

where (16), sensitization of the sensory fibers would in turn produce central sensitization, which is a long-lasting hyperexcitability of neurons in the central nervous system that can continue long after the originally sensitized input is reduced or eliminated (e.g., by surgery).

Second, sensory input arriving at the spinal cord from individual internal organs diverges within the cord. Thus, although information from different organs is delivered most densely to spinal neurons within the entry segments, it is also delivered, less densely, to widespread spinal regions extending for many segments rostrally and caudally (14). The anatomical divergence gives rise to considerable convergence of information on central neurons. This "viscero-viscero-somatic convergence" (13, 14) produces a situation in which the activity of somato-visceral neurons in the spinal cord and brain is dominated by information from individual peripheral structures but can be augmented, particularly in sensitized neurons, by events occurring elsewhere. Such convergence thereby provides a substrate by which sensitized input from ectopic implants augmenting that from healthy organs can have widespread influences on the activity of neurons normally associated with input from different individual organs and

tissues, a situation that has been demonstrated in women (17).

These results suggest that inconsistency in the various pains associated with the ectopic implants could reflect variability in a number of factors associated with the implants' nerve supply. These factors include the types of nerves that innervate the implants, agents that activate or sensitize them, sites in the central nervous system where the nerves deliver information, and how that information is modulated by estradiol—both peripherally (18) and centrally (19)—as well as by other central dynamic processes (14, 17, 20).

Much remains to be learned about how endometriosis comes to be associated so variably with pain symptoms and how those symptoms are ameliorated by a hypoestrogenic state. One promising area of research concerns the implants' sensory and autonomic nerve supply and its potentially estradiol-modulated influence on activity within the central nervous system.

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REVIEW

Uterine Fibroids: The Elephant in the Room

Cheryl Lyn Walker¹ and Elizabeth A. Stewart²

Uterine fibroids (leiomyomas) have historically been viewed as important chiefly as the major indication for hysterectomy. As new therapies are developed, the heterogeneity of this disease becomes therapeutically relevant. An awareness of the role of genetics, the extracellular matrix, and hormones in tumor etiology is key to understanding this disease.

Uterine fibroids (correctly called leiomyomas or myomas) are benign myometrial neoplasms enriched in extracellular matrix (ECM) (Fig. 1) (1). They are the primary indication for hysterectomy, accounting for over 200,000 hysterectomies annually in the United States, and are the cause of significant morbidity from profuse menstrual bleeding and pelvic discomfort. The range of clinical disease is extraordinary: Symptomatic lesions can be 10 mm in size or routinely exceed 20 cm. Tumors occur in 77% of women, and approximately 25% of Caucasians have clinically significant lesions (2). However, in African-American women, clinical disease is more severe and concordant with prevalence.

Rarer lesions such as the poor-prognosis leiomyosarcoma are providing insights into the

biology of these benign tumors. Although it has been debated whether leiomyomas and leiomyosarcomas are part of a disease continuum, cytogenetic studies have demonstrated that chromosome rearrangements in leiomyomas are similar to those seen in other benign tumors but are distinct from the complex rearrangements and aneuploid karyotypes characteristic of leiomyosarcomas (3). However, recent microarray data from the Morton laboratory identified a rare subset of leiomyomas with deletions of chromosome 1 that have transcriptional profiles that cluster with those of leiomyosarcomas (4), suggesting that some uterine leiomyosarcomas may in fact arise from a specific subset of leiomyomas. There are also related lesions with both benign and malignant features. Benign metastasizing uterine leiomyoma is characterized by leiomyoma-like lesions, usually in the lungs, in women with fibroids. Lymphangiopleiomyomatosis is a similar disease, affecting only women, in which the characteristic lung lesions originate

from "benign" renal angiomyolipomas (5). Similarly, intravenous leiomyomatosis (IVL) is a hormonally responsive disease that causes vermiform extensions originating in the uterus that can extend as far as the heart. These leiomyomas have cytogenetic alterations similar to those seen in atypical lipomatous tumors that are locally invasive but do not metastasize (6).

Risk Factors and Prevalence

The prevalence of clinically significant fibroids peaks in the perimenopausal years and declines after menopause (7). Obesity and early age at menarche, which increase a woman's overall lifetime exposure to estrogen, are known risk factors. The risk of developing fibroids is higher in African-American than in Caucasian women, and they often have more severe disease. Parity is also a significant risk factor, with age at the birth of the last child being inversely associated with risk, suggesting that pregnancy may remove nascent tumors or promote regression, as is thought to be the case with endometrial cancer. Pregnancy reveals the extraordinary extent to which myometrial smooth muscle cells (MSMCs) can grow without malignant transformation. One hypothesis, proposed by Barbieri and Andersen, is that

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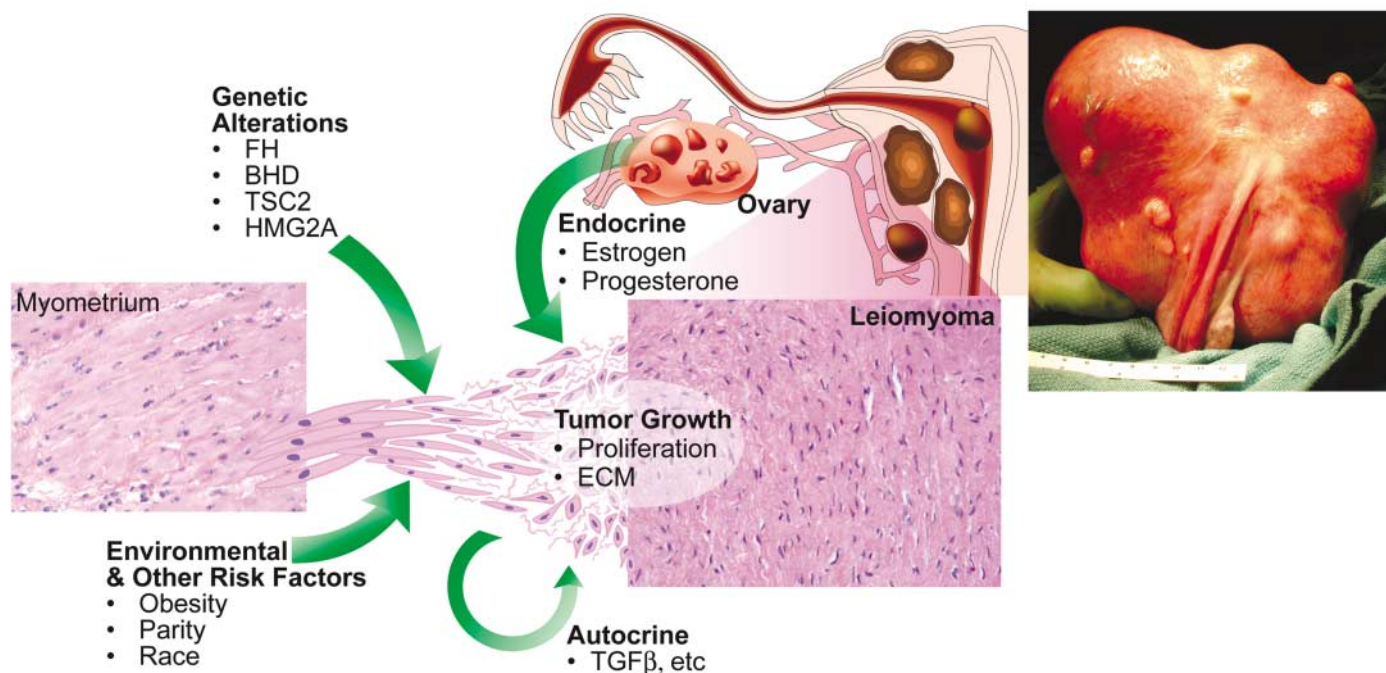


Fig. 1. Etiology of uterine fibroids. Leiomyomas are heterogeneous in their natural history and etiology. Hereditary defects in the *FH*, *BHD*, and *TSC2* genes and somatic alterations affecting *HMG2A* genes contribute to the development of fibroids, as do risk factors such as obesity, parity, and race. Tumor growth occurs by an increase in tumor cell number and ECM production and is promoted by both endocrine and autocrine growth factors.

leiomyoma cells have assumed the phenotype of MSMCs of pregnancy (8). Indeed, leiomyomas share many characteristics with the parturient myometrium, including increased production of ECM components; the expression of receptors for peptide and steroid hormones; and expression of the gap junction protein connexin 43, which is required for cell-cell communication and the synchronous contractions of labor. However, leiomyomas fail to regress via apoptosis and the dedifferentiation that is characteristic of the postpartum myometrium, potentially because of differences in the expression of COX-2 and prostaglandins, the final mediators of parturition (9). The protective effect of pregnancy, which would induce these mediators, is consistent with this hypothesis.

Genetics of Uterine Leiomyoma

Uterine leiomyomas were the first tumor for which glucose-6-phosphate dehydrogenase (G6PD) was used to establish that these tumors are clonal in origin (10). Although the majority of uterine leiomyomas are cytogenetically normal, approximately 40% display non-random cytogenetic alterations, frequently involving chromosome 12 (11, 12). Translocations involving this chromosome identified the target as the *HMG2A* (formerly *HMGI-C*) gene, a member of the high-mobility-group gene family of DNA architectural factors. *HMG2A* and *HMG1* (formerly *HMGI-Y*) are both frequently aberrantly expressed in fibroids and other benign mesenchymal lesions, including lipomas.

Several hereditary cancer syndromes predisposing to leiomyomas suggest a genetic linkage with renal cell carcinoma (RCC) (13). These syndromes include hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis complex (TSC), and Birt-Hogg-Dubé (BHD) syndromes. For example, individuals with HLRCC, who have mutations in the fumarate hydratase (*FH*) gene, develop papillary RCC and uterine and skin leiomyomas. Furthermore, Eker rats that carry a germline defect in the rat homolog of the *Tsc2* gene develop spontaneous RCC and uterine leiomyomas with a high frequency (14). TSC patients develop renal angiomyolipomas and are at increased risk for RCC, and many sporadic human leiomyomas exhibit loss of function of the *TSC2* gene product tuberin (15). Benign cutaneous lesions and uterine leiomyomas also arise in German shepherd dogs with germline mutations in the *Bhd* gene that develop RCC. Although the biological basis for this apparent shared genetic etiology is not clear, the fact that kidney epithelial cells share a mesenchymal lineage with myometrial cells may be an important clue (16).

Unfortunately, the clinical relevance of these genetic syndromes is not widely appreciated. The finding of cutaneous leiomyomas (as seen in HLRCC) should prompt screening of the family not only for RCC but for uterine sarcomas, which are more frequent in these patients. The fact that genetic heterogeneity underlies the dramatic clinical heterogeneity of leiomyomas is also becoming clear. For example, although *FH* alterations in nonsyn-

dromic leiomyomas are rare, in a cohort of patients we examined, *FH* alterations were seen in leiomyomas of Caucasian but not African-American women (17). This observation underscores the importance of genome-wide scanning in a racially diverse population, such as the Finding Genes for Fibroids Project (www.fibroids.net) at Brigham and Women's Hospital in Boston.

Hormones and Growth Factors in Pathogenesis

Like most reproductive tract tumors, fibroids are steroid hormone-dependent (18). Leiomyomas are hyperresponsive to estrogen and exhibit elevated levels of estrogen and progesterone receptors (ERs and PRs), with the expression of a dominant-negative ER inhibiting leiomyoma cell growth in vitro and in vivo (19). Leiomyomas also exhibit alterations in estrogen metabolism, including elevated aromatase levels (20). Although estrogen has traditionally been identified as the sole pathogenic influence, an alternative hypothesis posits that progesterone is the dominant steroidal influence. The "progesterone hypothesis" (21) is supported by increased mitotic rates in myomas during the secretory phase, when progesterone levels peak (22), and by clinical data indicating that progestins inhibit the therapeutic effect of GnRH agonists. The utility of mifepristone (RU486) in treating fibroids also supports this hypothesis. However, transdominant suppression of ER signaling by PR ligands has been demonstrated, with both progestins and antiproges-

tins capable of suppressing ER signaling and leiomyoma cell growth (18). These data suggest that cross-talk between ER and PR signaling occurs in uterine leiomyomas and that the effects of steroidal ligands may be mediated by disruption of ER, PR, or even androgen receptor signaling.

Many cytokines and growth factors may also foster leiomyoma growth through paracrine and/or autocrine mechanisms. These include transforming growth factor- β (TGF- β), insulin-like growth factors 1 and 2 (IGF-1/2), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) (23). In some instances, growth factor expression is modulated by steroids, suggesting that they are the ultimate effectors of steroid hormone action.

Given the low mitotic index of leiomyomas, growth factors probably contribute to myoma enlargement by stimulating the deposition of ECM. TGF- β in particular is thought to be a central player in ECM production (24). Leiomyoma cells express TGF- β receptors and SMADs and overexpress TGF- β relative to normal myometrium. Downstream targets of TGF- β signaling, such as tissue inhibitor of matrix metalloproteases and plasminogen activator inhibitor, which promote ECM production, are also overexpressed in myomas. Recently, transcriptional profiling identified a number of TGF- β -responsive genes overexpressed in leiomyoma cells, including interleukin-11, which plays a major role in other fibrotic disorders (25). GnRH agonists inhibit TGF- β expression, and reduced expression of this cytokine may underlie ECM reduction and clinical shrinkage in tumors in response to GnRH therapy. Aberrant TGF- β signaling is associated with decreased dermatopontin expression, hinting at a molecular link between leiomyomas and keloids (scar tissue), which are both more prevalent in African-American women (26). Recent work also suggests that hypoxia may participate in the development of myomas in HLRCC patients (13), lending support to the theory that fibroids form as a response to injury (27).

Growth factors and ECM also contribute to the profuse menstrual bleeding seen in women with leiomyomas (28). Besides stimulating the production of matrix components that promote angiogenesis, several of the growth factors expressed by fibroids are themselves vasoactive. These include bFGF, which promotes angiogenesis; parathyroid hormone-related protein, a potent vasorelaxant that reduces vascular tone; and prolactin, which can act either as a proangiogenic factor by inducing vascular endothelial growth factor or as an antiangiogenic factor when cleaved by cathepsin D. The abundant ECM also serves as a reservoir for many angiogenic heparin-binding growth factors such as bFGF and heparin-binding epidermal growth factor, as well as PDGF and

prolactin. Both mifepristone and onapristone have been shown to suppress prolactin production by leiomyomas *in vitro*, which may be linked to the clinical efficacy of progesterone-modulating therapy.

Model Systems

Several animal models for uterine leiomyoma exist. The best-characterized and most widely used is the previously mentioned Eker rat model (14), in which approximately 65% of female Tsc2^{E_k/+} carriers develop leiomyomas, a frequency similar to that seen in women. Eker rat leiomyomas share phenotypic, biochemical, and genetic characteristics with the cognate human disease, including ER and PR expression and responsiveness to steroid hormones, aberrant HMGA2 expression, overexpression of IGF-1, and the protective effects of pregnancy. Recently, this model was used to demonstrate that brief exposure to a xenoestrogen during the development of the myometrium can reprogram the response of this tissue to estrogen and promote leiomyoma development in the adult (29). Cell lines have been established from these tumors, which, unlike human leiomyoma cells, retain their hormone responsiveness *in vitro*. This *in vivo/in vitro* model system has demonstrated the potential efficacy of selective ER modulators (SERMs), PR modulators (SPRMs), and drugs that target peroxisome proliferator-activator receptors (PPARs) as therapeutic agents for fibroids (18).

A guinea pig model also exists. Approximately 8% of aged guinea pigs develop spontaneous leiomyomas, and ovariectomy in young animals combined with high-dose estrogen supplementation causes the development of uterine and abdominal leiomyomas with a high frequency. Preclinical studies in these animals also suggest that SERMs and PPAR ligands may be efficacious as therapeutic agents (30).

No mouse models for this disease are available, but a handful of studies have shown that the β -adrenoceptor antagonist levobunolol induces leiomyomas in mice and that transgenic mice expressing SV40 T antigen driven by the estrogen-responsive calbindin promoter develop leiomyomas (31, 32). Human myometrial and leiomyoma cells have now been immortalized through the expression of telomerase (33, 34), and these cell lines hold promise for future development of preclinical screening assays.

Therapy: Much Room for Improvement

Historically, there has been little innovation in treatments for fibroids, nominally because they are benign and cause morbidity, not mortality, and because leiomyoma research is underfunded as compared with that for other nonmalignant diseases (fig. S1). The standard

treatment of uterine fibroids—surgical excision and hysterectomy—has been promulgated as the one-size-fits-all solution. However, although the endoscopic resection of fibroids that are accessible from either surface of the uterus has been a surgical advance, the vast majority of fibroids lie within the uterine wall (are intramural) and are difficult to treat in a minimally invasive fashion.

In the past decade, uterine artery embolization (UAE) has provided an intramural leiomyoma treatment (36). Two embolic agents are approved for UAE, accounting for half of all U.S. Food and Drug Administration (FDA)-approved therapies for treating uterine fibroids. Nonetheless, the induction of global uterine ischemia is still a rather crude approach, and there are ongoing concerns regarding the impact of UAE on fertility and pregnancy.

Magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS) is a therapy for leiomyoma treatment that received FDA approval in October 2004. Although this technique promises noninvasive thermoablative therapy, its chief importance currently is that it is the first technology approved for fibroid treatment as the primary indication. The indications for this therapy are likely to expand, because MRgFUS is able to target specific leiomyomas and provide for outpatient therapy (37).

Medical therapy for fibroids is similarly limited. The only FDA-approved medical therapy is a GnRH agonist used preoperatively with iron. GnRH agonists abrogate both bleeding and bulk-related symptoms but induce significant menopausal side effects that limit therapy. Tumors also rapidly regrow if not removed surgically. Consequently, there is great interest in developing drugs to treat myomas. Unlike their success in preclinical studies, to date SERMs have yielded disappointing results in clinical trials. Current research is investigating progesterone modulation achieved with both traditional drugs such as mifepristone and newer SPRMs such as asoprisnil. Smaller studies are also seeking new avenues for fibroid treatments, including anti-fibrotic agents and growth factor antagonists.

Conclusion

The fact that fibroids are nonmalignant should not imply that they are benign in their impact on women's health. Although gonadal steroids play an important role in their pathogenesis, multiple other molecular targets for potential therapeutic innovation have been elucidated. The lack of discourse on all menstrual disorders, and particularly uterine fibroids, has placed affected women and interested scientists at a tremendous disadvantage. There is ample room for additional biomedical research and therapeutic innovation for dealing with this important disease.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/308/5728/1589/DC1
Fig. S1

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REVIEW

Latest Advances in Understanding Preeclampsia

Christopher W. Redman* and Ian L. Sargent

Preeclampsia is a relatively common pregnancy disorder that originates in the placenta and causes variable maternal and fetal problems. In the worst cases, it may threaten the survival of both mother and baby. We summarize recent work on the causes of preeclampsia, which reveals a new mode of maternal immune recognition of the fetus, relevant to the condition. The circulating factors derived from the placenta, which contributes to the clinical syndrome, are now better understood. This brief review on preeclampsia does not cover all aspects of this intriguing condition but focuses on some new and interesting findings.

Preeclampsia is a potentially dangerous complication of the second half of pregnancy, labor, or early period after delivery, characterized by hypertension, abnormal amounts of protein in the urine, and other systemic disturbances (1). The condition affects about 2.5 to 3.0% of women. It has the potential to kill either mother or baby or both, even in the developed world (although rarely). Eclampsia is an end stage of the disease characterized by generalized seizures. Preeclampsia cannot be prevented, so it is managed by screening symptomless women and inducing delivery when necessary. It is one of the most common reasons for induced preterm delivery.

Risk factors for preeclampsia have been analyzed in a recent systematic review (2). These factors include a previous history of preeclampsia, primiparity, obesity, family history of preeclampsia, multiple pregnancies, and

chronic medical conditions such as long-term hypertension or diabetes (2). Paradoxically, cigarette smoking reduces the risk (2). Thrombophilia, an inherited tendency to overactive coagulation, may also be a consideration. Although preeclampsia may develop at any time after 20 weeks of gestation, early onset disease is more severe and characterized by a higher rate of small size for gestational age neonates as well as a higher recurrence rate than with later onset disease.

It is generally agreed that preeclampsia results from the presence of a placenta (3) and, in particular, the trophoblast cells that are found only in this tissue. Multinucleate syncytiotrophoblast, which forms the epithelial layer of the villi, is one subset of trophoblast that is in direct contact with maternal blood. Mononuclear extravillous cytotrophoblast form a tissue interface in the lining of the uterus, the decidua. The clinical syndrome arises from secondary systemic circulatory disturbances that can be ascribed to generalized maternal endothelial dysfunction. There are two broad categories, maternal and placental. In placental preeclampsia, the problem arises from a placenta

that is under hypoxic conditions with oxidative stress. (4) Maternal preeclampsia arises from the interaction between a normal placenta and a maternal constitution that is susceptible to, or suffers from, microvascular disease, as with long-term hypertension or diabetes (5). Mixed presentations, combining maternal and placental contributions, are common.

Placental Preeclampsia

Placental preeclampsia appears to progress in two stages: preclinical and clinical (Fig. 1C). This variant arises from poor development of the early placenta and its maternal blood supply, called poor placentation. In the second stage, an increasingly hypoxic placenta causes the maternal signs of the condition, including hypertension and proteinuria as well as clotting and liver dysfunction. In severe, particularly early onset disease (before 34 weeks gestation), the fetus may suffer increasing nutritional and respiratory insufficiency, asphyxia, or death.

In the second two trimesters of pregnancy, the placenta requires increasing access to the maternal blood supply. This is created by extensive remodeling of maternal spiral arteries, which are the end arteries of the uteroplacental circulation that deliver blood directly into the placental intervillous space. Remodeling depends on one of the subtypes of the trophoblasts, which differentiates into tumor-like cells (extravillous cytotrophoblasts) that invade the lining of the pregnant uterus from weeks 6 to 18 of gestation (6).

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