring the costs of lost wages and longer hospital stay. The analysis indicated that the cost of the robot could become less expensive than laparoscopy if the cost of the disposable instruments could be significantly decreased (Barnett et al., 2010).

Laparoscopic single-site surgery and natural orifice surgery

Gynecologists have used both single-site and natural orifice surgery for many years. In 1969, Wheeless reported single-port laparoscopic tubal ligation, and the vagina has been used by gynecologists as both the primary route for surgery in vaginal hysterectomies or as a conduit to access the abdomen (Wheeless, 1969). Today, single-site surgery has re-emerged due to new and improving technology and as a natural extension of advancement in the field of minimally invasive surgery. By decreasing the number of abdominal entry points, the risks of bleeding, infection, scarring, and potential hernia in each individual port should consequently be diminished with the added benefit of improved cosmesis.

Multiple terms exist in reference to single-site surgery. Laparoendoscopic single-site surgery, or LESS, is the term adopted by the Laparoendoscopic Single-Site Surgery Consortium as standard terminology. Single-site surgery is also referred as single-port transumbilical laparoscopy, embryonic natural orifice transumbilical endoscopic surgery, single port access surgery (SPA), single incision laparoscopic surgery (SILS), and one-port umbilical surgery (OPUS). Natural orifice transluminal endoscopic surgery, or NOTES, differs from single-port surgery by its avoidance of any abdominal incisions (Escobar et al., 2010).

The most difficult aspect of single-site surgery is the issue of triangulation and external conflicts. In minimally invasive surgery, triangulation is necessary in order to achieve appropriate traction, countertraction, and visualization. Although the concept of single-port surgery in gynecology is well established, it has re-emerged in the field of minimally invasive surgery due to improvements in instrumentation and optics, and will likely be applied to fibroids.

There are limited studies evaluating single-site surgery and no prospective randomized control trials in gynecology, including for treatment of uterine fibroids. Gynecological procedures that have been performed with single-site surgery have shown comparable outcomes compared with multiport laparoscopy. Improved cosmesis is assumed but other benefits are less clear. Further studies are needed before definitive advantages or disadvantages are illuminated.

Natural orifice transluminal endoscopic surgery (NOTES) is also emerging on the minimally invasive front. The role of NOTES in gynecology is yet to be determined, including for treatment of uterine fibroids. Future technological advancements in instrumentation and optics may define the possible role of NOTES in the field of minimally invasive surgery and as a possible treatment for uterine fibroids.

Conclusion

Minimally invasive surgical approaches to uterine fibroids are now established options that are patient friendly, given the shorter recovery and similar surgical outcomes. Proper patient selection remains an

important consideration, given the variability of fibroid disease and differences in disease severity between patients. Many technological improvements have facilitated the resection of uterine fibroids using the procedures described in this chapter. Some procedures are proven and established but others have not been sufficiently studied to assess efficacy and outcomes, in comparison to more established treatments. In the hands of a skilled laparoscopic surgeon, the robotic approach may not be superior. However, in certain settings the robot may provide distinct advantages over laparoscopy. Most importantly, it may allow less proficient laparoscopic surgeons to offer their patients a minimally invasive approach. As technology improves, the future potential of minimally invasive surgery is exciting with the possibility of smaller instruments, improved maneuverability, improved haptics, and the use of robotics.

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10

Surgical Treatments and Outcomes

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Introduction

Uterine fibroids (leiomyoma) are the leading cause for hysterectomy in American women, accounting for approximately 39% of hysterectomies (Whiteman et al., 2008). The cumulative incidence of these tumors by the time a woman is age 50 differs by race, with greater than 80% of black women having fibroids based on ultrasound compared to 70% of white women.

As not all women with fibroids are symptomatic, treatment of fibroids should only be initiated in women with symptoms. Symptoms include pelvic pain, menorrhagia, anemia, bulk symptoms (bladder pressure, constipation), infertility, and miscarriage (see Chapter 3). Treatment of fibroids is often targeted at symptomatic management with the patient's desires for future fertility carefully considered. There are many options available for the management of fibroids which include medical (Chapter 6), radiological (Chapters 7 and 8), and minimallyinvasive surgical therapies (Chapter 9). More traditional surgical options include myomectomy and hysterectomy. The route of surgery (abdominal, hysteroscopy/vaginal or laparoscopic) is based on location and size of fibroids, local resources, and provider/patient choice. This chapter will discuss the surgical modalities of myomectomy and hysterectomy with a focus on patient selection and outcomes.

CASE REPORT

A 33-year-old G1P0 at 12 weeks gestational age presented with an incomplete spontaneous abortion. Her past medical history was significant for heavy menses and no sexually transmitted infections or pelvic inflammatory disease. She was in a long-term monogamous relationship. The patient underwent an ultrasound-guided suction dilation and curettage (D&C) at which time multiple fibroids were noted, including a large submucosal fibroid abutting and distorting the endometrial cavity. Two months later, the patient presented with continued menorrhagia and symptomatic anemia and was found to have a hematocrit of 29.5% (hemoglobin 9.5 mg/dL).

To further evaluate the ultrasound findings seen found at the time of her D&C, a saline sonohysterogram was performed which demonstrated multiple intramural fibroids with the largest measuring 6 cm and distorting the uterine cavity. The patient was counseled regarding options for management of her fibroids and menorrhagia and chose myomectomy. An abdominal myomectomy was performed, at which time, other than multiple fibroids, her anatomy was noted to be normal and both fallopian tubes were patent.

Fibroids, First Edition. Edited by James H. Segars.

She had an uncomplicated postoperative course and reported improvement in her menorrhagia. Fifteen months later, she presented to her gynecologist reporting inability to conceive despite regular unprotected intercourse with her long-term partner. A hysterosalpingogram (HSG) was performed and showed bilateral tubal occlusion and distortion of the uterine cavity consistent with extrinsic compression.

Myomectomy

For women with symptomatic fibroids who want to preserve their fertility, myomectomy is a conservative surgical treatment that preserves the uterus. However, following myomectomy, the recurrence rate of fibroid tumors approaches 60%. Recurrence often occurs between 3 and 5 years later.

Patient selection

Indications for myomectomy include pelvic pain or pressure, menorrhagia, urinary frequency or incontinence secondary to fibroid pressure on the bladder, bowel symptoms (constipation), dysmenorrhea, and rarely infertility. Abdominal myomectomy is appropriate when hysteroscopy or laparoscopy is not feasible or when laparotomy is indicated for treatment of other abdominal or pelvic pathology (Figure 10.1).

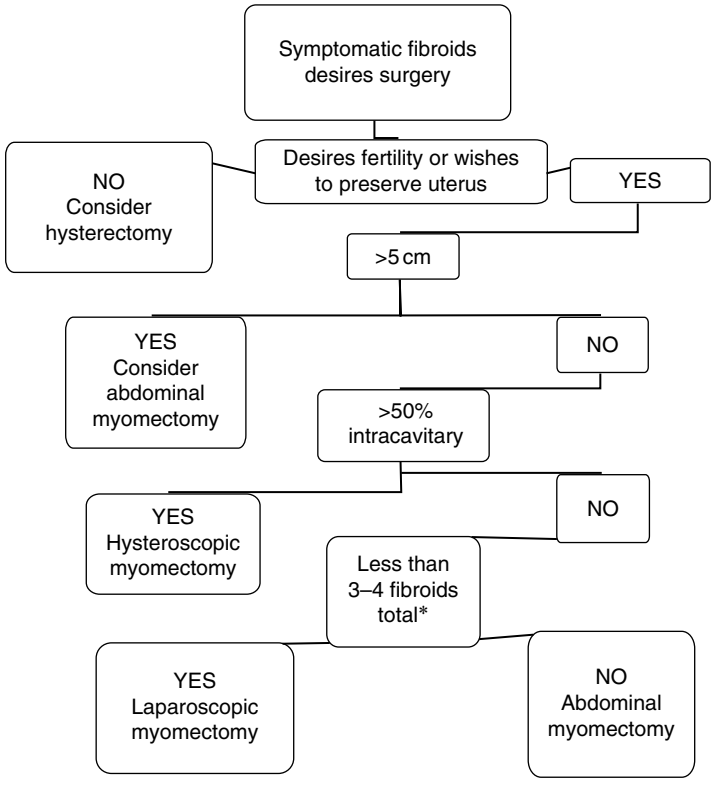

Figure 10.1 Possible surgical treatment algorithm for a patient presenting with symptomatic fibroids. At the first decision point, fertility is considered but myomectomy is also supported based solely on the patient's wishes to preserve her uterus. At the second decision point, size of 5 cm refers to intrauterine, submucosal fibroid requiring hysteroscopic resection, since with current instrumentation, sizes greater than 5 cm require a very experienced surgeon, and possibly a resection requiring two procedures. At the third decision point, intracavitary extension is considered, since resection hysteroscopically is simplified with fibroids that have a >50% intracavitary location. At the fourth decision point, the number of fibroids is considered. There are exceptions to the algorithm and it is provided as a general guideline to aid in clinical decision making.

The most critical factors in choosing abdominal myomectomy include size and location of the fibroids along with the patient's desire for future fertility (Plate 10.1). Few studies have addressed objective criteria for selecting laparoscopic myomectomy over abdominal myomectomy. Surgical expertise and experience, for example, are often important criteria but these factors cannot be objectively measured. Subserosal fibroids less than 3 cm or intramural fibroids with greater than 50% of the fibroid being intracavitary are best suited for hysteroscopic myomectomy. Fibroids which have an intracavitary portion less than 50% of their volume are best approached laparoscopically or abdominally (Cammani et al., 2010). Fibroids which are entirely intracavitary are classified as type 0. Type 1 fibroids have >50% of their surface area in the uterine cavity. Type 2 fibroids have <50% of their surface area in the uterine cavity.

A large prospective study of women undergoing laparoscopic myomectomy demonstrated leiomyoma characteristics that were significantly associated with major complications (e.g. bleeding requiring blood transfusion, visceral injury, procedural failure) which included: size of myoma >5 cm, >3 myomas removed, and intraligamentous location. Recommendations for abdominal myomectomy include uteri with more than 3–4 fibroids or size greater than 8–9 cm (Malartic et al., 2007). In experienced hands, up to seven fibroids and fibroids measuring 16 cm have been treated surgically via laparoscopy.

Future fertility considerations are frequently the primary factor in choosing myomectomy over hysterectomy. Myomectomy gives women the option of future fertility and child bearing. The American Congress of Obstetricians and Gynecologists' guidelines support myomectomy in symptomatic women who decline hysterectomy, even if they do not plan future conception.

Expected outcome

Reduction in menorrhagia symptoms following myomectomy is reported to be as high as 90%. Reduction in pain symptoms is less successful at 67%, likely because other pathologies contribute to pelvic pain symptomatology. Improvement in pregnancy rates and decreased miscarriage rates has been shown following removal of submucosal fibroids. About 50% of patients became pregnant following myomectomy and if there are no other associated infertility factors, the rate approaches 70%. Hysteroscopic treatment is beneficial for patients whose fibroids distort the endometrial cavity. Treatment benefit, however, was limited to those with type 0 or 1 fibroids, with no benefit achieved in those with type 2 (Olive, 2011).

Minor complications

Minor complications following myomectomy include postoperative fever, infection, and wound hematoma or separation. Fever within the first 48 hours is common, occurring in 12–33% of myomectomy patients (LaMorte et al., 1993). In comparison with abdominal hysterectomy, patients undergoing abdominal myomectomy have a relative risk of 3.29 of postoperative fever. The release of prostaglandins and cytokines, as a result of tissue damage, acts centrally in the brain to stimulate the production of fever. Inhibition of prostaglandin synthesis with nonsteroidal anti-inflammatory drugs (NSAIDs) can help suppress postoperative fever. Ketorolac is a nonspecific COX inhibitor which inhibits the production of cytokines and has been proven to reduce the incidence of postoperative fever (27% versus 41%) when compared to saline infusion (Held et al., 2002).

Infections, which include wound, urinary and respiratory sources, complicate approximately 2–5% of abdominal procedures. Surgical site infections are discussed in more depth later in this chapter in the section on complications following hysterectomy.

Major complications

Major complications associated with myomectomy include hemorrhage requiring blood product transfusion, ureteral or bladder injury, bowel injury, conversion to abdominal approach from laparoscopy, and conversion to hysterectomy. Ureteral and bladder injury occurs in 1–3% of cases, while damage to the bowel occurs in approximately 1% of cases.

☆ TIPS & TRICKS #1

Methods to reduce blood loss or transfusion during myomectomy

Intraoperative blood loss can be minimized by use of tourniquets, injection of vasopressin or epinephrine into the uterus during surgery. Intraoperative use of the cell-saver can also reduce the likelihood of transfusion.

EVIDENCE AT A GLANCE #1

Summary of Cochrane review of techniques to reduce blood loss at the time of myomectomy (Rhodes et al., 1999)

Shown to reduce intraoperative blood loss	Unsure/ unproven	Not proven to reduce intraoperative blood loss	Not studied
Tourniquet	Mesna	Oxytocin	Uterine artery embolization
Vasopressin	GnRH analogs	Myoma enucleation	
Bupivacaine + epinephrine			
Misoprostol			
Tranexamic acid			

Average blood loss varies from 200 to 800 mL, with rates of blood transfusion varying from 2% to 28%. Increases in blood loss are seen with increasing size and number of fibroids removed. Very rarely, excessive blood loss or surgical complications may also necessitate conversion from a myomectomy to hysterectomy, which is estimated to occur in up to 4% of cases (Viswanathan et al., 2007).

While several methods to reduce blood loss are popular, not all have been proven to reduce blood loss at the time of myomectomy.

Significant reductions in blood loss have been documented with pericervical tourniquet, vasopressin, bupivacaine plus epinephrine, misoprostol, and tranexamic acid (Kongnyuy and Wiysonge, 2011). The largest reduction in blood loss was seen with the occlusion of the uterine and/or ovarian arteries. Pericervical tourniquet demonstrated a mean difference (MD) in blood loss of 1870 mL (95% confidence interval (CI) 1192–2547 mL) and a reduction in need for blood transfusion (odds ratio (OR) 0.02). Vasopressin and bupivacaine are known local vasoconstrictors and likely reduce blood loss by reducing local blood flow at the time of surgery. The use of vasopressin (and analogs) demonstrated an MD of 298 mL (95% CI 4–593 mL). The MD in blood loss with bupivicaine plus epinephrine was 68 mL (95% CI 43–94 mL).

Misoprostol likely reduces blood loss by stimulating uterine contractions to reduce uterine blood flow. Vaginal misoprostol reduced blood loss by a MD of 149 mL (95% CI 68–229 mL) and increased postoperative hemoglobin (MD 0.8 g/dL). Tranexamic acid is an antifibrinolytic agent which blocks the process of fibrin clot breakdown. Tranexamic acid demonstrated a reduction in blood loss with a MD of 243 mL (95% CI 25–460 mL). The use of oxytocin, misoprostol, bupivacaine plus epinephrine, and tranexamic acid was also associated with a shortened duration of surgery.

No difference in blood loss was seen with the use of intravenous oxytocin or with myoma enucleation by morcellation. No clear evidence of decreased blood loss was seen with the use of chemical dissection (mesna) or gonadotropin-releasing hormone (GnRH) analogs. There have been no randomized controlled studies of uterine artery embolization preoperatively for reduction in intraoperative blood loss.

Postoperative adhesions

Another complication after surgical intervention is the formation of adhesions which may not always be evident until many years following the initial surgery (Tinelli et al., 2011). Adhesions to the uterus from bowel, adnexa, and other structures form in up to 90% of cases. Adhesions are much more likely to form after laparotomy (75–90%) compared to laparoscopy (12–40%). Adhesions are significantly more prevalent after posterior uterine incisions, found in up to 93% of cases, but occur in up to 55% of cases after fundal or anterior uterine incisions. Risk factors associated with increased adhesion formation include posterior uterine incision, presence of suture, concurrent adnexal surgery (i.e. ovarian cystectomy), and prior adhesive disease.

☆ TIPS & TRICKS #2

Techniques for adhesion prevention after abdominal or hysteroscopic surgery

Adhesion formation can be decreased but not totally eliminated. Techniques to decrease abdominal adhesion formation include gentle tissue handling, meticulous hemostasis, excision of necrotic tissue, minimizing ischemia, use of fine, nonreactive suture, and preventing infection. The use of adhesion barriers is associated with decreased adhesion formation when compared to no barrier use in both abdominal and laparoscopic myomectomy. Adhesions resulting after the use of a barrier were classified as filmy and less cohesive when compared to those adhesions resulting from no barrier use (Tinelli et al., 2011).

The efficacy of oxidized regenerated cellulose (ORC) for postsurgical adhesion prevention was demonstrated in a systematic review that compared ORC to no treatment. Use of this barrier at laparoscopy significantly reduced the incidence of new adhesions (OR 0.31, 95% CI 0.12–0.79) and reformation of adhesions (OR 0.19, 95% CI 0.09–0.42). Similar effects were seen with use during laparotomy. Data suggest that hyaluronic acid with carboxymethylcellulose sheets and fibrin sheets do not decrease the extent of adhesion formation.

No significant benefit was found from use of intraoperative irrigation or infusion of various drugs and liquids, including intraperitoneal steroids, dextran, icodextrin or heparin. The small number of studies and subjects preclude definitive conclusions, however. Antibiotic solutions are also ineffective in prevention of adhesions (Metwally et al., 2006). NSAIDs may play a role in adhesion prevention but there are no prospective randomized clinical trials documenting benefit. Evidence from animal studies demonstrates that ketorolac is efficacious in reducing adhesion formation.

Intrauterine adhesions have been reported to form in 31% of cases following removal of a single myoma, increasing to 45% of cases when multiple myomas were removed. Intrauterine adhesions form as a result of damage to the basalis layer of the endometrium, causing denuded, raw edges which fuse together during the healing process, resulting in tissue bridges. Adhesion formation can be decreased but not totally eliminated. Different adhesion prevention techniques are used for abdominal adhesion prevention and intrauterine adhesion prevention.

Surgical strategies for decreasing intrauterine adhesions include preventing excessive trauma to the endometrium and myometrium, reducing the use and wattage of electrocautery, postoperative high-dose estrogen use, and the use of a barrier method with either a catheter/balloon or adhesion barrier. A common practice for prevention of intrauterine adhesions involves the use of a postoperative intrauterine splint and administration of postoperative high-dose estrogen therapy. The use of a 12 Fr Foley catheter or balloon uterine stent conforms to the shape of the uterine cavity and maintains separation of the uterine cavity surfaces. This catheter is usually left in place for 3–10 days. A comparison study was done examining intrauterine adhesions, restoration of normal menstruation, and conception rate with a Foley catheter balloon versus an intrauterine contraceptive device (IUD). The Foley catheter balloon was demonstrated to be superior, with a higher percentage of women returning to normal menstruation (81% versus 63%), less persistent amenorrhea/hypomenorrhea (19% versus 37%), higher conception rates (34% versus 23%), and lower need for reoperation (14% versus 27%) (Orhue et al., 2003).

If the endometrial cavity is entered during abdominal resection of fibroids, oral micronized estradiol,

EVIDENCE AT A GLANCE #2

Methods for prevention of abdominal or intrauterine adhesions after myomectomy

Abdominal		**Hysteroscopy**	
Surgical technique	Meticulous hemostasis	Foley catheter	Intrauterine balloon
Nonreactive suture	Adhesion barriers	Estrogen	Adhesion barriers

☆ TIPS & TRICKS #3

Prevention of intrauterine adhesions during myomectomy

For cases where fibroids impinge upon the uterine cavity and the surgical approach is abdominal myomectomy, it is possible that the uterine cavity will be entered during resection of the fibroid. To aid identification of the uterine cavity, prior to abdominal incision a pediatric Foley catheter can be placed in the uterine cavity via the cervix and a dilute solution of methylene blue in normal saline can be used to stain the uterine cavity. Should the uterine cavity be entered during surgery, the endometrium will be obvious and repair can be accomplished with a 5-0 absorbable suture. This method will minimize inadvertent resection of endometrium, leading to intrauterine scarring.

2 mg twice daily, may be prescribed for 30–60 days to promote endometrial overgrowth and re-epithelialization of the scarred surfaces (March, 2011). Use of this method is more firmly established following hysteroscopic resection, where there is greater uterine thickness, width and volume when compared to those given no therapy. However, there are no published studies indicating that enhanced regeneration of the endometrium prevents intrauterine adhesions.

Intrauterine adhesion barriers have shown some promise in decreasing adhesions. A recent study demonstrated effectiveness in intrauterine adhesion prevention with the use of a polyethylene oxide-sodium carboxymethylcellulose gel. A significant reduction in adhesion incidence (6% versus 22%) and severity (mild, moderate or severe) was observed with use of the gel when compared to no treatment.

Obstetric considerations following myomectomy

There is a theoretical risk of obstetric complications after uterine surgery, specifically uterine rupture during the third trimester. Uterine rupture after classic cesarean section has been reported to occur in 12% of cases. Uterine rupture after myomectomy is reported to be less frequent, at 0.4–1.7% of cases (Landon and Lynch, 2011). While uterine rupture (during or prior to labor) after myomectomy is less frequent, it is still a complication to be considered. Operative delivery is frequently recommended if the endometrial cavity is entered (a transmural incision of the myometrium), but there are limited data to support this recommendation.

Recurrence

Although relief of symptoms approaches 80%, fibroids have a propensity to recur after removal (Parker, 2007). Studies following fibroid development after myomectomy have demonstrated recurrence and reoperation rates up to 60% and 9%, respectively, at 5 years post myomectomy. The number of fibroids initially removed plays the most important role in recurrence. Patients with multiple fibroids are at the highest risk of recurrence. At 5 years or more from initial myomectomy, 27% of patients after single myomectomy and 59% after multiple myomectomy had clinically detectable myomas. Follow-up surgeries occur on average 7.6 years (range 5–10 years) after the initial myomectomy for 11% of women with a single fibroid removed and 26% in those patients with multiple fibroids removed. Subsequent hysterectomy rates vary in the literature but in up to a third of cases, recurrence of myomectomy is the primary reason for hysterectomy (Fauconnier et al., 2000).

Predictors of lower risk of myoma recurrence after laparoscopic myomectomy include those patients with fewer than two myomas before surgery, no childbirth after procedure and age at index surgery less than 36 years old. The use of GnRH agonists preoperatively may increase the risk of recurrence. Those with uterine size less than 12 weeks at the time of initial myomectomy, multiple myoma removal, and weight gain greater than 30 pounds after the age of 18 are at increased risk of second surgery. The disadvantages of using GnRH analogs include menopause-like symptoms and the negative impact on bone health associated with an estrogen-deficient state. There is also a higher likelihood of recurrence of fibroids in the 6 months following myomectomy.

Hysterectomy

While myomectomy is the preferred surgical option for treatment of fibroids in women still desiring future fertility, the definitive cure for fibroids remains hysterectomy. Fibroids are the most

common indication (39%) cited for performance of hysterectomy (Whiteman et al., 2008). The optimal surgical approach is unclear as there are scant data from large, well-designed randomized trials on which to base a recommendation. The chosen surgical route depends ultimately upon the woman's clinical circumstances, the surgeon's technical expertise, extent of fibroid disease, location of fibroids, and physician and patient preferences. Counseling the patient with fibroids is discussed in more detail in Chapter 12.

Abdominal hysterectomy

It is estimated that over 500,000 hysterectomies are performed each year. The vast majority of these procedures are still performed via an abdominal approach (64%), with vaginal (22%) and laparoscopic (14%) approaches being less common (Jacoby et al., 2009). Historically, abdominal hysterectomy has been the primary approach for large fibroids that cannot be approached vaginally or laparoscopically, or in which coexisting abdominal/pelvic pathology is suspected. Common guidelines for an abdominal approach include uterine enlargement (uterine size greater than 12 weeks), narrow vaginal caliber (less than two finger-breadths), lack of uterine descent and mobility, presence of adnexal disease, prior pelvic surgery (myomectomy, cesarean section), malignancy, contracted pelvis, and need to explore the upper abdomen. Patients with extensive adhesive disease and significant pelvic pathology may benefit from preoperative or intraoperative consultation with an experienced pelvic surgeon or gynecological oncologist.

Outcomes

The most common patient-reported symptoms prior to hysterectomy include menorrhagia, pelvic pain or pressure, sleep disturbance, fatigue, urinary incontinence, and bloating. One multicenter study found at least one of these symptoms was present and severe in 20–70% of patients preoperatively, but relief from these symptoms was achieved in most patients during the 24-month follow-up period (Kjerulff et al., 2000a). Ninety-nine percent of patients indicated that the surgery either somewhat or completely resolved the problems present prior to surgery. Patient satisfaction rates were high, with one post-hysterectomy survey demonstrating that 85% of women were completely satisfied, 11% mostly satisfied, 3% somewhat satisfied, and less than 1% not satisfied (Kjerulff et al., 2000b).

Psychosexual functional can also be improved following hysterectomy. Sexual functioning at baseline, prior to hysterectomy, and compared again at 6, 12, 18, and 24 months postoperatively demonstrated that the percentage of women engaging in sexual relations increased from 71% to 77%, the rate of dyspareunia decreased from 19% to 4%, while those women experiencing orgasm increased from 92% to 95% (Rhodes et al., 1999). In recent years, a supracervical hysterectomy has become a popular request from patients concerned about postoperative sexual function. While little evidence suggests a difference in function postoperatively, the risk of leiomyoma in the cervix is negligible, and there are no significantly increased risks associated with the supracervical hysterectomy, provided there is no history of dysplasia.

Intraoperative and immediate postoperative complications

While the mortality rate for hysterectomy is low, 0.32 per 1000 procedures, there are still intraoperative and postoperative morbidities to be considered. These include hemorrhage, racial disparities in outcomes, postsurgical infections, deep venous thrombosis (DVT) or pulmonary embolus (PE), and injury to surrounding pelvic organ or structures.

EVIDENCE AT A GLANCE #3

The following outcomes were noted when comparing pretreatment with GnRH analogs compared to either no treatment or placebo (Lethaby et al., 2001).

- 3.1% increase in preoperative hematocrit
- Decrease in uterine size by 2.2 gestational weeks (95% CI –1.9 to –2.3)
- Reduction in duration of hospital stay by –1.1 days (95% CI –0.9 to –1.2)

Obtaining an accurate measurement of blood loss is difficult, with the average blood loss from abdominal hysterectomy reported to be in the range of 300–400 mL. Perioperative bleeding severe enough to require blood transfusion occurs in 2% of abdominal hysterectomies. Large uteri are associated with a higher complication rate, primarily due to blood loss. When comparing uterine weights of less than

500 g, 500–999 g, and greater than 1000 g, risks of experiencing blood loss over 500 mL, blood transfusion, major organ injury, and hospital readmission all increased as the weight of the uterus increased (Unger et al., 2002).

☆ TIPS & TRICKS #4

Preoperative use of GnRH analogs

Given that excessive uterine size contributes negatively to surgical outcomes, GnRH analogs are occasionally used to reduce uterine and fibroid size prior to surgery. A recent Cochrane database review examined the effect of GnRH on surgical outcomes following myomectomy or hysterectomy. Ability to convert to a transverse incision or conversion to vaginal hysterectomy has been attributed to decreased uterine size following GnRH analog treatment, but reduction of intraoperative blood loss and total operating time benefits were minimal. Estimated blood loss decreased by 58 mL (95% CI −40.3 to −75.7 mL) and operative time decreased by 5.2 minutes (95% CI −1.8 to −8.6 min), respectively.

Racial differences in disease course and surgical outcomes after hysterectomy have been documented by multiple authors. African-American women are three times more likely to have clinically problematic fibroids as compared to other racial groups. These women are also more likely to have worse symptoms and surgical outcomes owing to larger size and number of fibroids. African-American women more frequently need a blood transfusion (OR 2.3, 95% CI 1.1–5.0) secondary to large blood loss and are more likely to have surgical complications (OR 1.4, 95% CI 1.3–1.5) (Jacoby et al., 2010).

The most common nosocomial infection encountered during hospital admissions is surgical site infection (SSI) (Lazenby and Soper, 2010). The pooled rate for SSIs after abdominal hysterectomy is reported at 1.7% by the National Healthcare Safety Network but ranged from 1% to 11% (Olsen et al., 2009). Approximately 50% of all SSIs diagnosed in the United States are superficial incisional SSIs. Women who developed incisional infections tend to have a higher BMI, are more likely to have diabetes mellitus, more likely to require postoperative blood transfusion, and less likely to have private health insurance (Olsen et al., 2009). Previous studies have examined infection rates between transverse and vertical incisions and have noted no difference in the type of incision or type of closure (continuous versus interrupted).

Infections are not limited to the skin or superficial layers of the incision, and can arise in deep organ spaces in the pelvis. Vaginal cuff infections and pelvic abscesses have more serious consequences and may require repeat operations for management. One of the most serious complications of vaginal cuff infections is dehiscence. The incidence of vaginal cuff dehiscence ranges from 0.14% to 4.1% with the vast majority, 63%, occurring after vaginal hysterectomy. The true incidence of vaginal cuff dehiscence is difficult to estimate because of different definitions and reporting variations from study to study. The most serious complication of vaginal cuff dehiscence is evisceration which is estimated to occur in up to 70% of dehiscence cases.

Techniques and practices have been implemented in an effort to decrease SSI and include use of antiseptic skin preparations, antimicrobial prophylaxis, thermoregulation, and sterile technique. With current practices, postoperative infection rates have decreased by approximately 50% (Lazenby and Soper, 2010). The Centers for Disease Control and Prevention (CDC) and the American Congress of Obstetricians and Gynecologists (ACOG) both offer recommendations on proper and adequate preoperative antibiotic prophylaxis not only for hysterectomy but also for other gynecological procedures.

Deep venous thrombosis is a risk following major gynecological or abdominal surgery. DVTs are estimated to occur in as many as 15–30% of surgical patients, with fatal pulmonary embolism occurring 0.2–0.9% of the time, in those who do not receive any thromboprophylaxis with surgery. With the use of prophylactic anticoagulants, the rate of DVT drops to 0.2%. A past meta-analysis has demonstrated the effectiveness of intermittent compression stockings (ICS) in the prevention of DVT, but the combined use of intermitten pneumatic compression (IPC) and a pharmacological agent was found to be superior to IPC alone in reducing the incidence of DVT (1.8% versus 4.2%) (Kakkos et al., 2008). A review of the evidence is less convincing regarding the efficacy of graduated compression stockings and care should be taken in assuming equivalence of this modality.

Injury to other pelvic structures, i.e. bladder, bowel and ureters, is an uncommon but significant complication during surgery. As stated previously, ureteral and bladder injury occurs in 1–3% of cases, while damage to the bowel occurs in approximately 1% of cases. In a retrospective study including over 62,000 hysterectomies, the total incidence of ureteral injury after all hysterectomies was 1.0 of 1000 procedures and only 0.4 of 1000 procedures after total abdominal procedures (Härkki-Sirén et al., 1998).

Long-term complications

Not all complications related to surgery are evident in the immediate postoperative period. Some complications may not be evident for many months or even years after the procedure. These complications include apical vaginal prolapse, urinary incontinence, fistula formation and even post procedure regret. An increased risk of prolapse after hysterectomy was demonstrated in a study following 160,000 women who underwent hysterectomy. Post hysterectomy, women were more likely than age-matched controls to require subsequent pelvic floor surgery (3.2% versus 2.0%); the overall hazard ratio (HR) for prolapse surgery was 1.7 (95% CI 1.6–1.7) (Altman et al., 2008). The study, however, did not reveal whether the women underwent hysterectomy for prolapse as an indication for the first surgery. For women without pre-existing prolapse, the risk for prolapse after hysterectomy is less clear. One prospective study found no association with prior hysterectomy in women in whom the hysterectomy was performed for nonprolapse indications.

It has been shown that hysterectomy increases risk for subsequent stress urinary incontinence (SUI). In contrast, one recent study reported that 30% of the women were already burdened with SUI prior to hysterectomy compared to only 8% in a random population sample. The true incidence of SUI caused by hysterectomy remains controversial (Roovers et al., 2000).

Fistula formation is an uncommon complication following hysterectomy with a prevalence generally less than 1% but as high as 4% after radial hysterectomy. Abdominal hysterectomy has been associated with the highest risk of fistulas, with some studies reporting up to 90% of fistulas resulting from this mode of surgery. Hysterectomy via laparotomy may introduce a higher risk for pelvic organ fistula disease because of its greater invasiveness and higher incidence of infections compared with the vaginal approach.

As hysterectomy in most cases is an elective procedure, one could assume that the incidence of regret would be low, given most women are likely to have completed their child-bearing years. Surprisingly, rates of regret range from 6% to 30% following surgery for benign indications, with a peak incidence at 2 years postoperative (Leppert et al., 2007). However, satisfaction with the surgery after 3 years was reported at greater than 90%. At 5 years post hysterectomy, long-term health was not noticeably different from women who had not undergone hysterectomy and there was a noted decrease in pelvic pain, urinary frequency, and depression scores compared to before hysterectomy.

Approach to extrauterine fibroids

The vast majority of fibroids can be found at various locations within the uterus: subserosal, intramural or submucosal (abutting or distorting the uterine cavity). Less commonly, fibroids can also occur at sites outside the uterus (extrauterine). These are histologically identical to the fibroids found within the uterus and are estrogen and progesterone receptor positive. Whenever extrauterine fibroids are encountered, leiomyosarcoma should be ruled out. The most common sites of extrauterine fibroids include the remainder of the genitourinary tract (broad ligament, bladder, vulva, ovaries, and urethra), the mesentery and other intraperitoneal locations and the pulmonary system. However, there have also been case reports describing extrauterine fibroids in even less common locations such as retroperitoneally, within the spinal canal (compressing the spinal cord), and intravascularly. This suggests the mechanism for these extrauterine occurrences may include hematogenous spread of neoplastic uterine smooth muscle cells from the uterus.

There have also been case reports of metastatic leiomyomas termed "benign metastasizing leiomyoma" (BML). First described in the 1930s, this term has become more widely accepted to describe recurrent extrauterine leiomyomas that have no malignant potential and are histologically identical to the patient's known uterine fibroids but recur in other anatomical locations within the body (see Chapter 11 for discussion of BML and cellular fibroids).

The typical first-line treatment for most patients suffering from extrauterine fibroids is medical management with oral contraceptive pills or GnRH agonists. However, for some patients, the specific

Table 10.1 Comparison of effectiveness and complications of myomectomy, hysterectomy, uterine artery embolization (UAE), and MRI-guided focused ultrasound (MRg-FUS)

Procedure	Size reduction	Reintervention (any therapy modality)*	Adverse event rate (major complication)	Transfusion	Febrile morbidity
Abdominal myomectomy	100%**	23–51%	3–7%	Up to 20%	Up to 36%
Laparoscopic myomectomy	100%**	23–51%	1–3%	Up to 20%	Up to 36%
Hysterectomy	100%	0%	3–23%	Varies based on route	15–25%
UAE	30–50%	8–37%	1.5%	NA	2%
MRg-FUS	33%	28%	1%	3–6%	6%

*Varies based on time from initial procedure (i.e. 1, 3, 5 or 8 years).
**Initial reduction. Recurrence percentage depends on length of time since initial procedure.
Numbers cited are based largely on Bradley (2009), Gupta et al. (2006),Kongnyuy and Wiysonge (2011), and Morita et al. (2008).
NA, not applicable.

extrauterine location of a fibroid may lead to functional or life-threatening symptoms that warrant surgical excision and may require co-ordination of the primary gynecological team in concordance with a gynecological oncologist, other surgical subspecialist or interventional radiology, depending on the tumor location.

Conclusion

Leiomyoma(s) of the uterus are extremely common. Surgical treatment of fibroids remains an option for women with symptoms (pain, bleeding, and infertility) who still desire future fertility or those women who are not willing to undergo a hysterectomy. The only known cure for fibroids remains hysterectomy. Surgical treatment of fibroids does not come without risks, as both myomectomy and hysterectomy carry the potential for unwanted outcomes, both immediate and delayed (Table 10.1). By optimizing patient selection and surgical technique, many women can have a successful and satisfying outcome. Even with the ever-expanding role of nonsurgical therapies, there remains a role for the surgical treatment of fibroids.

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11

Rare Fibroid Syndromes

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Management considerations in patients with rare fibroid syndromes

The practicing gynecologist is likely to encounter common uterine leiomyomas, but there are a number of rare fibroid syndromes that present clinical challenges. Because of the rarity of these disorders, management cannot be based on large clinical trials. Distinguishing characteristics of each syndrome may provide important diagnostic clues to such cases. Rare fibroid syndromes present with a constellation of physical and systemic findings that can be distinguished by genetic testing, specific imaging modalities, and physical examination. The objective of this review is to provide the clinician with management recommendations for these conditions (Figure 11.1).

Hereditary leiomyomatosis and renal cell cancer

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an inherited syndrome characterized by leiomyomas of the skin and uterus, and a susceptibility to develop aggressive renal cell malignancies. The cutaneous lesions of HLRCC are multiple, firm, skin-colored nodules on the trunk and extremities that may be associated with paresthesias and tenderness (Plate 11.1). The lesions are benign, highly penetrant, and typically present early in life (Toro et al., 2003). Uterine leiomyomas in HLRCC occur earlier in life compared to the general population, with a mean age at diagnosis of 30 years (Toro et al., 2003). The leiomyomas tend to be large and numerous, associated with menstrual irregularities and dysmenorrhea, and frequently result in hysterectomy at an earlier age as well (Toro et al., 2003). A subset of affected individuals will develop an aggressive renal cell cancer (usually type 2 papillary renal cell cancer, occasionally collecting duct carcinomas) which may be metastatic at the time of diagnosis (Toro et al., 2003).

Hereditary leiomyomatosis and renal cell cancer is inherited in an autosomal dominant pattern and is caused by a germline mutation of *fumarate hydratase* (FH), that encodes a Krebs cycle enzyme. Without this enzyme, fumarate builds up and ultimately leads to an accumulation of hypoxia-inducible factor (HIF) with subsequent stabilization of HIF (Ashrafian et al., 2010). While the exact mechanism of tumorigenesis has yet to be fully elucidated, the most widely accepted theory is that HIF stabilization induces expression of antiapoptotic and proliferative genes that stimulate angiogenesis and tumor growth (Al Refae et al., 2007; Ashrafian et al., 2010). Recent studies suggest that FH deficiency may also change the metabolic profile in affected individuals, resulting in an environment that not only accommodates but also contributes to tumor growth (Ashrafian et al., 2010).

Fibroids, First Edition. Edited by James H. Segars.

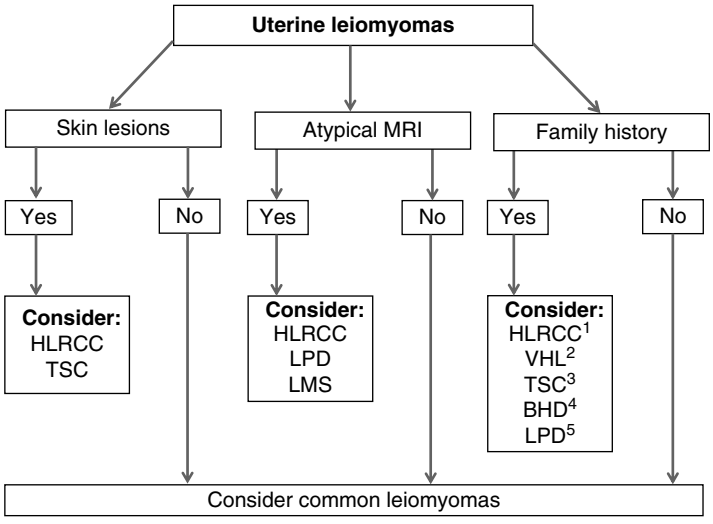

Figure 11.1 Management considerations in patients with rare fibroid syndromes. [1] Papillary renal cell cancer. [2] Clear type renal cell cancer. [3] Renal angiomyolipoma, multiorgan hamartomas. [4] Chromophobe renal cell cancer, hybrid chromophobe oncocytoma, spontaneous pneumothorax. [5] One reported case of familial clustering and association with Raynaud syndrome and prurigo nodularis (Halama et al., 2005).

Clinical considerations

A thorough history and physical examination are essential for the diagnosis of HLRCC, and often the family history alone will provide evidence to support the diagnosis. Affected individuals may initially present to the gynecologist with pressure symptoms from an enlarging fibroid uterus or with menstrual irregularities. Because the uterine leiomyoma of HLRCC develop at an earlier age of onset, many individuals also have a history of fertility-sparing myomectomies. If a hysterectomy was previously performed, it was likely done at an earlier age because of symptomatic leiomyomas. Affected individuals may also note a long history of painful, raised skin lesions that may have prompted prior dermatological evaluation.

Patients with HLRCC will frequently have a family history of uterine leiomyomas and early hysterectomies. In addition, males and females in the family may have a documented history of the cutaneous lesions found in HLRCC, as well as a history of early death from renal cell cancer for both sexes. If previous genetic testing for HLRCC has been performed, there may even be family members with documented FH mutations noted.

The appropriate evaluation can distinguish HLRCC from other potential differential diagnoses, including isolated benign uterine leiomyomas, uterine sarcomas, von Hippel–Lindau syndrome (VHL), nonfamilial renal cell cancers, metastatic carcinoma from an unknown primary, or benign renal cysts. Initial screening by the gynecologist usually includes an ultrasound of the uterus to identify the presence of leiomyomas; however, further characterization should be obtained through the use of various imaging modalities, biopsy, and genetic testing, detailed in the section below.

☆ TIPS & TRICKS #1

Assessment of suspicious leiomyomas should include T2-weighted MRI because atypical leiomyomas will often show enhancement (see Figure 11.2). To assess for renal tumors, CT or MRI of the abdomen and pelvis are preferred as the lesions may be incorrectly diagnosed as renal cysts on ultrasound given their isoechoic (or hypoechoic) appearance. Additionally, renal lesions in HLRCC tend to be unilateral, whereas the lesions in VHL are typically bilateral (Al Refae et al., 2007). A biopsy of the cutaneous lesions of HLRCC will confirm a benign smooth muscle histopathology. Genetic testing for mutation of the FH gene can confirm the diagnosis in the majority of cases.

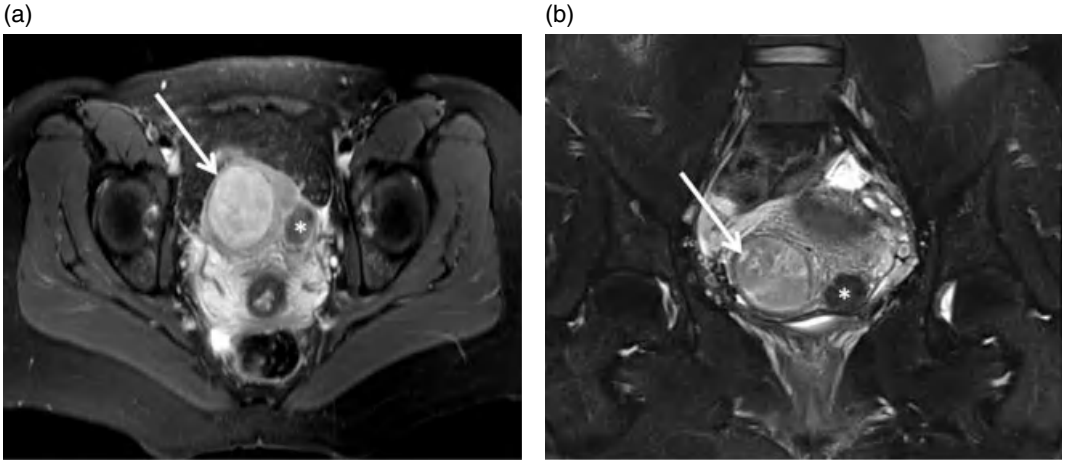

Figure 11.2 T2-weighted MRI findings of HLRCC leiomyomas. A single uterus in a patient with HLRCC may have both atypical leiomyoma and "common-appearing" leiomyoma. Axial (a) and coronal (b) T2-weighted images of the pelvis obtained with fat saturation demonstrate a 4.1 cm diameter T2 hyperintense leiomyoma in the right lateral body of uterus (*white arrow*), with an adjacent 2.1 cm diameter T2 hypointense leiomyoma in the left lateral body of uterus (*white asterisk*). T2 hyperintensity within leiomyomatas has been associated with cystic degeneration and/or necrosis, although it has also been observed in patients with HLRCC whose leiomyomata are atypical at histopathological assessment. Common fibroids are typically hypointense on T2-weighted imaging, as shown by the white asterisk. Note the increased signal (*white arrow*) with irregular, inhomogeneous signal of an atypical leiomyoma in a patient with HLRCC.

Recommended treatment and follow-up guidelines

Early detection of HLRCC is critically important, as renal cell cancer is the most lethal consequence of a delay in diagnosis. Unlike other familial renal cell cancers, the lesions in HLRCC are aggressive in nature and require resection or even total nephrectomy as soon as identified (Al Refae et al., 2007). Symptomatic uterine leiomyomas can be managed medically with standard agents; however, many individuals with HLRCC have already undergone surgical management with myomectomy or hysterectomy at an early age prior to diagnosis (Al Refae et al., 2007). Although not typically required, management of the cutaneous lesions utilizes medications to treat the symptoms of pain and paresthesias, or surgical interventions, such as cryoablation or excision (Al Refae et al., 2007).

Once diagnosed with HLRCC, effective treatment requires regular evaluations and a multidisciplinary team approach. Genetic counseling should be offered to the affected individual, and family members should be tested for the FH mutation. T2-weighted magnetic resonance imaging (MRI) should be performed as a baseline and when clinically indicated (Figure 11.2). Annual gynecological examinations and imaging should be performed to identify new or rapidly enlarging uterine leiomyomas, as there is the potential, albeit rare, for the affected individual to develop uterine leiomyosarcoma. A multidiscipline management approach involving the gynecologist, urologist, dermatologist, and genetic counselor can lead to timely diagnosis and subsequent treatment at an early stage of disease when cure may still be possible.

Benign metastasizing leiomyoma

Benign metastasizing leiomyoma (BML) is characterized by single or multiple extrauterine smooth muscle tumors in women with a history of uterine leiomyomas or concurrent uterine leiomyomas. First described by Steiner in 1939, the most common site of metastases is the lung, although case reports of nodules found in the skin, soft tissues, mediastinum, bones, lymph nodes, brain, and heart have been documented. Most cases occur in women of reproductive age who have had previous surgical intervention for leiomyomas, with the median

interval of diagnosis from time of initial surgery to discovery of metastatic lesions being 14.9 years (Ip et al., 2010).

While the name itself suggests a malignant etiology, the exact pathogenetic mechanism by which this condition occurs is still debated. The most widely accepted theory is that disease spreads via lymphatic or vascular routes, which is supported by a majority of the affected individuals having had a history of hysterectomy or myomectomy (Rivera et al., 2004). There is a small subset of affected individuals, however, that are simultaneously diagnosed with BML and uterine leiomyomas with no history of prior surgery, which suggests that other mechanisms may be responsible. Other explanations include metaplastic transformation of the coelomic epithelium, peritoneal seeding with metastatic implantation, or that the lesions of BML are actually low-grade leiomyosarcomas (Awonuga et al., 2010).

While the pathogenesis of this rare entity is not fully understood, it is well documented that progression of BML lesions is an indolent process, and there is abundant evidence to suggest that gonadal hormones heavily influence the growth patterns. Multiple case reports have shown a decrease in size or complete resolution of pulmonary lesions following menopause, pregnancy, and cessation of hormonal therapy (Nasu et al., 2009). Likewise, progression of lesions has been documented in premenopausal women or women on hormone replacement therapy (Nasu et al., 2009). The responsiveness of BML to estrogen and progesterone is important therapeutically.

Clinical considerations

Due to the slow-growing nature of BML and the classic presentation years after treatment for leiomyomas, the history and physical examination may not be diagnostic. Most affected individuals are asymptomatic, and pulmonary lesions are typically found incidentally on imaging; however, advanced disease in the lungs can manifest with symptoms such as chest pain, dyspnea or cough (Ip et al., 2010). When BML lesions occur outside the lungs, the presenting symptoms are usually due to mass effect (Ip et al., 2010). If extrauterine lesions are found in conjunction with uterine leiomyomas, or if the individual notes a history of uterine leiomyomas with subsequent surgical intervention and/or hormone replacement therapy, BML should be considered in the differential diagnosis. Because of the potential for BML to mimic the metastatic lesions of a malignancy, it is imperative that the gynecologist perform the appropriate evaluation to confirm the diagnosis.

While malignancy is the most crucial diagnosis to differentiate from BML, other conditions may be ruled out with the assistance of imaging and histopathology. The pulmonary lesions of BML are typically bilateral, multiple, well-circumscribed, discrete nodules on chest x-ray. On chest computed tomography (CT) or MRI, the lesions typically enhance homogeneously and have a nonspecific appearance (Fasih et al., 2008). Cavitation or calcification is rare, but has been documented (Fasih et al., 2008).

☆ TIPS & TRICKS #2

Leiomyomatous hyperplasia and lymphangioleiomyomatosis (LAM) may be considered in the differential diagnosis; however, both entities tend to show diffuse involvement of the lungs rather than discrete nodules. Hamartomas and primary pulmonary leiomyomas may also have a similar appearance on imaging, but the lesions tend to be solitary; this characteristic feature will often distinguish them from BML. In addition, hamartomas are typically calcified and more often found in males (Wentling et al., 2005). Other possible diagnoses to consider are sarcoidosis, amyloidosis, infectious granulomas or rheumatoid nodules (Fasih et al., 2008).

A definitive diagnosis of BML can only be obtained after biopsy or resection of the suspected BML lesion with histopathological examination. On gross examination, the extrauterine nodules will have the appearance of uterine leiomyomas, and will demonstrate white and whorled patterns on cut sections. To differentiate from leiomyosarcoma, the key features to analyze are the mitotic index, the degree of cytological atypia, and whether or not coagulative necrosis is present (Rivera et al., 2004). Unlike leiomyosarcoma, BML lesions are well differentiated with fewer than five mitoses per 10 high-power fields (HPFs), have minimal or no cellular atypia, and show no evidence of coagulative necrosis (Awonuga et al., 2010; Rivera et al., 2004). Additionally, tissue cultures derived from BML show lower cell proliferation compared to leiomyosarcoma as evidenced by statistically significant differences in the Ki-67 index (Awonuga et al., 2010). Immunohistochemistry characteristically

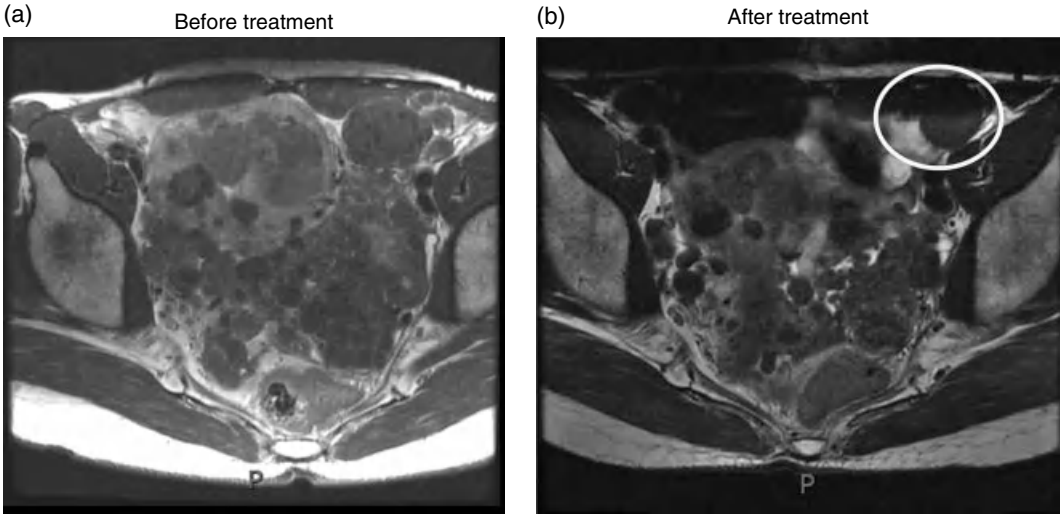

Figure 11.3 BML uterine lesions before and after leuprolide treatment. (a) MRI of pelvis before treatment. (b) MRI of pelvis demonstrating reduction in size of a circled lesion after treatment with the GnRH agonist, leuprolide.

stains positive for estrogen and progesterone receptors, which may help confirm the diagnosis of BML (Rivera et al., 2004). Smooth muscle tumors, including BML lesions, will also stain positive for actin, vimentin, and desmin (Nasu et al., 2009). Further immunohistochemical staining for human melanoma black (HMB45) will help differentiate BML from lymphangioleiomyomatosis (LAM), as only LAM lesions will stain positive for this marker (Wentling et al., 2005).

Recommended treatment and follow-up guidelines

Surgical intervention is required to diagnose BML and to exclude malignancy. Because of the rarity of this disease, there is no standard surgical approach for BML; however, if the affected individual is symptomatic, lesions require resection (Ip et al., 2010). Additionally, as the lesions of BML are typically sensitive to estrogen and progesterone, bilateral oophorectomy in premenopausal women may be helpful. This approach has been shown to be effective in controlling further tumor growth in several case reports (Nasu et al., 2009; Rivera et al., 2004). If the BML lesions are unresectable, if there is residual disease or if the affected individual refuses surgery, medical management can be considered (Figure 11.3).

Medical management of BML is aimed at suppressing the production of gonadal hormones and decreasing the peripheral conversion of estrogen. If an affected individual is on oral contraceptives or hormone replacement therapy, these should be discontinued. While there are no standard hormonal therapy regimens for BML, different strategies have been utilized with varying success. An individualized approach should be used to identify the optimal treatment strategy for BML. The gynecologist must factor in the individual's age and fertility status, the size and location of metastatic lesions, the hormone receptor status of the tissue, and also the willingness of the individual to undergo medical or surgical treatment with their potential side-effects.

EVIDENCE AT A GLANCE #1

Therapeutic strategy	Outcome
Gonadotropin-releasing hormone (GnRH) agonists	Clinical responsiveness and radiological regression in many affected individuals, although there are cases of further progression of disease despite this therapy
Progestins Progesterone	Mixed results on effectiveness
Aromatase inhibitors	Effective in cases of unresectable disease for long-term suppression therapy

Selective estrogen receptor modulators (SERMs)	Raloxifene used singly or in combination with aromatase inhibitors show overall clinical improvement

Awonuga et al. (2020); Nasu et al. (2009); Rivera et al. (2004); Wentling et al. (2005).

CAUTION #1

While the use of raloxifene has reported effectiveness for treatment of BML, not all SERMs have shown this same effect. The use of tamoxifen has actually been shown to worsen symptoms and induce tumor progression in affected individuals, and is not recommended (Riveral et al., 2004). Additionally, progesterone antagonists have been used in the treatment of BML; however, cystic degeneration has been observed in one case.

Affected individuals with BML have a good prognosis overall as the disease is indolent in nature. Long-term follow-up is recommended because of the potential for recurrence or progression of disease, although there are no specific guidelines regarding the frequency of evaluations. Some investigators believe the lesions to be low-grade leiomyosarcomas, which would argue for long-term follow-up of affected individuals.

Leiomyomatosis peritonealis disseminata

Leiomyomatosis peritonealis disseminata (LPD), also referred to as disseminated peritoneal leiomyomatosis, is another rare fibroid syndrome that affects women of reproductive age or, occasionally, postmenopausal women. LPD is characterized by multiple peritoneal and subperitoneal nodules that vary in size from 0.5 mm to 50 mm (Al-Talib and Tulandi, 2010). Despite the benign microscopic features of LPD, the disease may mimic diffuse peritoneal carcinomatosis macroscopically (Al-Talib and Tulandi, 2010). Often there are associated uterine leiomyomas present at the time of diagnosis or in the history of the affected individual. Similarly to BML, progression of LPD is associated with increased levels of gonadal hormones, which suggest a role in the etiology of this entity.

Although the pathogenesis of LPD remains unknown, several explanations have been proposed. The most strongly supported hypothesis suggests that LPD lesions originate from subperitoneal mesenchymal stem cells that undergo metaplasia into smooth muscle cells, likely under the influence of gonadal hormone stimulation (Al-Talib and Tulandi, 2010). Based on genetic analysis, other authors suggest that the lesions of LPD originate from a single uterine leiomyoma following peritoneal implantation and subsequent proliferation (Al-Talib and Tulandi, 2010). One report of a familial clustering of LPD in an autosomal dominant fashion suggests that genetics may play a more significant role than previously considered (Halama et al., 2005). There are now multiple reports of "LPD" following laparoscopic myomectomy where morcellation was utilized (Al-Talib and Tulandi, 2010). To our thinking, spontaneous LPD should be distinguished from iatrogenic LPD caused by morcellated fragments of atypical uterine leiomyomas that subsequently grow into the multiple nodules in the peritoneal cavity (Al-Talib and Tulandi, 2010).

Clinical considerations

Most affected individuals with LPD are asymptomatic and the diagnosis is made only after incidental findings during laparoscopy or laparotomy. Advanced disease may produce symptoms that prompt presentation to a gastroenterologist or gynecologist. If symptomatic, affected individuals most often present with nonspecific abdominal complaints, such as distension or discomfort from an expanding mass (Al-Talib and Tulandi, 2010; Halama et al., 2005). Although rare, an acute abdomen from intestinal obstruction may be the presenting symptom (Al-Talib and Tulandi, 2010). Other nonspecific symptoms include rectal or vaginal bleeding or pelvic pain.

Various imaging modalities provide clues to the diagnosis of LPD. An awareness of the malignant conditions that may mimic LPD (i.e. metastatic ovarian or peritoneal carcinoma, metastatic gastrointestinal cancer, lymphoma, mesothelioma) will assist the gynecologist when evaluating characteristics of each imaging modality. Although nonspecific, ultrasound may be utilized in the initial evaluation or to assess for recurrence of disease. Further characterization with the use of MRI is of specific clinical utility as the lesions

of LPD often exhibit an altered T2 signal intensity. Additionally, the use of CT and positron emission tomography (PET) should be considered.

☆ TIPS & TRICKS #3

Imaging modality	Notable features suggestive of LPD
Ultrasound	Multiple, solid, homogeneous, hypoechoic nodules with low to moderate vascularity, and no evidence of ascites
Contrast-enhanced computed tomography (CT)	Solid lesions that display heterogeneous uptake in the arterial and venous phase, with gradual progression to homogeneous uptake in the late phase
Magnetic resonance imaging (MRI)	Characteristic isointensity with skeletal muscle on T1- and T2-weighted images; if gadolinium is administered, the lesions also demonstrate homogeneous uptake in the late phase
Positron emission tomography (PET)	Demonstrate no uptake of fluorodeoxyglucose (FDG), whereas malignant lesions will typically demonstrate avid uptake

Talebian Yazdi et al. (2010).

The diagnosis of LPD relies on histopathological evaluation which is required to definitively exclude malignancy. On gross examination, the peritoneal lesions of LPD appear identical to uterine leiomyomas and are characteristically well-circumscribed, firm, white-to-gray nodules (Al-Talib and Tulandi, 2010). Microscopically, the nodules show smooth muscle cell proliferation without atypia, few or no mitotic figures, and no evidence of necrosis (Al-Talib and Tulandi, 2010). Specific cellular components may include fibroblasts, myofibroblasts, decidual cells, or occasionally endometrial stromal cells (Al-Talib and Tulandi, 2010). Lesions typically stain positive for estrogen and progesterone receptors, smooth muscle and muscle-specific actin, vimentin, and desmin (Al-Talib and Tulandi, 2010). Findings of increased mitotic figures, cellular atypia, and tumor cell necrosis are suggestive of malignancy and are not found in LPD.

Recommended treatment and follow-up guidelines

Similar to other rare fibroid syndromes, there is no consensus on standard management for individuals affected with LPD. The general recommendation is for immediate cessation of any hormonal therapy followed by conservative medical management with or without surgical debulking, especially in women that desire future fertility. Surgical treatment consists of excision of all visible LPD nodules as well as omentectomy (Al-Talib and Tulandi, 2010). If the affected individual is postmenopausal or has completed child bearing, then a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and debulking may be offered as definitive treatment (Al-Talib and Tulandi, 2010). Cases have been reported of complete resolution of LPD without recurrence following surgical intervention (Halama et al., 2005).

Medical management of LPD is similar to BML and centers on the sensitivity of the lesions to gonadal hormones. Once all exogenous hormones have been discontinued, gonadotropin-releasing hormone (GnRH) agonists or progestins may be used for ovarian suppression. Other agents that are used in BML, such as aromatase inhibitors, selective progesterone receptor modulators (SPERMs) and selective estrogen receptor modulators (SERMs), may show clinical utility; however, evidence is limited to case reports due to the rarity of the disease. Selection of medical therapy is based upon treatments that are effective in the treatment of leiomyoma.

EVIDENCE AT A GLANCE #2

Therapeutic strategy	Outcome
Gonadotropin-releasing hormone (GnRH) agonists	Reported success with regression of leiomyomatosis peritonealis disseminata nodules in affected individuals with and without surgery

Progestins	Megestrol acetate has been shown to be effective in cases where surgical treatment was not an option, or to treat residual tumor when optimal debulking could not be performed
Chemotherapeutic agents	Reported effectiveness of chemotherapeutic agents in a case of progressive unresectable disease with lesions that do not express estrogen or progesterone receptors

Al-Talib and Tulandi (2010); Lin et al. (2009).

Long-term follow-up is recommended for individuals with LPD. Despite a good overall prognosis and survival rate, recurrence of disease has been reported even with optimal surgical and medical interventions (Halama et al., 2005; Talebian Yazdi et al., 2010). Regular gynecological examinations, including the use of imaging modalities such as ultrasound, CT or MRI, may be the best recommendation to screen for recurrent disease.

CAUTION #2

Although rare, there is the potential for LPD to undergo malignant transformation, with a reported incidence of approximately 6% (Lin et al., 2009). If the gynecologist suspects leiomyosarcoma, PET should be considered as well.

Uterine smooth muscle tumors of uncertain malignant potential

When uterine smooth muscle tumors display features that lie between benign and malignant, they are classified as uterine smooth muscle tumors of uncertain malignant potential (STUMP). The World Health Organization created this classification scheme for any tumors that could not be unequivocally designated as benign or malignant, or that display features that are worrisome for malignancy but that do not fulfill all diagnostic criteria for leiomyosarcoma (Ip et al., 2010). STUMPs are categorized on the basis of mitotic index, the degree and extent of cellular atypia, and the presence or absence of coagulative tumor cell necrosis. The four STUMP subgroups are: atypical leiomyoma with limited experience (AL-LE), atypical leiomyoma with low risk of recurrence (AL-LRR), smooth muscle tumor with low malignant potential (SMT-LMP), and mitotically active leiomyoma with limited experience (MAL-LE) (Ip et al., 2010). Despite specific criteria that define each of these entities, misdiagnosis and overdiagnosis of STUMP occur due to subjective interpretation when reviewing tissue samples.

Caring for an affected individual with STUMP can present a challenge for the gynecologist. There is limited experience with each of the subgroup entities, and evidence in the literature is based primarily on case reports. It is unclear whether these tumors represent an overlap between benign and malignant uterine smooth muscle tumors, or if they are an intermediate in the progression of benign to malignant disease. In addition, the uncertain clinical behavior of these tumors makes standardization of management impractical given the current level of knowledge.

Clinical considerations

Affected individuals with STUMP typically present with the same symptoms as an individual with common benign leiomyomas. They are usually of reproductive age or postmenopausal, and may present to the gynecologist with complaints of irregular menses, pelvic pressure or pain, symptoms of anemia or increasing abdominal size. Studies have shown that women diagnosed with STUMP who later develop a recurrence are more likely to be younger than those who do not develop recurrent disease (Ip et al., 2010). Other studies have attempted to distinguish characteristics such as race/ethnicity and tobacco use that make recurrence more likely; however, there does not appear to be a significant difference in affected individuals with or without recurrence (Guntupalli et al., 2009). Unfortunately, there are no specific discriminating features that the gynecologist can identify during the history and physical examination that will lead to the diagnosis of STUMP. Diagnosis relies solely on the histopathological findings from resected tissue.

Table 11.1 Classification of uterine smooth muscle tumors of uncertain malignant potential (Ip et al., 2010)

Subgroup	Mitotic index	Cellular atypia	Coagulative tumor cell necrosis
Atypical leiomyoma with limited experience (AL-LE)	≤10 mitoses per 10 HPFs	Focal or multifocal, moderate to severe	Absent
Atypical leiomyoma with low risk of recurrence (AL-LRR)	<10 mitoses per 10 HPFs	Diffuse moderate to severe	Absent
Smooth muscle tumor with low malignant potential (SMT-LMP)	<10 mitoses per 10 HPFs	Absent to mild	Present
Mitotically active leiomyoma with limited experience (MAL-LE)	≥20 mitoses per 10 HPFs	Absent	Absent

As previously noted, the diagnosis of STUMP requires microscopic evaluation of the following three features: mitotic index, the degree and extent of cellular atypia, and the presence or absence of coagulative tumor cell necrosis. These histological features are also defined in leiomyomas and leiomyosarcomas, and both entities are used as reference points for the diagnosis of STUMP. The current classification scheme of STUMP includes four subgroups and is outlined in Table 11.1 (Ip et al., 2010).

Immunohistochemical staining can also help to identify cases of STUMPs that are more likely to develop recurrence of disease (Ip et al., 2009). Studies have shown that STUMP lesions which have overexpression of both p53 and p16 are more likely to exhibit clinically aggressive behavior, which is similar to what is seen in leiomyosarcoma (Ip et al., 2009). This additional testing may be a useful tool in determining which affected individuals should receive more frequent surveillance. Unlike BML or LPD, there is inconsistent evidence on the presence or significance of estrogen and progesterone receptors (Ip et al., 2009).

Recommended treatment and follow-up guidelines

Standard treatment guidelines have yet to be implemented for this rare fibroid syndrome. Most recommendations are based on a limited number of cases and have changed over time due to the evolving diagnostic classification scheme of STUMP lesions. As most cases of STUMP are diagnosed only after hysterectomy, further surgical intervention is not recommended. If STUMP is diagnosed after myomectomy, it is reasonable to consider hysterectomy if the affected individual has completed child bearing. For those affected individuals who desire future fertility, the gynecologist should strongly caution the patient about the potential for recurrence or progression into leiomyosarcoma (Ip et al., 2010).

Strict follow-up is thus required in all cases of STUMP, regardless of hysterectomy status. A referral to a gynecological oncologist is also advised.

EVIDENCE AT A GLANCE #3

Screening modality	Interval surveillance recommendations
Pelvic exam	Every 6 months for 5 years, then annually for another 5 years
Chest x-ray	Annually to exclude metastases
Pelvic ultrasound, computed tomography or magnetic resonance imaging	Annually to detect recurrence

Ip et al. (2010).

Treatment for recurrence is typically surgical resection of new lesions with or without adjuvant therapy. Reported use of progesterone, GnRH agonists, pelvic irradiation, and chemotherapy has shown effectiveness in stabilizing the disease process (Ip et al., 2010). It should be noted, however, that there have also been reports of patients who have not had recurrence or progression of disease with no adjuvant therapy (Ip et al., 2010).

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an inherited syndrome in which affected individuals develop multiple hamartomas in various organs, including the brain, kidney, skin, heart, lung, and liver. Inherited in an autosomal dominant fashion, TSC exhibits high penetrance and variable expressivity. The pathogenetic mechanism by which TSC occurs is via the "two-hit" theory of inheritance which requires both alleles of the gene to be mutated in order for the disease to manifest (Borkowska et al., 2011). The tumor suppressor genes responsible for the findings in TSC are aptly named TSC1 and TSC2, and are located on chromosomes 9q34 and 16p13, respectively (Borkowska et al., 2011). TSC1 codes for the protein hamartin and TSC2 codes for the protein tuberin; together, they form a complex that activates GTPase and reduces the activation of the mammalian target of rapamycin (mTOR). Under normal conditions, mTOR is able to detect nutrient availability, hypoxia, and growth factor stimulation, and is involved in cell cycle progression, transcription and translation control, and nutrient uptake (Curatolo et al., 2008). When TSC mutations are present, mTOR activation is increased, resulting in disorganized cellular overgrowth, abnormal cellular differentiation, and tumor formation (Curatolo et al., 2008). Studies of the Eker rat model provided significant evidence that germline defects in the homolog of the TSC2 gene were responsible for the development of uterine leiomyomas in rats (Cook and Walker, 2004). In a similar fashion, loss of function of the TSC2 gene protein, tuberin, has been shown to produce sporadic cases of uterine leiomyomas in humans (Cook and Walker, 2004). It is possible that the phenotype of individuals affected with a TSC2 mutation may feature the development of uterine leiomyomas.

The phenotype of a TSC-affected individual is highly variable and the same genotype can produce different manifestations of disease even within the same family (Borkowska et al., 2011). TSC hamartomas may develop in the lungs of reproductive-aged women as LAM, a related rare fibroid syndrome. LAM is characterized by lung cysts that may obstruct the airway and lymphatics, and patients may present with symptoms of dyspnea, cough or chest pain (Curatolo et al., 2008). LAM can lead to respiratory failure or death, and most affected individuals require lung transplantation within 10–15 years of diagnosis (Borkowska et al., 2011). Cutaneous lesions associated with TSC (i.e. hypomelanotic macules, facial angiofibromas, shagreen patch, fibrous fibroid plaques) are commonly seen on exam and may provide the gynecologist with clues as to the diagnosis (Curatolo et al., 2008). Following the discovery of the role of the mTOR pathway in TSC, studies performed with rapamycin (also known as sirolimus) have shown a reduction in the tumor burden of affected individuals (Borkowska et al., 2011). Unfortunately, once rapamycin is discontinued, tumor regrowth has been documented (Borkowska et al., 2011). Future studies to determine the optimal regimen for rapamycin treatment need to be performed.

Birt–Hogg–Dubé syndrome

Birt–Hogg–Dubé (BHD) syndrome is an inherited condition characterized by cutaneous hamartomas, pulmonary cysts, and a predisposition to developing renal cancer. Like TSC, this autosomal dominant condition follows the "two-hit" theory of inheritance, and the specific aberration of BHD is located on chromosome 17p11.2 (Menko et al., 2009). Under normal conditions, the tumor suppressor folliculin gene (FLCN) encodes for the protein folliculin, whose function is still not completely understood (Menko et al., 2009). One of the proposed pathogenetic mechanisms by which the syndrome occurs involves the mTOR pathway. Unlike TSC mutations which lead to mTOR activation, FLCN mutations appear to lead to mTOR inhibition and subsequent tumor formation (Menko et al., 2009). While there have been no reported cases of uterine leiomyomas in humans affected with BHD, canine studies show evidence of a hereditary BHD syndrome that includes skin lesions, uterine leiomyomas, and renal cell cancer in German Shepherd dogs (Cook and Walker, 2004). The genetic mutation for this syndrome has been mapped to the canine chromosome that contains the homolog of the human BHD gene (Cook and Walker, 2004). Future studies evaluating the association between human cases of BHD and uterine leiomyoma need to be performed, as a thorough evaluation of the possible link has yet to be investigated in human studies.

The phenotype of BHD is highly variable, even within the same family, which can make the diagnosis challenging. The cutaneous lesions of BHD are distinctive and appear as multiple, flesh-colored or whitish dome-shaped papules that cover the face, neck, ears or upper trunk (Menko et al., 2009; Palmirotta et al., 2010). Although asymptomatic and benign, the numerous cutaneous lesions of BHD are burdensome and individuals often request treatment. Genetic testing should be performed despite a minority of affected individuals not having an identifiable FLCN gene mutation on screening. Finally, new therapeutic options using rapamycin are being investigated since the pathogenetic mechanism is thought to involve the mTOR pathway (Menko et al., 2009).

Von Hippel–Lindau disease

Von Hippel–Lindau (VHL) disease is the most common inherited renal cancer syndrome and affected individuals are prone to developing numerous extrarenal lesions. The pathogenetic mechanism by which VHL disease manifests clinical disease has been well studied and is similar to that of HLRCC. VHL disease is inherited in an autosomal dominant fashion and is highly penetrant with variable expressivity (D'Angelo and Prat, 2010). The tumor suppressor VHL gene is located on chromosome 3p25 and disease follows the "two-hit" theory of inheritance. The VHL gene normally codes for the protein pVHL which forms a complex with other proteins to target and regulate HIF (Linehan et al., 2009). When both alleles of the VHL gene have been mutated, the pVHL complex is unable to degrade HIF, which leads to an accumulation of HIF (Linehan et al., 2009). As previously noted, HIF is a transcription factor that is responsible for the downstream expression of multiple proteins that regulate angiogenesis and tumor growth under normal conditions (Linehan et al., 2009). In VHL disease, the end result is increased levels of growth factors that create an environment in which cancer cells proliferate and flourish.

Fibroids and malignancy

For the rare fibroid syndromes previously discussed, malignant associations specific to each syndrome have been reviewed; this section will focus exclusively on malignancy associated with typical benign uterine leiomyomas, specifically uterine leiomyosarcomas. Leiomyosarcomas account for only 1–2% of all uterine malignancies and are the malignant smooth muscle cell counterpart to benign uterine leiomyomas. The most common leiomyosarcomas are of the spindle cell histological subtype, although epithelioid and myxoid variants are possible (D'Angelo and Prat, 2010). Leiomyosarcoma may be found concurrently with or, rarely, may originate from a benign uterine leiomyoma (D'Angelo and Prat, 2010). Because there are no pathognomonic imaging features that can distinguish leiomyosarcoma from benign leiomyoma, and because the clinical characteristics are so similar as well, identification of this rare malignancy often occurs after surgery for a presumed benign condition. Once diagnosed, the clinical behavior of leiomyosarcoma can be unpredictable; however, they are generally regarded as very aggressive tumors that have a poor prognosis even if diagnosed at an early stage or even if confined to the uterus (D'Angelo and Prat, 2010). Recent changes in FIGO staging are noted in Table 11.2.

Controversy exists regarding the pathogenesis of uterine leiomyosarcomas. Sporadic cases are most

Table 11.2 FIGO staging for uterine leiomyosarcomas (2009) (D'Angelo and Prat, 2010)

Stage	Definition
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

frequently encountered, although cases of leiomyosarcoma arising from pre-existing uterine leiomyomas have been reported (D'Angelo and Prat, 2010). Additionally, there is evidence to suggest that FH mutations put affected individuals at a higher risk of developing uterine leiomyosarcomas, as well as benign uterine leiomyomas (D'Angelo and Prat, 2010). These tumors are considered to be genetically unstable with complex chromosomal aberrations and the disease likely manifests after an accumulation of multiple genetic defects have occurred (D'Angelo and Prat, 2010).

Clinical considerations

The signs and symptoms of a uterine leiomyosarcoma can be identical to those of a benign uterine leiomyoma, which makes preoperative diagnosis challenging. Most affected individuals present after the fifth decade of life. Symptoms are likely to include abnormal vaginal bleeding, a palpable pelvic mass or pelvic pain (D'Angelo and Prat, 2010). The gynecologist should be suspicious for a uterine leiomyosarcoma if tumor growth is noted in a menopausal or postmenopausal woman (D'Angelo and Prat, 2010). Less frequently, affected individuals may present with symptoms related to tumor rupture (i.e. acute abdomen from hemoperitoneum), tumor extension beyond the uterus (i.e. enlarging abdomen or compression of adjacent structures) or metastases (D'Angelo and Prat, 2010). Ultimately, the diagnosis lies in the histopathological findings following surgical resection.

There are no pathognomonic features to definitively diagnose uterine leiomyosarcoma by any imaging modality, but there are certain clues that may raise the gynecologist's suspicion for malignancy. Ideally, using a combination of PET with MRI or CT will assist the gynecologist in obtaining information about the biological activity and anatomy of the suspected tumor.

☆ TIPS & TRICKS #4

Imaging modality	Notable features of leiomyosarcoma
Ultrasound	Large oval-shaped growths with heterogeneous internal echoes, a thin myometrium, and central necrosis of the tumor
Magnetic resonance imaging (MRI)	Diverse findings may include: • mass with focally infiltrative margins • sharply marginated mass with low-signal intensity resembling a benign leiomyoma • lobulated mass of high-signal intensity on T2-weighted images Hemorrhagic foci, necrosis, and the absence of calcifications on MRI suggest leiomyosarcoma
Positron emission tomography (PET)	Avid uptake of fluorodeoxyglucose suggests malignancy, although small and low-grade tumors may not be detected, and it is possible for benign tumors to demonstrate uptake

Amant et al. (2009).

Leiomyosarcomas are diagnosed histopathologically when at least two of the following three features are present: ≥10 mitoses per 10 HPFs, diffuse cellular atypia, and coagulative tumor cell necrosis (Guntupalli et al., 2009). Additional features frequently seen include hypercellularity, infiltrative borders, large tumor size (>10 cm), and extrauterine extension (D'Angelo and Prat, 2010). These characteristic features are based on the spindle cell histological subtype of uterine leiomyosarcoma, which is the most common subtype found.

CAUTION #3

The histological subtypes of epithelioid and myxoid leiomyosarcomas may demonstrate different pathological features, making the diagnosis of these rare variants a challenge (D'Angelo and Prat, 2010). In both variants, cellular atypia may be more mild and the mitotic index may be <3 mitoses per 10 HPFs

(D'Angelo and Prat, 2010). Epithelioid leiomyosarcomas may not demonstrate coagulative tumor cell necrosis, and myxoid leiomyosarcomas may be hypocellular rather than hypercellular (D'Angelo and Prat, 2010). Diagnosis of these rare variants is thus based on the presence of infiltrative borders with the other characteristic features described above (D'Angelo and Prat, 2010). The gynecologist should also be aware of the challenges in diagnosing leiomyosarcoma via frozen section; confirmation of this serious condition requires a thorough evaluation of all sections of suspicious tissue.

Immunohistochemical staining and identification of specific tissue markers may also be helpful in the diagnosis of uterine leiomyosarcomas. Although not specific for leiomyosarcoma, expression of the smooth muscle markers desmin, h-caldesmon, smooth muscle actin, and histone deactylase 8 is usually seen (D'Angelo and Prat, 2010). Studies have shown that estrogen, progesterone, and androgen receptors are present in only 30–40% of cases (D'Angelo and Prat, 2010). The Ki-67 index is frequently measured and studies have shown a statistically significant elevation of levels in uterine leiomyosarcoma compared to benign leiomyoma (D'Angelo and Prat, 2010). Overexpression of p16 and p53 has also been shown in uterine leiomyosarcomas, and may provide additional support for a malignant versus benign tumor (D'Angelo and Prat, 2010).

Recommended treatment and follow-up guidelines

The aggressive nature of uterine leiomyosarcoma paired with ineffective treatment options result in the poor prognosis associated with this disease. Total abdominal hysterectomy with debulking of extrauterine disease by a gynecological oncologist is the recommended surgical treatment. Bilateral oophorectomy is typically performed as most affected individuals are menopausal or postmenopausal, although ovarian preservation may be considered in premenopausal women with early-stage disease (D'Angelo and Prat, 2010). The small possibility of pre-existing ovarian metastases or a low-grade hormone-sensitive uterine leiomyosarcoma is also a consideration for bilateral oophorectomy at the time of hysterectomy (Amant et al., 2009). Lymphadenectomy is not a standard surgical recommendation as it has not been shown to be an independent prognostic factor for survival; however, controversy exists regarding this approach given the small percentage of metastases that have been shown in studies (D'Angelo and Prat, 2010).

The effect of adjuvant therapy on survival is still unclear. For advanced or recurrent disease, doxorubicin or docetaxel with gemcitabine has been shown to have some effectiveness (D'Angelo and Prat, 2010). Radiation therapy has also shown some effectiveness for control of local recurrences (D'Angelo and Prat, 2010). Despite these therapeutic options, recurrence rates range from 53% to 71%, and the overall survival rate ranges from 15% to 25% with a median survival of only 10 months (D'Angelo and Prat, 2010).

Postoperative surveillance in cases of uterine leiomyosarcomas should be strict. The optimal follow-up management plan includes regularly scheduled visits and pelvic examinations with a gynecological oncologist, as well as directed imaging to detect recurrent, progressive or metastatic disease.

Conclusion

This chapter is intended to provide information that will be helpful to the clinician managing rare fibroid disorders. Because of the rare nature of these diseases, no large randomized trials can be used in clinical decision making. Most patients will benefit from a multidisciplinary approach, as well as multimodal imaging. Medical management is often based on extrapolation of drug studies for the treatment of common fibroid tumors. Combination medical therapy may stabilize disease in some cases. Additional research is needed to develop targeted therapies for these uncommon conditions.

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12

Counseling the Patient with Uterine Fibroids

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Introduction

After a diagnosis of fibroids is made, a woman is faced with a growing range of options regarding management from simple changes in lifestyle with observation to hysterectomy. Healthcare providers play a key role in appropriately matching treatment in women with fibroids based on individual patient needs and symptoms. In this chapter we will provide a background for counseling women with fibroids about management options, prevention of progression and recurrences, and available educational resources.

Long-term management of the patient with fibroids

Assessing patient desires and extent of fibroid disease

As many treatment options for fibroids exist, a thorough initial history and physical exam are needed to tailor therapy to women's individual needs. In gathering the patient's history, find out first what symptoms the patient has and what has transpired in the past with her medical care and ask what goals the patient has for her treatment. Many women will be asymptomatic while others will develop menorrhagia, dyspareunia, urinary frequency, constipation, pelvic pressure and pain, and rarely acute renal insufficiency or failure due to ureteral compression. Detailed information regarding vaginal bleeding patterns, including a menstrual diary, is helpful in characterizing bleeding. Obtaining a detailed obstetric history, including future reproductive plans, is essential in assisting patients with treatment options as definitive therapy is never an option for women wanting to maintain child-bearing capacity. Medical history, including anemia, is critical in assessing urgency of therapy as some women may need to be on iron therapy or even require blood transfusion due to menorrhagia associated with fibroids. Presence of major comorbidities and history of multiple abdominal surgeries encourage alternatives to hysterectomy as the risk of invasive surgery may be high.

In terms of family history, there are rare syndromes (hereditary leiomyomatosis and renal cell cancer) and genetic conditions (fumarate hydratase mutations) which may make a woman more susceptible to fibroids or may dictate a team of specialists for patient care (discussed in detail in Chapter 11). Thorough review of systems may reveal symptoms that were not initially revealed in the history of present illness. Physical exam should focus carefully on the abdominal and pelvic exam. Size and mobility of uterus are helpful in determining therapeutic approach.

As there are many modalities for establishing a diagnosis of fibroids, it is important to use the appropriate one. Imaging modalities used to detect fibroids are discussed in greater detail in Chapter 2. Exact characterization of fibroid location facilitates management of fibroids. Determining location of fibroids in relation to patient symptoms and preferences can guide patient therapy. Determining relative number, size, and location of fibroid(s)

Fibroids, First Edition. Edited by James H. Segars.

(anterior, posterior, fundal, lateral, lower uterine segment, etc.) can help determine the best therapeutic approach, since it is essential to individualize treatment based on the fibroid disease present, which will vary greatly between patients.

In counseling women with fibroids, providing patients with detailed information regarding their specific diagnosis and the multitude of treatment options is best for facilitating management. The study by Solberg et al. (2010) used the following patient preferences to assist with informed decision making: immediate symptom relief, fertility preservation, definitive treatment, low failure rate, minimal postoperative recovery, avoidance of medications, and improved sexual functioning. If fertility preservation is a priority or the patient wishes to retain her uterus, uterine-sparing alternatives to hysterectomy are the ones to be presented and discussed with the patient. It is important to remember that hysterectomy remains the only definitive curative therapy; all other methods of treatment may allow for small or undetectable fibroids to grow or new fibroids to form. Patients were more satisfied with the decision when their individual preferences were taken into account and decision-making tools were provided compared to those who were simply told what was in their best interest.

Management options vary in degree of level of invasiveness and include medical (reviewed in Chapter 6), procedural (see Chapters 7 and 8), and surgical therapies (see Chapters 9 and 10). In terms of conservative management, many women who are completely asymptomatic may require no therapy beyond expectant management with annual pelvic exams with or without pelvic ultrasound monitoring. A rare but notable exception to this rule is if the patient becomes suddenly symptomatic or fibroids rapidly grow during monitoring.

CAUTION

Leiomyosarcoma

As the most common uterine sarcoma, leiomyosarcoma account for 1–2% of uterine malignancies. Risk factors for leiomyosarcoma include: rapid growth, large size (typically >10 cm) and can be associated with vaginal leeding and pelvic pain. Diagnosis is established by a review of the surgical pathology specimen and includes the following histological criteria: hypercellularity, severe nuclear atypia, and >15 mitotic figures per 10 HPF field. It is important to remember that the risk of leiomyosarcoma is very rare (17.1/1,000,000), and they are associated with a poor prognosis even with early detection. If suspicion for leiomyosarcoma exists, surgical removal for pathological evaluation is essential for confirmation. However, the vast majority of rapidly growing fibroids will prove to be benign and patients should be reassured. MRI may be helpful in some cases, as described in Chapter 11.

Long-term medical management for the patient with fibroids

Many factors must be considered when discussing medical management of fibroids. One must take into account medical comorbidities, smoking history, patient age and preferences, symptoms, and duration of therapy when determining if medical therapy is appropriate for a patient. Medical management is typically hormonal, including combined oral contraceptive pills, progestin-only pill, aromatase inhibitors, antiprogestins or selective progesterone receptor modulators, levonorgestrel-releasing intrauterine device, or gonadotropin-releasing hormone (GnRH) agonists such as depot leuprolide injection with add-back hormonal therapy. Many of these options do not provide long-term symptomatic relief but may be beneficial in the short term if the patient is perimenopausal or has significant contraindications to procedural or surgical-based therapies. Use of tobacco in women over 35 years or certain comorbidities may preclude use of estrogen-containing therapies. Consider the following case.

CASE REPORT #1

Mrs Johnson was a 45-year-old P0 ½-pack per day smoker who presented with pelvic pressure/pain and dysuria. Pelvic organ prolapse quantification (POP-Q) revealed stage 0

prolapse. Urinalysis was negative for hemoglobin, leukocyte esterase, and nitrites. Urine culture showed no growth and cytology was negative. Chlamydia testing was negative. Pelvic pain/urinary frequency (PUF) questionnaire score was <10. Postvoid ultrasound of bladder revealed 25 mL urine. Incidentally with the ultrasound of the bladder, a large pelvic mass was seen and MRI of pelvis was ordered, revealing multiple intramural fibroids, with the largest measuring 5 cm. Her priority is immediate symptom relief and she wanted to avoid surgery and UAE, if possible. While the patient would be a good candidate for UAE, the number and size of the fibroids would make her a poor candidate for MR-guided focused ultrasound. In discussing medical options with this patient, you review the risk of tobacco smoking with oral estrogen therapy. As her symptoms may be related to the size of the uterus, GnRH agonist therapy was discussed, as it has been shown to be effective in decreasing volume of fibroids. Upon review of systems, the patient stated she was experiencing hot flashes and that her mother went through menopause at 47 years of age. The patient was informed that GnRHa therapy for fibroid is off label per FDA indications and that risk of headache, vasomotor symptoms, failure to relieve symptoms, and initial heavy vaginal bleeding and pain may occur. Potential benefits include decrease in volume of fibroids from 6–50%, although the patient should be informed that this may or may not relieve her symptoms. If patient has symptom relief, discontinuing GnRHa therapy will cause an eventual return of symptoms, if menopause does not occur during treatment.

Role of new procedures and surgery in the long-term management of the patient with fibroids

Many new procedural-based options for fibroid therapy have been developed and access has expanded over the last decade. Uterine artery embolization (UAE), global endometrial ablation, and magnetic resonance (MRI)-guided high-intensity focused ultrasound fibroid ablation all provide less invasive outpatient options for managing fibroids and results; these approaches are reviewed in Chapters 7 and 8. Surgical options including myomectomy (via laparotomy, laparoscopy with or without robot assistance or hysteroscopy) and hysterectomy (vaginal, laparoscopic with or without robot assistance or laparotomy) are still the most commonly performed options. Myomectomy is typically reserved for those who desire future fertility, but there is no reason why this option cannot be applied in patients where this more conservative surgical approach addresses the symptoms and goals of the patient.

☆ TIPS & TRICKS

Myomectomy

When performing a myometomy in a woman who desires future fertility, it is important to avoid entering intrauterine cavity if possible. With intrauterine entry, there is a small risk of intracavitary adhesion formation with subsequent amenorrhea and reduced fertility. Studies show a low rate (1.56%) of intrauterine adhesions upon second look hysteroscopy 24 months after myomectomy, but this was an overall rate and did not take into account documented cases of intrauterine entry.

The following case illustrates surgical counseling considerations for patients with uterine fibroids.

CASE REPORT #2

Ms Smith is a 39-year-old P1001 nonsmoker with menometrorrhagia and symptomatic anemia. She has no prior surgeries or medical comorbidities and she had a normal spontaneous vaginal delivery 2 years ago. Her chief complaint is "heavy periods." In assessing her preferences, immediate symptom relief is her key priority in guiding therapy but she would also like to preserve fertility, if possible. Bimanual exam reveals a small, mobile uterus with a projecting mass palpated anteriorly. Transabdominal ultrasound reveals a single, 8 cm intramural fibroid located anteriorly with intramural and subserosal components. Fertility testing revealed a normal day 3

follicle-stimulating hormone of 7.8 mIU/mL. The patient is counseled regarding risk of myomectomy as her fertility testing is reassuring. Depending on the skill and experience of the surgeon, a laparoscopic approach may be preferable as it has been associated with less postoperative pain, shorter hospital stay, and recovery compared to abdominal myomectomy.

Pregnancy after treatment for fibroids

Women who receive treatment for fibroids and desire future fertility should receive counseling regarding what may happen with their future pregnancies. Below we answer a few common questions one may encounter when counseling women regarding pregnancy after fibroid therapy.

Is it safe to have a vaginal delivery after a myomectomy?

Women who have a history of myomectomy with a transmural incision are advised to undergo cesarean section at term to minimize the risk of uterine rupture with active labor. This risk is very low but the potential grave consequences to the baby and mother if it should occur dictate this recommendation. If transmural incision was not performed, a trial of labor may be allowed as the overall rate of uterine rupture following hysteroscopic myomectomy or resection of a subserosal leiomyoma for treatment is ≤1%. However, a high index of suspicion for potential uterine rupture during labor must be maintained if a trial of labor is attempted.

Is it safe to have children after procedural-based therapies?

Although successful pregnancies have been reported after UAE, these procedures may compromise ovarian blood supply, leading to diminished ovarian reserve and infertility and in some cases the damage is severe enough to induce early menopause. Also, an increased risk of abnormal placentation and fetal intrauterine growth retardation (IUGR) may occur after UAE. Pregnancy after global endometrial ablation is also not recommended as the endometrium will be severely compromised and may also lead to adverse pregnancy outcomes such as IUGR and an increased risk of placenta accreta. Pregnancies have been reported following MRI-guided focused ultrasound and clinical studies are currently under way to see if the Food and Drug Administration restriction for this indication may be revised in the future to allow this approach to women interested in future child bearing.

New insights into the pathogenesis of leiomyomas

Answering patients' question of how and why fibroids develop

The molecular basis for the development of uterine leiomyomas is largely unknown, but at the cytogenetic level they share common features with other benign and malignant neoplasms such as endometrial polyps, pulmonary chondroid hamartomas, keloids, prostate cancer, breast cancer, and others. Like these other tumors, the growth of uterine leiomyoma cells depends not only on an increased proliferation of cells but also on a decreased rate of cell death or apoptosis. Apoptosis, traditionally described as "programmed cell death," is the process by which an injured or aged cell self-destructs in response to specific chemical signals. Apoptosis is activated by a cascade of cellular mediators that co-ordinate an internally programmed series of events ultimately leading to the activation of proteolytic enzymes responsible for cell death. The presence of these cellular mediators may promote cell viability while their deprivation can be a potent apoptotic signal. Cellular mediators may be hormones, growth factors or cytokines. Cellular mediators known to be involved in the pathogenesis of uterine leiomyomas include insulin-like growth factor (IGF)-1, epidermal growth factor (EGF), B-cell leukemia/lymphoma2 (bcl-2), estrogen, and progesterone.

The role of estrogen and progesterone

The ability of sex steroids, particularly estrogen, to modulate growth of uterine leiomyomas (fibroids) has been well documented. Fibroids grow in the presence of estrogen and regress in its absence, as seen in women following menopause or with (GnRH) agonist therapy. Fibroids have a higher local intracellular estrogen concentration, have more estrogen receptors, bind more estrogen, and convert estradiol to the less potent estrone more slowly than

normal myometrium. The mitogenic effects of estrogen on uterine leiomyoma growth are thought to be mediated through local growth factors, such as IGF-1 and EGF which exert both autocrine and paracrine effects on fibroid cells.

Traditionally, estrogen alone has been considered to be the major promoter of uterine leiomyoma growth but recent studies also implicate a key role for progesterone. Uterine leiomyomas have higher progesterone receptor concentrations relative to normal myometrium, and increase in size and exhibit greater mitotic activity during treatment with synthetic progestins. Furthermore, the addition of progesterone to GnRH agonist therapy eliminates the GnRH agonist-mediated decrease in uterine volume. Progesterone acts by increasing bcl-2 production in leiomyomas, potentially delaying or inhibiting apoptosis. Other evidence supporting responsiveness of leiomyomas to progesterone is that growth is halted and regresses when treated with the antiprogesterone agent RU-486, despite estrogen levels remaining at midfollicular levels and endometrium showing changes consistent with unopposed estrogen. RU-486 has been shown to decrease uterine blood flow and increase resistive indices noted within uterine vessels following administration.

Taken together, these data suggest that both estrogen and progesterone are needed to sustain tumor growth.

New therapies on the horizon

Current clinical medical management of uterine leiomyomas with GnRH agonists takes advantage of the dominant role of ovarian sex steroids in the pathogenesis of tumor growth and relies on creating a local hypoestrogenic and hypoprogestational environment within the tumor. Unfortunately, GnRH agonist therapy cannot be used for long-term management of leiomyomata due to increased risks of cardiovascular disease and osteoporosis. While RU-486 does not appear to result in bone loss, unopposed estrogen exposure makes this agent also an unsafe long-term option. A new class of medications known as selective progesterone receptor modulators (SPRMs) is currently under investigation as a promising new avenue for treatment of leiomyomata. SPRMs act as progesterone receptor ligands with agonist–antagonist properties *in vivo*. These agents have been shown to suppress menstruation and reduce leiomyoma volume without altering basal estrogen levels. Additionally, unlike RU-486, SPRMs induce endometrial atrophy and may provide a viable long-term therapy for women with uterine fibroids; current evidence is reviewed in Chapter 6. Clinical trials are currently under way to evaluate this class of medications for both their efficacy and safety.

Can fibroids be prevented?

Modifying known risk factors

Risk factors associated with altered incidence of leiomyomas include ethnicity, age of menarche, parity, use of exogenous hormones, cigarette smoking, and obesity. While Caucasian and African-American women have been found to have similar lifetime risks of developing fibroids, 70% and 80% respectively, African-American women are three times more likely to have symptomatic fibroids. Data concerning other races are less available but Asian-Americans appear to have a slightly decreased risk of leiomyomata compared with Caucasian women while Hispanic women have a slightly increased risk. No classic Mendelian genes have been identified for the development of leiomyomata, but familial tendencies have been described. Monozygotic twins have a higher incidence of concordant leiomyomata than dizygotic twins. Furthermore, similar operative findings and molecular features have been described in leiomyomata of women from families with a high incidence of fibroids.

Other demographic factors associated with an increased incidence of fibroids are those that potentially put women at risk for long-term exposure to estrogens. Due to the presence of increased levels of circulating estrogens via aromatization of androgens by peripheral fat stores, obese women have been found to have increased risk of developing leiomyomas. Conversely, athletic women seem to have a lower prevalence of uterine leiomyomata compared with women who do not engage in athletic activities. Early menarche may increase the risk of uterine leiomyomas by increasing lifetime exposure to circulating sex steroids. Oral contraceptives create a hormonal milieu in which estrogen is opposed by progesterone, and appears to have a protective effect on fibroid development and progression. Epidemiological studies suggest that cigarette smoking decreases a woman's risk

of developing leiomyomas by 20–50%. Finally, multiparity has been associated with reduced risk of developing fibroids by as much as 50%.

Advice on dietary changes for patients with uterine leiomyomas

Little is known about the potential effect of diet on uterine fibroids; however, diet has been shown to be involved in modulating hormone levels, such as estrogen. A diet-induced imbalance in estrogen metabolism may explain certain epidemiological evidence purporting a higher prevalence of estrogen-related disease, especially breast cancer, in societies consuming a diet low in total vegetable content and high in animal fats. One case–control study conducted in Italy evaluated dietary consumption of various food items and noted that women with myomas reported higher rates of beef, other red meat and ham consumption and less frequent consumption of green vegetables, fruit, and fish. After adjusting for potential confounders, the protective effects of green vegetables and fish were confirmed (odds ratio (OR) 0.5, 95% confidence interval (CI) 0.4–0.7; OR 0.7, 95% CI 0.6–0.9, respectively). Additionally, diets higher in glycemic index are associated with slightly higher risk of uterine leiomyoma development.

These differences in diet may also help to explain racial differences in the prevalence of leiomyomas, based on the different eating habits among various ethnic groups. Several studies have investigated potential associations of specific dietary factors and their implication in fibroid development (Table 12.1). These studies and others will be further highlighted specifically focusing on their potential molecular mechanism of action and efficacy.

Vitamin D

Vitamin D is a fat-soluble steroid that is either produced in the skin after exposure to ultraviolet B light from the sun or consumed exogenously in dietary foods. Vitamin D_3, also known as cholecalciferol, is the form generated in skin when light energy is absorbed by a precursor molecule, 7-dehydrocholesterol. Dietary sources of vitamin D include grain, fish oil, meat, and a number of plants. Products such as milk, flour, and margarine have also been artificially fortified with vitamin D. The plant source of vitamin D, ergosterol, is converted to vitamin D_2 in the human body. Both vitamin D_3 and D_2 are converted to a hormonally active form (calcitriol) that is important in regulating body levels of calcium and phosphorus, and in the mineralization of bone. Calcitriol, at the molecular level, binds to intracellular receptors in a wide variety of cells and functions as a transcription factor to modulate gene expression. More recent studies of vitamin D have shown that this hormone has biological effects that extend far beyond just the regulation of calcium and bone mineral metabolism.

Laboratory, animal, and epidemiological evidence suggest that vitamin D may be protective against some tumors. Studies on breast, prostate, and colon cancer cell lines have demonstrated that vitamin D_3 compounds can block the mitogenic activity of insulin and IGF-I. Additionally, vitamin D and its metabolites have been shown to act on a number of physiological processes involved in the pathogenesis of uterine leiomyomas. Leiomyomas widely express the vitamin D receptor and treatment with 1,25-dihydroxycholecalciferol vitamin D_3 has been shown to inhibit leiomyocyte proliferation at physiological doses. Active metabolites of vitamin D, 1-,25-dihydroxycholecalciferol vitamin D_3, and its analogs, have also been demonstrated to downregulate epidermal growth factor receptors (EGFR) known to be active in mitogenic pathways in uterine leiomyomas. Downregulation of this receptor has been shown to decrease growth and differentiation of tumor cells. These observations suggest that there may be a role for vitamin D in the treatment and/or primary prevention of uterine leiomyomas.

Recently, two studies examined the effects of the most bioactive form of vitamin D (1,25(OH)2D3) *in vitro* and showed inhibition of growth of leiomyoma cells in both primary cell culture and cell lines. Additionally, one prospective cohort study of American black women examined dairy intake given the antitumorigenic constituents, including vitamin D, calcium, butyric acid, branched chain fatty acids, and milk proteins. Incidence rate ratios assessing the risk of uterine fibroids as seen by ultrasound or by surgery were significantly reduced with increasing number of servings per day.

Vitamin A/carotenoids

Vitamin A belongs to a family of naturally occurring lipid-soluble molecules (retinoids) that are needed by the body for proper development, growth, vision

Table 12.1 Dietary compounds and their anti-/pro leiomyoma effects

Dietary compounds	Examples	Sources	Effect
Polyphenols			
Flavonoids	Quercetin, epigallocatechin gallate, curcumin, silibinin	Berries, tea, grapes, olive oil, dark chocolate, walnuts, citrus fruits (grapefruit)	Inhibits IGF-1 signaling, estrogen receptor antagonist, alters cell cycle
Resveratrol		Grapes, red wine, mulberries, dark chocolate	Induces apoptosis modulating expression of cell cycle proteins, weak estrogen receptor agonist/antagonist, decreases collagen production
Carotenoids	Lycopene	Tomatoes, guava, rosehip, watermelon, papaya, pink grapefruit	Interferes with IGF-1 signaling
Vitamins			
Vitamin D		Grain, fish oil, meat, mushrooms, milk, flour, margarine	Decreases mitogenic activity of insulin and IGF-1
Vitamin A		Carrots, broccoli, spinach, collard greens, pumpkin, egg, liver	Binds nuclear retinoid receptors involved in cell growth and apoptosis, downregulates IGF-1 and TGF-beta pathways
Alcohol		Beer, wine, liquor	Associated with higher levels of endogenous estrogens
Caffeine		Coffee, tea, chocolate	Associated with enhanced sex steroid production
Dietary fiber		Whole grains (rye, wheat, brown rice), green vegetables, fruits	Absorbs estrogen in the intestinal tract aiding in excretion

IGF, insulin-like growth factor; TGF, transforming growth factor.

and reproductive function. Vitamin A can be found in two principal forms in foods: retinyl esters found in animal products (liver, eggs), and carotenoids (a group of provitamins) synthesized in plants, mostly green leafy vegetables. Both are able to be converted by the body into retinol and other related forms of the vitamin A family such as retinal and retinoic acid.

Retinoids are important in regulating development, differentiation, and physiological response to diverse stimuli throughout the body (eye, skin, bone, immune system, reproduction). Vitamin A, aside from its role in improving health in the malnourished or vitamin A deficient, is therapeutically recommended as part of the treatment of dermatological disorders, vision loss, and some cancers (e.g. acute promyelocytic leukemia). Vitamin A functions by binding to nuclear retinoid receptors which regulate a number of genes involved in expression of prostaglandins, cell growth, differentiation, and apoptosis. Diets rich in vitamin A decrease the risk of developing some types of cancer, including cervical, breast, and prostate cancer. Retinoids also have been shown to suppress development of hyperproliferative tumors such as malignancies involving skin, breast, oral mucosa, lung, prostate, bladder, liver, and pancreas. The mechanism by which retinoids regulate cell differentiation and tissue morphogenesis has not been completely elucidated but retinoids have been shown to affect multiple signal transduction pathways, including IGF-1 and transforming growth factor (TGF)-beta dependent pathways. Alterations in both IGF-1 and TGF-beta signaling pathways have been shown to have a role in the pathogenesis of uterine leiomyomas. Studies on uterine smooth muscle cells have shown that the retinoid pathway is active in both normal myometrium and in fibroids; however, this pathway appears to be altered in fibroids. Furthermore, recent studies have shown that treatment of fibroid smooth muscle cells with retinoic acid downregulated the TGF-beta pathway and reduced synthesis of extracellular matrix proteins and growth by leiomyoma cells.

Ingestion of preformed vitamin A from animals results in significant increases in retinol by the small intestine that is not well regulated and as a result is more likely to lead to toxicity if taken in excess. Supplementation is usually recommended in moderation or through plant-derived carotenoids. In general, toxicity associated with retinoids has limited their general use for prevention of diseases or conditions. Current efforts are aimed at developing synthetic retinoids with lowered toxicity and improved pharmacokinetics.

Lycopene

Lycopene is an open-chain, unsaturated carotenoid found in tomatoes, guava, rosehip, watermelon, papayas, and pink grapefruit. Lycopene, unlike other carotenoids, has no vitamin A activity but is an important intermediate metabolite in the biosynthesis of other carotenoids (such as beta-carotene) and has significant antioxidant properties. Lycopene is better absorbed from the diet if processed into juice, sauce or paste because heating makes the compound more easily absorbed in the digestive system.

While the number of studies investigating the effects of lycopene on leiomyoma development and growth is limited, extensive work has been done in hormone-dependent tumors such as prostate cancer. One cohort study that examined the impact of dietary carotenoids on prostate cancer found that of all the carotenoids studied, only lycopene consumption was related to lower risk of developing prostate cancer. This same study concluded that high intake of lycopene-rich foods, namely tomato-based products accounting for 82% of dietary lycopene, was inversely associated with prostate cancer. Japanese researchers found an inverse association between high blood levels of lycopene and incidence of lung cancer in Japanese men. A Canadian case–control study of patients with histologically confirmed pancreatic cancer and control patients without cancer, after adjustment for variables, showed that dietary lycopene was associated with a 31% reduction in pancreatic cancer risk among men when comparing the highest and lowest quartiles of intake.

There have been several studies examining the effect of dietary lycopene on hormonally responsive tissue of the female reproductive tract, with varying results. Four studies examining lycopene and cervical neoplasia showed a protective effect of lycopene, while only one of three studies showed a protective effect against human papillomavirus (HPV) persistence in cervical tissue. One study in women over 50 showed no association between dietary or plasma lycopene levels and breast cancer risk. Conversely, lycopene has been shown to

interfere with IGF-1 signaling in breast cancer cells by reducing IGF-1 stimulation of tyrosine phosphorylation of insulin receptor substrate 1 and binding capacity of the activator protein (AP)-1 transcription complex. Only two studies have examined the direct relationship between lycopene ingestion and leiomyomas. In humans, one secondary analysis of the Nurse's Health Study II examined lycopene intake as reported by food frequency questionnaires and risk of being diagnosed with fibroids and noted no protective effects. However, a more well-controlled study investigating the effect of diets supplemented with lycopene on leiomyomata development and growth in an animal model did demonstrate decrease in total number and size of leiomyoma in Japanese quail, a bird that develops spontaneous leiomyomas of the oviduct.

Polyphenols/bioflavonoids

Epidemiological studies of other hormonally dependent solid tumors such as breast cancer highlight the strong role diet can play as a contributing environmental factor. The fact that the incidence of breast cancer in Asian women is 4–6 times lower than in American women and that migration studies have shown that the incidence in Asian-American women approaches that of European-American women after several generations of residence in the USA strongly suggests that the marked difference is not due to genetic factors but may be secondary to environmental exposures such as the adoption of a typical high-fat American diet. Epidemiological studies have also demonstrated a decreased incidence of uterine leiomyomas in Asian women. Asians also tend to consume a much higher proportion of soy-based food products that are rich in bioflavonoids and these compounds tend to be found in blood and urine samples at significantly elevated concentrations.

Bioflavonoids are secondary metabolites that occur naturally in certain plant families. For example, they can be found in legumes, nuts, onions, apple, broccoli, red wine, green tea, cocoa powder, and dark chocolate. The most well-characterized antitumor flavonoids are epigallocatechin gallate (from green tea), genistein (from soy and red clover), curcumin (from turmeric), silibinin (from milk thistle), quercetin (from many yellow vegetables such as onions), and resveratrol (from grapes and red wine). Bioflavonoids have traditionally been used only in holistic medicine but several population studies have reported an inverse association between flavonoid intake and the risk of malignant tumors. The reported biological activities of various flavonoids include the induction of apoptosis, cell cycle arrest, antiproliferative and anti-inflammatory effects, and protection against oxidative stress.

Resveratrol (3,4′,5 trihydroxystilbene) has been the subject of much research because of its strong antiproliferative and cardioprotective properties. Resveratrol is found in a variety of plant species including grapes, peanuts, and berries and is generated in response to injury, UV irradiation, and fungal attack. Resveratrol has been shown to cause cell cycle arrest and induce apoptosis in a wide variety of tumor cells. It modulates the expression of genes involved in cell cycle regulation and apoptosis, such as cyclins, cdks, p53, bcl-2, bcl-xL, Bax, and caspases, resulting in inhibition of cellular growth. Studies have also shown that resveratrol inhibits the activation of the transcription factors AP-1, Egr-1, and NF-kappa B. Resveratrol also acts as a weak estrogen receptor (ER) agonist/antagonist. In the absence of estrogen, resveratrol acts like estradiol and is an estrogen receptor agonist. In the presence of estrogen, it acts as an estrogen antagonist and inhibits growth of malignant tumor cells. This apparent paradox may be due to competition between resveratrol and estradiol for estrogen receptor-binding sites. Since many of these genes or pathways have been implicated in the pathogenesis of uterine leiomyomas, it is possible that leiomyoma growth may also be inhibited by resveratrol. *In vitro* studies of human leiomyomas have shown that resveratrol induces apoptosis and reduces collagen and extracellular matrix production.

Dietary fiber

Epidemiological studies have implicated low fiber intake as a possible risk factor for estrogen-responsive tumors. Fiber is the nonstarch polysaccharide component of food that is resistant to chemical digestion. Fiber-rich foods include whole grains, fruits, leafy green vegetables, rye, brown rice, and wheat. Fiber affects the concentration of estrogen in the body. The liver routinely filters estrogen from the bloodstream and deposits estrogen into the intestinal tract via the bile duct. Once in the intestinal tract, estrogen can be reabsorbed back into the bloodstream to exert its effect on hormone-responsive tissue. Fiber easily

binds and helps excrete estrogen from the body. Without adequate fiber, estrogen can be reabsorbed from the intestines, thereby increasing the concentration of estrogens in the bloodstream. Studies have shown that women on a vegetarian/high-fiber diet have lower levels of circulating estrogen. Lower levels of estrogens may mean less estrogen stimulation of hormone-responsive tissues such as uterine leiomyomas; however, one study of Japanese women found no distinct association between dietary fiber intake and alteration in incidence of uterine fibroids.

Advice regarding alcohol and caffeine

Alcohol and caffeine are two additional common occurrences in modern diets that may have direct or indirect effects on incidence and development of uterine fibroids. Several studies have shown that both are capable of altering endogenous hormone levels through changes in ovarian function or alterations in metabolism. Increased alcohol consumption has been shown to increase the incidence of fibroids. The Black Women's Health Study, a prospective cohort study of US black women aged 21–69, found significant associations with leiomyoma-related clinical concerns with years and amount of alcohol consumption as reported in self-administered questionnaires. Additionally, after stratifying for source of alcohol, the strongest correlations were found in beer drinkers as compared to wine. This association was confirmed in a cohort study of Japanese women who were similarly surveyed for several dietary factors, again showing a correlation between increased alcohol intake and risk of uterine fibroids.

Regarding caffeine consumption, the same authors from the Black Women's Health Study also evaluated total amount and types of caffeine consumption and subsequent risk of uterine fibroids. While a significant increase in the incidence ratio was noted among women under age 35, no significant relationships were noted with regard to dose or source when looking at all women pooled together.

Diet "bottom line" summary

Several dietary factors have been shown to alter the risk of developing symptomatic uterine leiomyomas. Potential protective factors include several vitamins, especially vitamins A and D, and several nonnutritive constituents of food, including resveratrol and fiber. These dietary components may work indirectly by modifying the local hormonal milieu and more directly interrupting various molecular pathways involved in the pathogenesis of leiomyomas. Though little is known at the present time about the direct effects of specific dietary modifications, the current evidence is sufficient to make several practical recommendations. These include emphasis on diets low in fat, high in fiber and high in fruit/vegetable content. Red wine and dark chocolate (given their richness in resveratrol) may have beneficial effects on the development of symptomatic leiomyomas. However, more research is needed in this field. Elucidation of the diet–tumor relationships may provide alternative courses of early interventions and prevention strategies for uterine leiomyomas which are currently lacking.

Resources for patients with uterine fibroids

Guiding women to appropriate online resources, books, and support groups can aid in counseling the patient with fibroids. The American College of Obstetricians and Gynecologists (ACOG) has generated a factsheet regarding fibroids, which is accessible to patients through its website (www.acog.org/publications/faq/faq074.cfm). This is a brief overview of the associated symptoms, diagnosis, and medical and surgical treatment options for uterine fibroids. It is medically accurate, yet written in language understandable to patients. The relative indications for, and risks associated with, each treatment modality are clearly laid out in this document. An additional online resource which contains accurate patient information is the NIH website (www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5043).

Advocacy and support groups

Additional resources for patients can be found through the National Uterine Fibroids Foundation (www.nuff.org/), a nonprofit organization. Along with providing patient information, the website also provides access to an online support group for women with fibroids. Additional access to support groups, fundraising opportunities, surveys, and a message board can be found through the online fibroid network (www.fibroidnetworkonline.com/), run by a nonprofit organization from the UK. While the content on these websites is not monitored for medical accuracy, patients may find the peer support services valuable.

Books on fibroids and other resources

Many women faced with a diagnosis of fibroids may find more detailed information helpful when considering their management options. Several books regarding uterine fibroids are available in lay language. One that is highly recommended by readers is *Uterine Fibroids: The Complete Guide*, written by Elizabeth A. Stewart MD. This comprehensive overview aimed at patients and the lay public provides readers with the knowledge to make informed decisions.

Finally, patients may be interested in learning about ongoing research regarding uterine fibroids. Information regarding active clinical trials can be found through the National Institutes of Health (http://clinicaltrials.gov). Recent research findings and plans for future research are summarized at (http://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=50).

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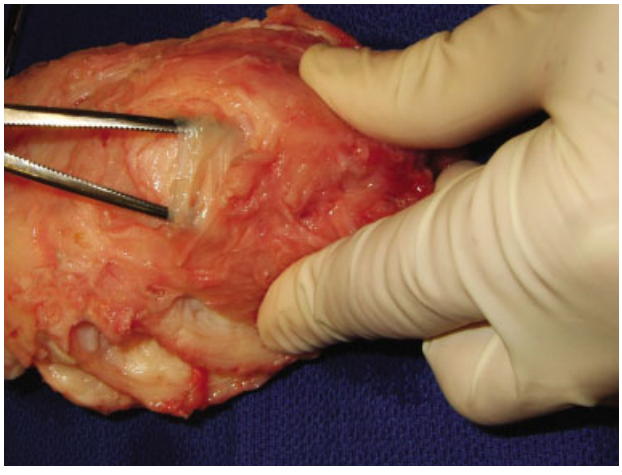

Plate 1.1 Examination of a surgically excised fibroid. As is typical, this fibroid has complex layers of connective tissue that, in part, resemble the layers of an onion. The layers have been dissected apart with the surgical instrument. Note that the fibroid is several centimeters in size, which is not unusual.

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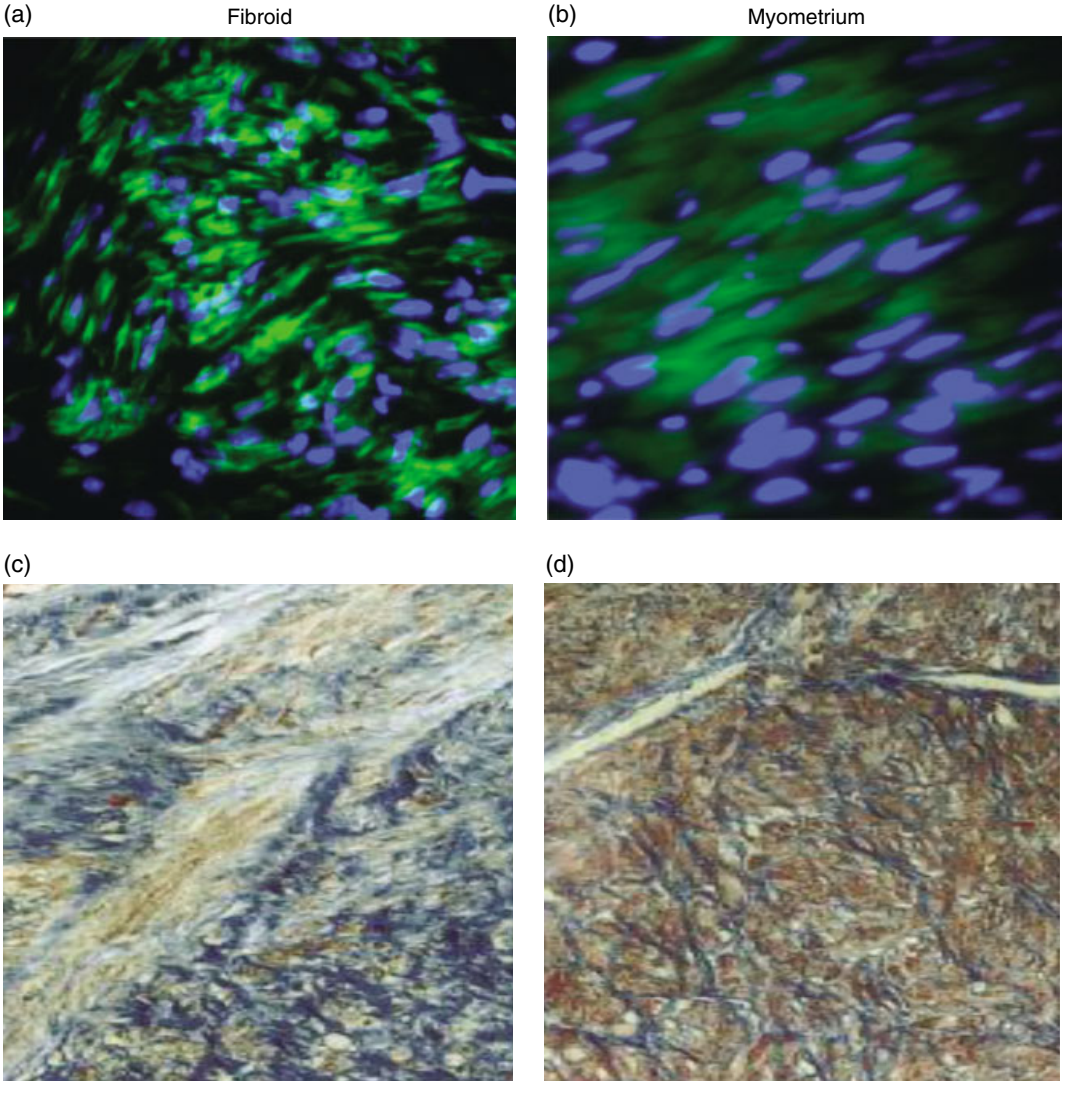


Plate 1.2 Microscopic studies of uterine fibroids and normal uterine myometrium. *Upper panel*: Fibroid specimen (a) and matched myometrial specimen (b) stained for actin filaments (FITC-phalloidin) and cell nuclei (DAPI). The actin filaments show strong green staining; the nuclei stain blue. Note the increased actin staining and irregular actin filaments in fibroid (a) compared to patient-matched myometrium (b). *Lower panel*: Fibroid specimen (c) stained for tissue collagen = blue and muscle tissue = red. Note the increased collagen in (c), compared to the myometrium (d) which contains more muscle and less collagen. Weigert's iron hematoxylin counterstained with Biebrich scarlet-acid fuschin (×40).

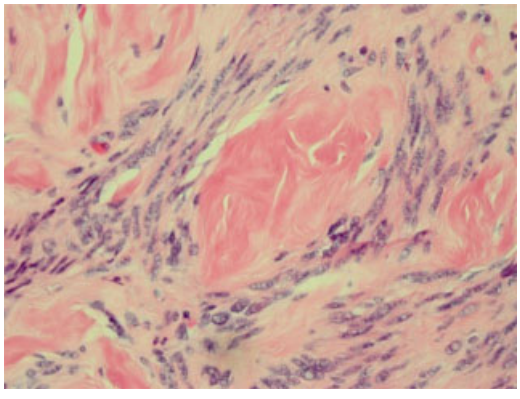
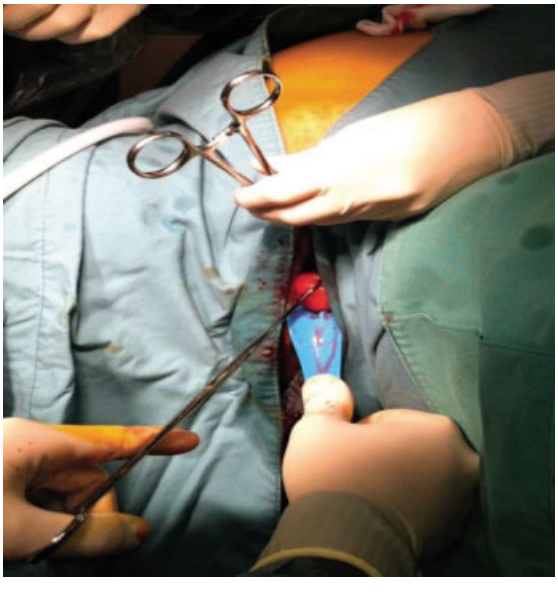


Plate 1.3 Fibroids feature an abundant extracellular matrix. Fibroid specimen stained with hematoxylin and eosin (×40) shows increased ECM clearly visible in the center of the image. Studies have shown that increases in size greater than 4 cm are largely due to accumulation of ECM.

(a)



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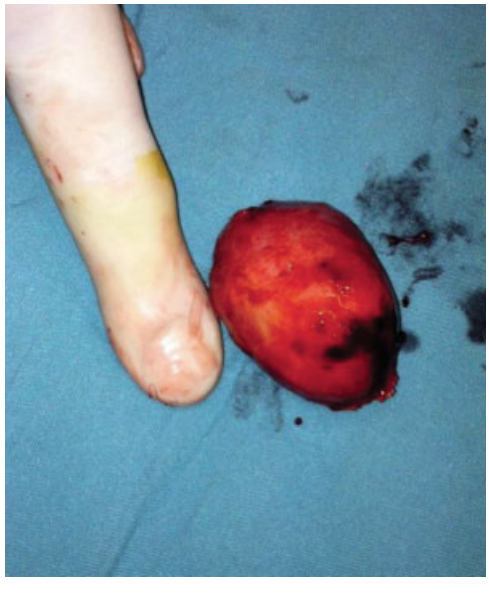
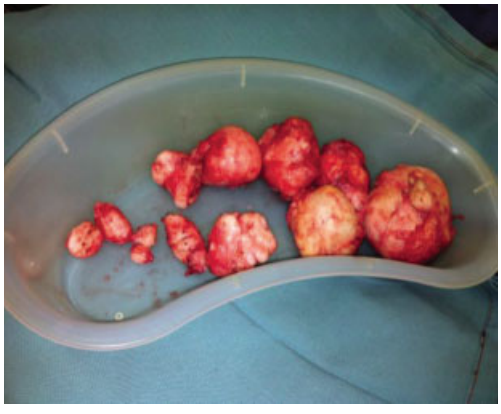


Plate 5.1 (a) Vaginal removal of pedunculated fibroid presenting at the cervix. (b) Fibroid after removal.

(a)



(b)

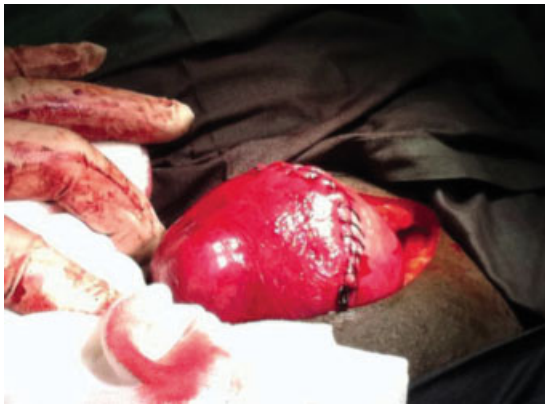
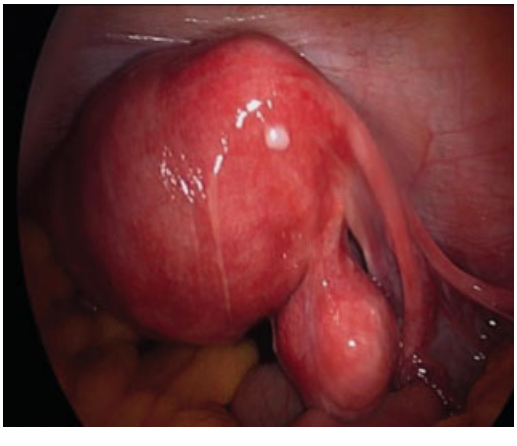


Plate 5.2 (a) Multiple fibroids (12) removed at abdominal myomectomy are shown. The largest was 4–5 cm, the smallest 0.7 cm. (b) Uterus following removal of fibroids at abdominal myomectomy. A single uterine incision as shown can be used to remove many tumors to reduce the number of incisions in the uterus, and minimize the likelihood of postoperative adhesions. Use of adhesion barriers (reviewed in Chapter 10) may further reduce adhesion formation.

(a)



(b)

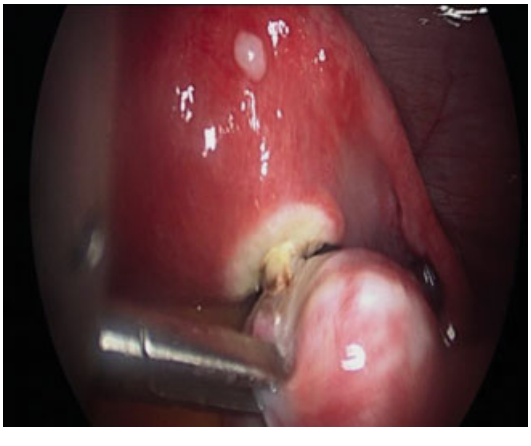


Plate 5.3 (a) View of posterior uterus and pedunculated subserosal fibroid (*lower right*). (b) The fibroid base has been cauterized and the fibroid, held by a laparoscopic grasper, now appears whitish. Further dissection will remove the fibroid from the posterior uterus.

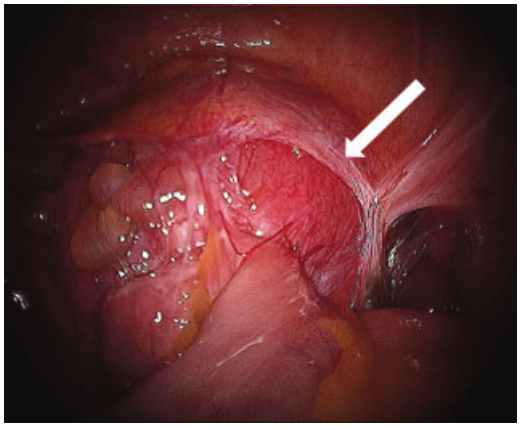


Plate 5.4 Laparoscopic view of pelvis in a patient who has previously undergone myomectomy. The bladder, located at the top of the photograph, is attached to the uterus through dense adhesions, seen as whitish bands (*white arrow*). Also, the posterior uterus is encased in adhesions involving large bowel, shown in the middle of the photo, denoted by the bowel serosa and epiploic fat.

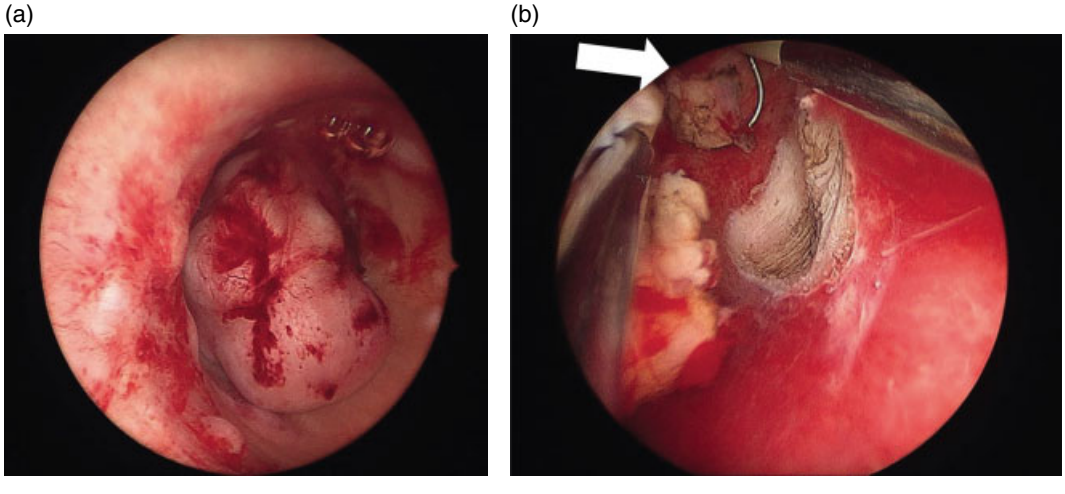


Plate 5.5 (a) Hysteroscopic view of an intracavitary uterine fibroid attached by a small stalk, located in the middle of the uterine cavity (*mid photo*). There are several possible surgical methods for removing such fibroids, including the resectoscope or a hysteroscopic morcellator. (b) A loop resectoscope (*white arrow*) is shown after being used to incise a fibroid surface at hysteroscopy. Note there is a bit of char at the base of the divot where the resectoscope was used to incise the tumor. Submucosal fibroids can be excised piecemeal with the resectoscope or quartered into removable fragments. Occasionally, larger fibroids may require a planned partial resection and a second procedure to complete resection. Risks include intrauterine scarring but this is generally not a concern in the older woman who has completed child bearing.

(a) (b)

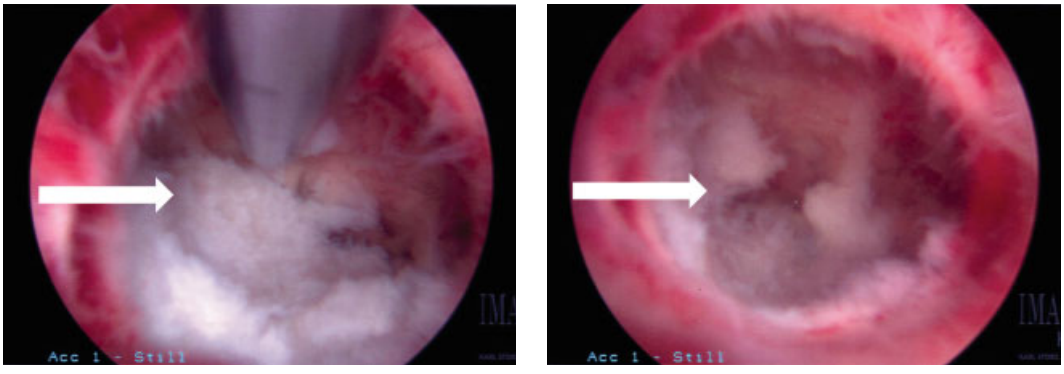


Plate 9.1 Hysteroscopic resection of a submucosal fibroid. (a) The fibroid is visible in the center of the photograph as a fuzzy sphere (*white arrow*). The hysteroscopic morcellator (TRUCLEAR®) is shown entering the field of vision as a metallic object from above. The fibroid shown corresponded to the fibroid imaged in Figure 2.1. (b) The central portion of the fibroid has been removed and the hysteroscopic morcellator retracted back into the hysteroscope. Note the removal of the central core of the fibroid, but the absence of fragments (*white arrow*; compare with a). For this case, vasopressin was used via cervical injection prior to the resection.

(a) (b)

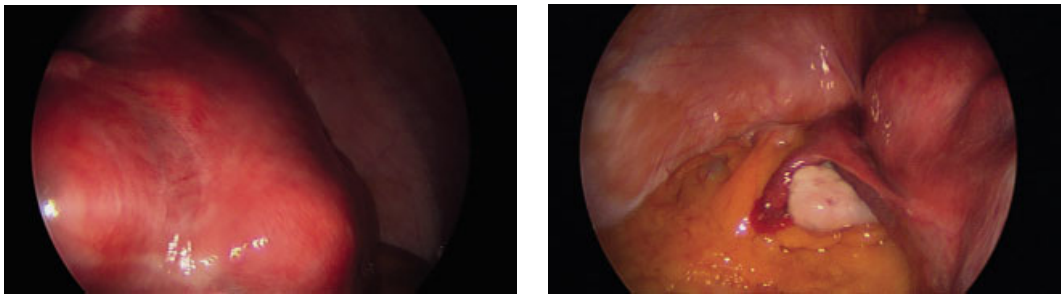


Plate 9.2 Laparoscopic appearance of a uterus with multiple leiomyoma at the start of a laparoscopic supracervical hysterectomy. (a) Note the globular appearance of the uterine fundus. (b) The uterine fundus has been pushed up and out of the pelvis to gain access to the adnexa and uterine vessels. The ovary and adnexae are clearly seen after this manipulation.

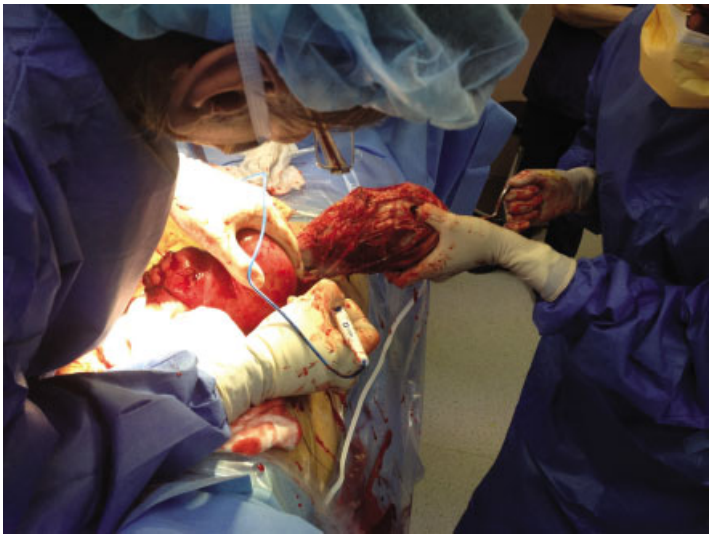


Plate 10.1 Intraoperative photograph of an abdominal myomectomy for a large uterine fibroid. The assistant applies traction to the fibroid (*right of photo*), while the surgeon stabilizes the uterus and applies electrocautery to the remaining tissue connections between the fibroid and uterus. Courtesy of Dr Beverley Vollenhoven.

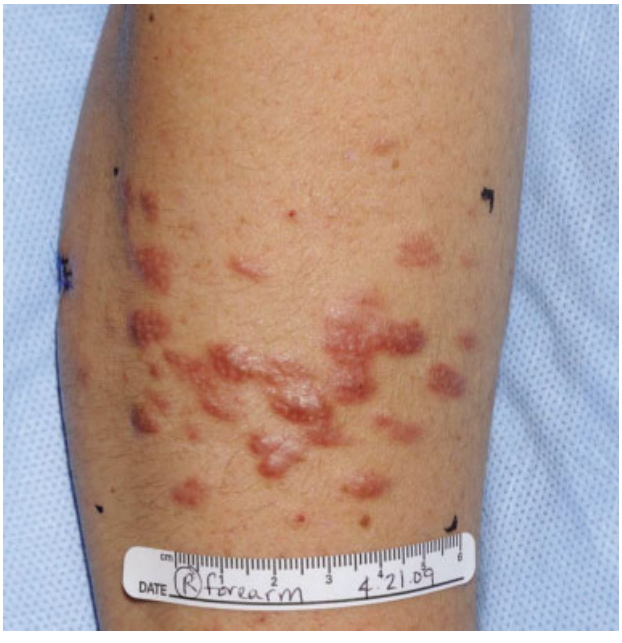


Plate 11.1 Cutaneous lesions of HLRCC. Typical fibrous nodules are visible on the forearm.