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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,

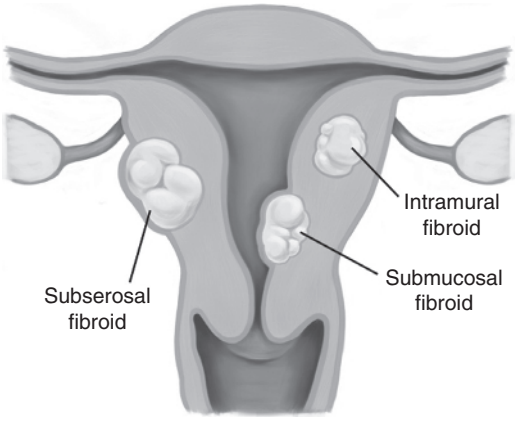

Figure 1.1 Uterine leiomyoma may be classified based on location in the uterine muscle. Submucous, intramural, and subserosal types of fibroids are shown. Such a system is useful for communication but does not account for fibroid size or overall uterine size in cases of more severe disease when multiple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

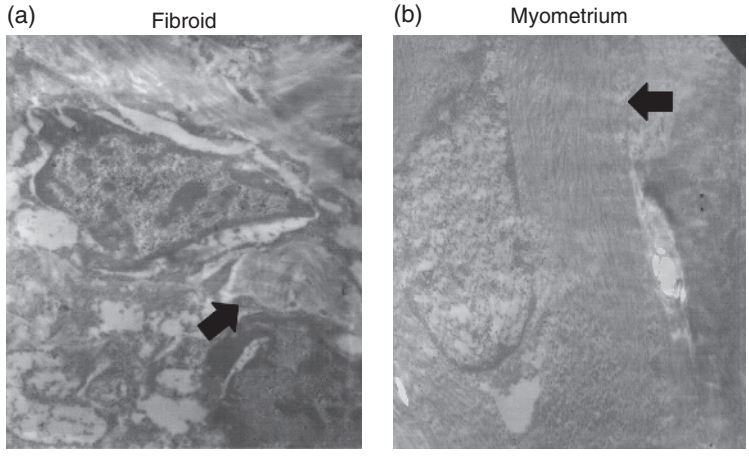

Figure 1.2 Electron microscopy images of matched fibroid and myometrial tissues.
(a) The fibroid cell nucleus is angular and notched. Also, note the disordered structure of the ECM and collagen fibers in the fibroid tissue (*black arrow*; ×15,000). (b) Image of myometrium from the same patient. Note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

Bibliography

Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003; **188**: 100–107.

Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol* 2012; **206**(3): 211.

Catherino WH, Leppert PC, Stenmark M, et al. Reduced dermatopontin expression is a molecular link between uterine leiomyomata and keloids. *Genes Chromosomes Cancer* 2004; **40**: 204–217.

Chwalisz K, Larsen L, Mattia-Goldberg C, Edmonds A, Elger W, Winkel CA. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. *Fertil Steril* 2007; **87**: 1399–1412.

Ciarmela P, Islam MS, Reis FM, et al. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. *Hum Reprod Update* 2011; **17**: 772–790.

Coronado GD, Marshall LM, Schwartz SM. Complications in pregnancy, labor and delivery with uterine leiomyomas: a population based study. *Obstet Gynecol* 2000; **95**: 764–769.

Cramer SF, Patel A. The frequency of uterine leiomyomas. *Am J Clin Pathol* 1990; **94**: 435–438.

Cramer SF, Mann L, Calianese E, Daley J, Willians K. Association of seedling myomas with myometrial hyperplasia. *Hum Pathol* 2009; **40**: 218–225.

Ezzati M, Norian JM, Segars JH. Management of uterine fibroids in the patient pursuing assisted reproductive technologies. *Womens Health* 2009; **5**: 413–421.

Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. *Am J Obstet Gynecol* 2006; **195**: 955–964.

Ishikawa H, Reierstad S, Demura M, et al. High aromatase expression in uterine leiomyoma tissues of African-American women. *J Clin Endocrinol Metab* 2009; **94**: 1752–1756.

Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. *Am J Obstet Gynecol* 2008; **198**: 357–366.

Laughlin SK, Baird DD, Savitz DA, Herring AH, Kartmann KE. Prevalence of uterine leiomyomas in the first trimester of pregnancy: an ultrasound screening study. *Obstet Gynecol* 2009; **113**: 630–635.

Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. *Semin Reprod Med* 2010; **28**: 204–217.

Leppert PC, Baginski T, Prupas C, Catherino WH, Pletcher S, Segars JH. Comparative ultrastructure of collagen fibrils in uterine leiomyomas and normal myometrium. *Fertil Steril* 2004; **82**: 1182–1187.

Leppert PC, Catherino WH, Segars JH. A new hypothesis about the origin of uterine fibroids based on gene expression profiling with microarrays. *Am J Obstet Gynecol* 2006; **195**: 415–420.

Luo X, Ding L, Xu J, Chegini N. Gene expression profiling of leiomyoma and myometrial smooth muscle cells in response to transforming growth factor-beta. *Endocrinology* 2005; **146**: 1097–1118.

Malik M, Norian J, McCarthy-Keith D, Britten J, Catherino WH. Why leiomyomas are called fibroids: the central role of extracellular matrix in symptomatic women. *Semin Reprod Med* 2010; **28**: 169–179.

Mauskopf J, Flynn M, Thieda P, Spalding J, Duchane J. The economic impact of uterine fibroids in the United States: a summary of published estimates. *J Womens Health* 2005; **14**: 692–703.

Morton CC. Genetic approaches to the study of uterine leiomyomata. *Environ Health Perspect* 2000; **108(**Suppl 5): 775–778.

Norian JM, Owen CM, Taboas J, et al. Characterization of tissue biomechanics and mechanical signaling in uterine leiomyoma. *Matrix Biol* 2012; **31**: 57–65.

Peddada SD, Laughlin SK, Miner K, et al. Growth of uterine leimomyomata among premenopausal black and white women. *Proc Natl Acad Sci USA* 2008; **105**: 19887–19892.

Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 2009; **91**: 1215–1223.

Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. *Fertil Steril* 2010; **93**: 2027–2034.

Salman T, Davis C. Uterine fibroids, management and effect on fertility. *Curr Opin Obstet Gynecol* 2010; **22**: 295–303.

Somigliana E, de Benedictis S, Vercellini P, et al. Fibroids not encroaching the endometrial cavity and IVF success rate: a prospective study. *Hum Reprod* 2011; **26**: 834–839.

Sozen I, Arici A. Interactions of cytokines, growth factors, and the extracellular matrix in the cellular biology of uterine leiomyomata. *Fertil Steril* 2002; **78**: 1–12.

Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. *Hum Reprod* 2010; **25**: 418–429.

Walker CL, Stewart EA. Uterine fibroids: the elephant in the room. *Science* 2005; **308**: 1589–1592.