Etiology, symptomatology, and diagnosis of uterine myomas

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Objective: To review the currently available literature regarding the biology, etiology, symptoms, and diagnosis of uterine myomas.

Design: Literature review of 220 articles pertaining to uterine myomas.

Result(s): Although uterine myomas presently are not well understood, many advances have been made in the understanding of the hormonal factors, genetic factors, growth factors, and molecular biology of these benign tumors. Prospective, longitudinal studies are underway to characterize the risk factors for their development. When needed, the position of myomas can be best imaged by sonohysterography or magnetic resonance imaging. Evidence suggests that only submucous myomas appear to interfere with fertility, and only very rarely do myomas effect pregnancy outcome.

Conclusion(s): A summary of the available literature regarding the biology, etiology, symptomatology, and diagnosis of myomas shows that, although they are still not well understood, much has been learned about uterine myomas. (Fertil Steril® 2007;87:725–36. ©2007 by American Society for Reproductive Medicine.)

Key Words: Uterine myomas, myomas, fibroids, myomas and pregnancy, myomas and fertility, uterine sarcoma, myoma biology, myoma diagnosis, myoma symptoms

Twenty-five years ago, *Fertility and Sterility* published Buttram and Reiter's (1) classic review on uterine myomas. At that time, little was known about the biology of myomas. Although myomas are still not well understood, much has been learned in the interim about the genetic factors the lead to the formation of myomas and the proteins that stimulate their growth. Epidemiologic studies have illuminated the risk factors for the development of myomas, and approaches to their diagnosis have been clarified. Better evidence regarding the effect of myomas on fertility and pregnancy is now available.

Despite the prevalence of this condition, myoma research is underfunded compared with other nonmalignant diseases. It is likely that innovation has been slow to come to myoma treatment because myomas are benign, many women with myomas are asymptomatic, and myomas almost always cause morbidity rather than mortality (2). This article summarizes the available literature regarding the biology, symptomatology, and diagnosis of myomas.

UTERINE MYOMAS

Description

Myomas are benign, monoclonal tumors of the smooth muscle cells of the myometrium. They are composed of large amounts of extracellular matrix containing collagen, fibronectin, and proteoglycan. Collagen type I and type III are abundant, but the collagen fibrils are formed abnormally and are in disarray, much like the collagen found in keloid formation (3–5).

Incidence

Myomas are remarkably common. Fine serial sectioning of uteri from 100 consecutive women who underwent hysterectomy found myomas in 77%, including some as small as 2 mm (6). Myomas were found no less frequently in women who had a hysterectomy for other indications than for uterine myomas, although they were smaller and less numerous. Because most imaging techniques lack resolution <1 cm., they underestimate the true incidence of this condition, although small myomas may be of no clinical significance. The hysterectomy specimens from premenopausal women with myomas have had an average of 7.6 myomas; postmenopausal women have had on average 4.2 myomas (6).

A random sampling of women aged 35 to 49 who were screened by self-report, medical record review, and sonography found that by age 35 the incidence of myomas was 60% among African-American women; the incidence increased to over 80% by age 50 (Fig. 1). Caucasian women have an incidence of 40% by age 35, and almost 70% by age 50 (7).

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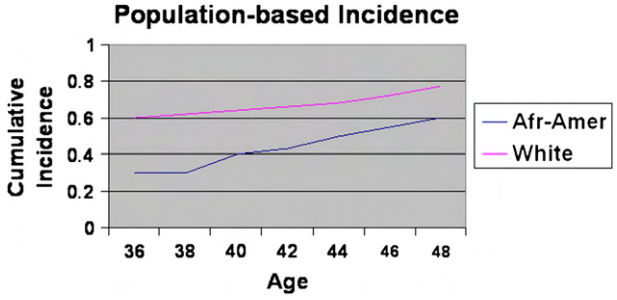
FIGURE 1

Population-based incidence of myomas relative to age for African-American and Caucasian women in the United States. (Reprinted from Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7. Copyright 2003 Elsevier, Inc., with permission.)



Parker. Uterine myomas. Fertil Steril 2007.

Myomas are an enormous healthcare concern; they were the primary indication for surgery in 199,000 hysterectomies and 30,000 myomectomies performed in the United States in 1997 (8). Inpatient surgery for myomas cost $2.1 billion in the United States in 1997, and the cost of outpatient surgeries, medical and nonmedical costs, and time away from work or family adds significantly to these expenditures (9).

Etiology

Although the precise causes of myomas are unknown, advances have been made in the understanding of the hormonal factors, genetic factors, growth factors, and molecular biology of these benign tumors (10). Factors possibly responsible for the initiation of acquired genetic changes found in myomas include intrinsic abnormalities of the myometrium, congenitally elevated estrogen receptors in the myometrium, hormonal changes, or a response to ischemic injury at the time of menses. Once established, these genetic changes are influenced by promoters (hormones) and effectors (growth factors).

Myoma Genetics

Myomas are monoclonal, and about 40% are chromosomally abnormal (11). Commonly found abnormalities include translocations between chromosomes 12 and 14, deletions of chromosome 7, and trisomy of chromosome 12 (12). Cellular, atypical, and large myomas are most likely to show chromosomal abnormalities. The remaining 60% may have undetected mutations.

More than 100 genes have been found to be up-regulated or down-regulated in myoma cells, including the sex-steroid associated genes estrogen receptor α, estrogen receptor β, progesterone receptor A, progesterone receptor B, growth hormone receptor, prolactin receptor, and extracellular matrix genes, and collagen genes (13). Many of these genes appear to regulate cell growth, differentiation, proliferation, and mitogenesis.

Uterine Sarcoma Genetics

Genetic differences between myomas and leiomyosarcomas indicate they most likely have distinct origins, and leiomyosarcomas do not result from malignant degeneration of myomas (2). Although myomas are proliferative tumors, they remain differentiated and have chromosomal rearrangements similar to other benign lesions. In contrast, leiomyosarcomas are undifferentiated and have complex chromosomal rearrangements and aneuploid karyotypes. Cluster analysis of 146 genes in leiomyosarcomas has shown that the majority are down-regulated, but in myomas or myometrium they are not. Comparative genomic hybridization has not found specific anomalies shared by myomas and leiomyosarcomas (14).

Hormones

Both estrogen and progesterone appear to promote the development of myomas. Myomas are rarely observed before puberty, are most prevalent during the reproductive years, and regress after menopause. Factors that increase overall lifetime exposure to estrogen, such as obesity and early menarche, increase the incidence. Decreased exposure to estrogen found with exercise and increased parity is protective (15).

Although blood levels of estrogen and progesterone are similar in women with and without clinically detectable myomas, levels of estradiol within myomas are higher than in normal myometrium. De novo production of estrogen within myoma tissue is suggested by increased levels of aromatase, an enzyme that converts androgens to estrogen. Low levels of enzymes that convert estradiol to estrone have been found in myoma cells and may promote accumulation of estradiol within the cells, leading to up-regulation of estrogen and progesterone receptors, hyperresponsiveness to estrogen, and myoma growth. Consistent with this idea, myomas show a higher proliferative index than normal myometrium throughout the menstrual cycle (15).

Biochemical, clinical, and pharmacologic evidence confirm that progesterone is important in the pathogenesis of myomas. Myomas have increased concentrations of progesterone receptors A and B compared with normal myometrium (16, 17).

The highest mitotic counts are found during the secretory phase at the peak of progesterone production, and mitotic counts are higher in women treated with medroxyprogesterone acetate (MPA) than in untreated controls (5, 18). Gonadotropin-releasing hormone (GnRH) agonists decrease the size of myomas, but progestin given concurrently with GnRH prevents a decrease in size. One study found that use of progestin-only injectable contraceptives was inversely associated with risk of having myomas (19). Mifepristone, a progesterone-receptor modulator, decreases myoma size (20).

Growth Factors

Growth factors, proteins or polypeptides produced locally by smooth muscle cells and fibroblasts control the proliferation of cells and appear to stimulate myoma growth, primarily by increasing extracellular matrix. Some of the identified myoma-related growth factors are transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and prolactin (10). Growth factors affect cells in complex ways, and the response to combinations of growth factors may be different from the response to an individual factor.

Many of these growth factors are overexpressed in myomas and either increase smooth muscle proliferation (TGF-β, bFGF), increase DNA synthesis (EGF, PDGF), stimulate synthesis of extracellular matrix (TGF-β), promote mitogenesis (TGF-β, EGF, IGF, prolactin), or promote angiogenesis (bFGF, VEGF) (10). It is likely that other myoma-related growth factors will be discovered, and it remains to be seen which factors will be important.

Risk Factors

The literature regarding predisposing risk factors for development of myomas should be interpreted with caution. Analysis is limited by the paucity of studies available, the study populations (mostly in Caucasian women), and the conflicting results, which suggests other unexamined factors may be involved.

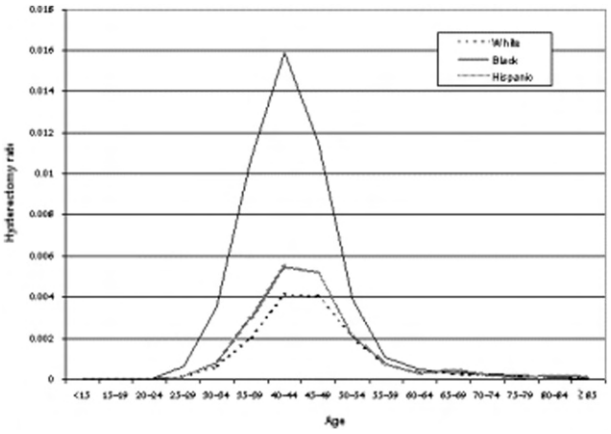
The high background prevalence of myomas, and possible detection bias as a consequence of increased medical surveillance of symptomatic women, may make interpretation of epidemiologic data difficult. The reliability of self-reported diagnoses may be questioned; the development of myomas may have preceded the exposure to risk factors but may not have been recognized until after presentation to a healthcare provider. Prospective, longitudinal studies are underway to better characterize the factors that influence the development of uterine myomas.

Age Women are most likely to be diagnosed with myomas during their forties; however, it is not clear whether this is because of increased formation or increased myoma growth secondary to hormonal changes during this time. Another factor that might distort the incidence may be the willingness of physicians to recommend, and for women to accept, hysterectomy only after they have completed the childbearing years (Fig. 2).

Endogenous hormonal factors Early menarche (<10 years old) has been found to increase (relative risk [RR] 1.24) and late menarche (>16 years) to decrease (RR 0.68) the risk of uterine myomas (21). Myomas are smaller and less numerous in hysterectomy specimens from postmenopausal women when endogenous estrogen levels are low; myoma cell size is significantly smaller in postmenopausal women (6, 22).

FIGURE 2

Cumulative incidence of hysterectomy for African-American, Caucasian, and Hispanic women. (Reprinted from Myers E, Barber M, Couchman G, Datta S, Gray R, Gustilo-Ashby T, et al. Management of uterine fibroids. Vol. 1. AHRQ Evidence Reports, no. 24. AHRQ publication no. 01-E052, July 2001. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.47755. Reprinted with permission from the author.)



Parker. Uterine myomas. Fertil Steril 2007.

Family history First-degree relatives of women with myomas have a 2.5 times increased risk of developing myomas (23, 24). Women reporting myomas in two first-degree relatives are more than twice as likely to have strong expression of VEGF-α (a myoma-related growth factor) than women who have myomas but no family history (25). Monozygous twins are reported to be hospitalized for treatment of myomas more often than dizygous twins, but these findings may be the result of reporting bias (26).

Ethnicity A large study of women screened for the presence of myomas by self-report, medical record review, and sonography found that African-American women had a 2.9 times greater risk of having myomas than Caucasian women, and that this risk was unrelated to other known risk factors. African-American women also have myomas present at a younger age, and have more numerous, larger, and more symptomatic myomas (27, 28).

It is unclear whether these differences are genetic or due to known differences in circulating estrogen levels, estrogen metabolism, diet, or environmental factors. However, a recent study found that the Val/Val genotype of an enzyme essential to estrogen metabolism, catechol-O-methyltransferase (COMT), is found in 47% of African American women but only 19% of white women. Women with this genotype are more likely to develop myomas, which may explain the higher prevalence of myomas among African-American women (29). It is also interesting that myomas and keloids,

both more common in African-American women, have similar gene characteristics.

Weight A prospective study found that the risk of myomas increased 21% with each 10 kg increase in body weight and with increasing body mass index (30). Similar findings have been reported in women with greater than 30% body fat (31). Obesity increases conversion of adrenal androgens to estrone and decreases sex hormone–binding globulin. The result is an increase in biologically available estrogen, which may explain an increase in myoma prevalence and/or growth.

Diet Few studies have examined the association between diet and the presence or growth of myomas. One study found that beef, other red meat, and ham increased the incidence of myomas, but green vegetables decreased it. These findings are difficult to interpret because the study did not measure calorie and fat intake (32). It is not clear whether vitamins, fiber, or phytoestrogen might be responsible for the observed effects.

Exercise Former college athletes are noted to have a 40% lower prevalence of myomas compared with nonathletes. It is not clear whether this difference represents the effects of exercise or lower conversion rates of androgens to estrogens due to lean body mass (33).

Oral contraceptives There is no definite relationship between oral contraceptives and the presence or growth of myomas. One study found an increased risk of myomas with oral contraceptives (34), but a subsequent study found no increased risk with use or duration of use (35). Although another study found a decreased risk, women with known myomas may be prescribed oral contraceptives less frequently, leading to selection bias (21, 30, 36).

Menopausal hormone therapy For the majority of postmenopausal women with myomas, hormone therapy will not stimulate uterine growth. If the uterus does grow, it is more likely related to the dose of progesterone than estrogen. Postmenopausal women with myomas were given 2 mg of oral estradiol daily and randomized to 2.5 or 5.0 mg of medroxyprogesterone acetate (MPA) per day. Myomas were measured sonographically before and 1 year after treatment (37). Seventy-seven percent of women taking 2.5 mg of MPA had either no change or a decrease in myoma diameter, and 23% had a slight increase. However, 50% of women taking 5 mg of MPA had an increase in myoma size (mean diameter increase of 3.2 cm).

Postmenopausal women with myomas treated with 0.05 mg of transdermal estradiol daily were randomized to either low-dose MPA at 2.5 mg daily or placebo (38). After 1 year, 74% of women taking MPA had no change or a decrease in uterine size, and 26% had a slight increase in uterine size. Similar changes were found in the women using transdermal estradiol alone.

Postmenopausal women with myomas who were treated with 0.625 mg of conjugated equine estrogen (CEE) and 5 mg of MPA were compared over 3 years with a similar group of women who were not taking hormone therapy (39). Although a few women in the treatment and control groups had very slight increases (1.5 cm^3) in myoma volumes after the first and second years, by the end of the third year only 3 of 34 (8%) treated and 1 of 34 (3%) untreated women had any increase in myoma volume over baseline. Postmenopausal women with known myomas, followed with sonography, were noted to have an average 0.5-cm increase in the diameter of myomas after using transdermal estrogen patches plus oral progesterone for 12 months. Women taking oral estrogen and progesterone had no increase in size (40). Postmenopausal women treated for 12 months with raloxifene, a selective estrogen-receptor modulator, had decreased myoma size. Even at high doses of raloxifene, however, there was no effect in premenopausal women (15).

Pregnancy Increased parity decreases the incidence and number of clinically apparent myomas (41–43). Myomas share some characteristics with normal myometrium during pregnancy, including increased production of extracellular matrix and increased expression of receptors for peptide and steroid hormones. The postpartum myometrium returns to normal weight, blood flow, and cell size via apoptosis and dedifferentiation (44). This remodeling process may be responsible for the involution of myomas. Another theory postulates that the vessels supplying myomas regress during involution of the uterus, depriving myomas of their source of nutrition (45).

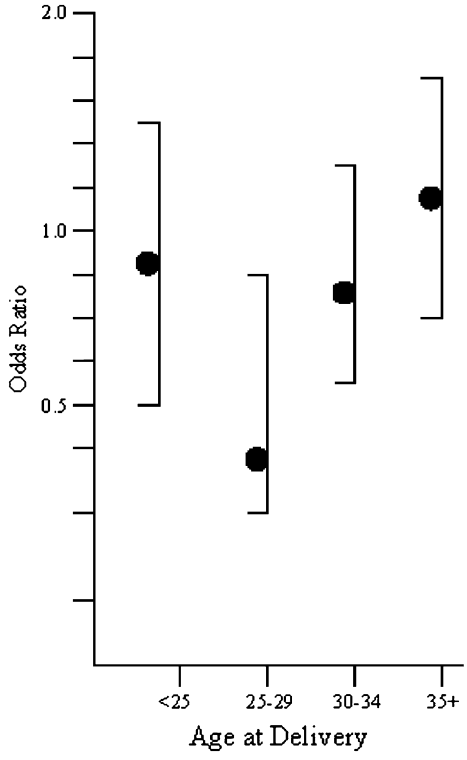
Childbearing during the midreproductive years (age 25 to 29 years) provides the greatest protection against myoma development. Pregnancies early in the reproductive years, before age 25, may occur before the formation of myomas, and pregnancies after age 30 may occur when myomas are too large to regress (Fig. 3) (43).

Smoking Smoking may reduce the incidence of myomas. A number of factors decrease bioavailability of estrogen at the target tissue; reduced conversion of androgens to estrone secondary to inhibition of aromatase by nicotine, increased 2-hydroxylation of estradiol, or stimulation of higher sex hormone–binding globulin levels (46–48). An epidemiologic study of African-American women did not find an increased risk of myomas among smokers, and postulated that a decrease in estrogen may be countered by cell proliferation stimulated by components of smoke such as dioxin (49, 50).

Tissue injury Cellular injury or inflammation resulting from an environmental agent, an infection, or hypoxia have been proposed as mechanisms for initiation of myoma formation (51). However, no increased incidence has been found in women who have had sexually transmitted infections, an increased number of sexual partners, a younger age at first intercourse, prior intrauterine device use, or prior talc exposure. Herpes simplex virus I or II, cytomegalovirus,

FIGURE 3

The relative risks of increased fibroid development associated with age at delivery among 624 participants in the U.S. National Institute of Environmental Health Sciences Uterine Fibroid Study. (Reprinted from Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology 2003;14:247–50. Copyright 2003 Lippincott Williams & Wilkins, with permission.)



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Epstein-Barr virus, or chlamydia have not been found in myomas. Vasoconstriction-induced hypoxia during menstruation has been proposed, but not confirmed, as another possible source of myometrial injury.

SYMPTOMS

Although the presence of myomas is almost never associated with mortality, myomas may cause morbidity and affect quality of life.

Abnormal Bleeding

The association of myomas with abnormal uterine bleeding, principally menorrhagia, has not been clearly established. The presence of myomas does not necessarily lead to menorrhagia, so other possible etiologies should be considered, including coagulopathies such as von Willebrand disease (52).

When a population-based, non-care–seeking cohort of women was evaluated by abdominal and transvaginal sonography, myomas were detected in 73 women (21.4%). After adjustment for covariates, the presence of any myoma was not statistically significantly related to length of the menstrual cycle (P=.40) or heaviness of flow (odds ratio [OR] 1.3, confidence interval [CI] 0.7–2.5). Neither the number, volume, subserosal or intramural location (insufficient numbers to analyze submucosal), nor anterior or posterior position of myomas were related to menstrual cycle characteristics (53).

A random sample of women aged 35 to 49 was evaluated by self-reported bleeding patterns and by abdominal and transvaginal sonography to determine presence, size, and location of myomas (54). Of the 878 women screened, 564 (64%) had myomas, and 314 (36%) did not. Forty-six percent of the women with myomas reported "gushing blood" during their menstrual periods compared with 28% without myomas. Gushing blood and length of periods were related to size of myomas (large myomas RR = 1.9, CI 1.5–2.5), but not to presence of submucous myomas or to multiple myomas.

The same study found that women with myomas used 7.5 pads or tampons on the heaviest day of bleeding compared with 6.1 pads or tampons used by women without myomas. Women with myomas larger than 5 cm had slightly more gushing and used about three more pads or tampons on the heaviest day of bleeding than women with smaller myomas (54).

Some women with myomas may have menorrhagia, and theories for the possible cause include venous ectasia resulting from mechanical compression of veins by myomas, or altered function, expression or storage of vasoactive growth factors produced by myomas (51, 55, 56). A variety of myoma-related growth factors increase proliferation or vascular caliber or promote angiogenesis. The initial molecular biology-derived therapy will likely be targeted at angiogenesis.

Pain

Women with myomas are only slightly more likely to experience pelvic pain than women without myomas. Transvaginal sonography was performed on a population-based cohort of 635 non-care–seeking women with an intact uterus to determine the presence of uterine myomas. Concurrent symptoms of dyspareunia, dysmenorrhea, or non-cyclic pelvic pain were measured by visual analog scales. The 96 women found to have myomas were only slightly more likely to report moderate or severe dyspareunia (OR = 2.8, CI 0.9–8.3) or noncyclic pelvic pain (OR = 2.6, CI 0.9–7.6), and had no higher incidence of moderate or severe dysmenorrhea (OR = 1.1, CI 0.59–2.6) than women without myomas. Neither the number or total volume of myomas was related to pain (57).

Urinary Symptoms

Few studies have examined the relationship of myomas to urinary symptoms. Fourteen women with large myomas and urinary symptoms were given six monthly injections of GnRH agonist with a resulting 55% decrease in uterine

volume. Following therapy, a decrease in urinary frequency, nocturia, and urgency was found, but there were no changes in urge or stress incontinence as measured by symptoms or urodynamic studies. It is not clear whether these findings are related to a decrease in uterine volume or other effects of GnRH treatment (58).

Following a 35% mean uterine volume reduction after uterine artery embolization, frequency and urgency was greatly improved in 53% of women (n = 306), moderately improved in 15%, slightly improved in 18%, and unchanged or worse in only 14%. This finding suggests that increased uterine volume associated with myomas is related to urinary symptoms (59).

Natural History of Myomas

Few longitudinal studies of myoma growth have been conducted. One study evaluated 64 asymptomatic premenopausal women using saline-infusion sonograms performed at baseline (average age: 41) and 2.5 years later (60). Eleven women (16%) had myomas at baseline (mean diameter: 19 mm), and 17 (27%) had myoma diagnosed at the follow-up evaluation (mean diameter: 27 mm). The rate of growth varied from −0.9 cm to +6.8 cm. Nine women were found to have new myomas after 2.5 years (60).

A recent ongoing study of myoma growth followed 120 women with four magnetic resonance imagining (MRI) examinations over 1 year. A computer-aided image analysis program evaluated 1076 volumes of myomas classified as small (<7 cm^3), medium (7 to 50 cm^3), or large (>50 cm^3). It is interesting that 1 year later all myomas were noted to be larger. Large and medium myomas grew more than small myomas, and intramural myomas grew more than subserous or submucosal myomas. Measured rates of growth were similar for different races and ethnic groups (61). Continued follow-up studies of these women should provide a better understanding of this important issue.

Rapid Myoma Growth

In premenopausal women, "rapid uterine growth" almost never indicates presence of uterine sarcoma. One study found one sarcoma among 371 (0.26%) women operated on for rapid growth of presumed myomas. No sarcomas were found in the 198 women who had a 6-week increase in uterine size over 1 year (62). The association between rapid growth of presumed myomas and sarcoma has not been substantiated.

Uterine Sarcoma

Most women found to have uterine sarcoma are clinically suspected of having a pelvic malignancy (62, 63). Of nine women, aged 64 to 86, found to have uterine sarcomas, eight had been admitted with abdominal pain and vaginal bleeding and were thought to have gynecologic malignancies: presumed uterine sarcoma in four, endometrial carcinoma in three, and ovarian cancer in one. One additional woman had prolapse surgery, and a sarcoma was found incidentally (62). Between 1989 and 1999, the U.S. National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database reported 2098 women with uterine sarcomas with an average age of 63 years (64); however, a review of the literature found a mean age of 36 years in women who had undergone myomectomy (62). Thus, the age of the patient and clinical presentation may help distinguish growing myomas from sarcoma.

DIAGNOSIS

Pelvic Examination

Clinically significant subserosal and intramural myomas can usually be diagnosed by pelvic examination based on findings of an enlarged, irregularly shaped, firm, and nontender uterus (65, 66).

Uterine size, as assessed by bimanual examination, correlates well with uterine size and weight at pathologic examination, even in most obese women (body mass index >30) (65). Routine sonographic examination is not necessary when the diagnosis is almost certain. However, submucous myomas often require saline-infusion sonography, hysteroscopy, or MRI for definitive diagnosis.

Imaging

The optimal selection of patients for medical therapy, noninvasive procedures, or surgery depends on an accurate assessment of the size, number, and position of myomas. Imaging techniques available for confirming the diagnosis of myomas include sonography, saline-infusion sonography, hysteroscopy, and MRI.

Transvaginal sonography is the most readily available and least costly technique and may be helpful for differentiating myomas from other pelvic conditions. Large myomas may be best imaged with a combination of transabdominal and transvaginal sonography. Sonographic appearance of myomas can be variable, but frequently they appear as symmetrical, well-defined, hypoechoic, and heterogenous masses. However, areas of calcification or hemorrhage may appear hyperechoic, and cystic degeneration may appear anechoic. Sonography may be inadequate for determining the precise number and position of myomas, although transvaginal sonography is reasonably reliable for uteri <375 mL in total volume or containing four myomas or fewer (67).

Saline-infusion sonography uses saline inserted into the uterine cavity to provide contrast and better define submucous myomas, polyps, endometrial hyperplasia, or carcinoma. Magnetic resonance imagine is an excellent method to evaluate the size, position, and number of uterine myomas and is the best modality for exact evaluation of submucous myoma penetration into the myometrium (68). The advantages of MRI include no dependence on operator techniques and the low interobserver variability in interpretation of images for submucous myomas, intramural myomas, and

adenomyosis when compared with transvaginal sonography, saline-infusion sonograms, and hysteroscopy (67, 69).

Magnetic resonance imaging may differentiate adenomyosis from myomas. In 22 women scheduled for hysterectomy, MRI (sensitivity 64%, specificity 88%) was superior to transvaginal sonography (sensitivity 59%, specificity 79%) for the diagnosis of adenomyosis. The presence of adenomyosis was associated with junctional zone thickness of more than 15 mm (or 12 mm in a nonuniform junctional zone). Focal, not well-demarcated, high-intensity or low-intensity areas in the myometrium also correlate with adenomyosis (70).

Preoperative transvaginal sonography, saline-infusion sonography, hysteroscopy, and MRI were all performed in each of 106 women scheduled for hysterectomy, and the findings were compared with the results of the pathologic examination. Submucous myomas were best identified with MRI (100% sensitivity, 91% specificity). Identification was about equal with transvaginal sonography (sensitivity 83%, specificity 90%), saline-infusion sonography (sensitivity 90% specificity 89%), and hysteroscopy (sensitivity 82%, specificity 87%) (68).

Magnetic resonance imaging allows the evaluation of submucous, intramural, and subserosal myomas, helps define what can be expected at surgery, and might help the surgeon avoid missing myomas during surgery (71).

Uterine Sarcoma

The preoperative diagnosis of leiomyosarcoma may be possible. Diagnosis with total serum lactic acid dehydrogenase (LDH), LDH isoenzyme 3, and gadolinium-enhanced MRI (Gd-DTPA) with initial images taken between 40 and 60 seconds has been reported to be highly accurate. A study of 87 women with uterine myomas, 10 women with leiomyosarcomas, and 130 women with degenerating myomas reported 100% specificity, 100% positive predictive value, 100% negative predictive value, and 100% diagnostic accuracy for leiomyosarcoma (72) (Fig. 4).

MYOMAS AND FERTILITY

The presence of submucous myomas decreases fertility, and their removal increases fertility to baseline rates. Neither intramural nor subserosal myomas appear to affect fertility rates, and their removal has not been shown to increase fertility (73). Unfortunately, the literature relating myomas and fertility is limited by a lack of prospective, randomized, controlled studies examining this important question. Existing studies were mostly observational and have had disparate designs, with some studies omitting important information such as myoma diagnostic methods, type of evaluation of the uterine cavity (hysteroscopy or saline-infusion sonography), size and number of myomas, patient ages, and type of fertility treatment. Most studies lack the statistical power to make valid conclusions.

Proper evaluation of the uterine cavity is important for any study of myomas and fertility. If the submucous component of an intramural myoma is not appreciated, then any decrease in fertility will be attributed to an intramural myoma rather than a submucous myoma. As noted previously, both hysteroscopy and saline-infusion sonography have been shown to be far superior in detecting submucous myomas than transvaginal sonography or hysterosalpingography (68). Although MRI is the best method, it is expensive and not often used for this evaluation.

To help clarify the relationship between myomas and infertility, a meta-analysis was performed (73). Eleven studies, each with its own shortcomings, were analyzed. Submucous myomas with distortion of the uterine cavity appear to decrease fertility as pregnancy rates decrease by 70% (RR 0.32, CI 0.13–0.70). In women undergoing IVF, resection of submucous myomas restored fertility to equal that of infertile controls who do not have myomas and underwent in vitro fertilization (RR 1.72, CI 1.13–2.58). Neither the presence of intramural nor subserosal myomas decreased fertility (intramural: RR 0.94, CI 0.73–1.20; subserosal: RR 1.1, CI 0.06–1.72). Removal of intramural or subserosal myomas by abdominal or laparoscopic myomectomy did not improve fertility. Unfortunately, insufficient data exist to help evaluate the impact on fertility rates of size or number of myomas. An updated meta-analysis including studies published after 2001 came to the same conclusions (E. A. Pritts, personal communication).

The risks of myomectomy include operative and anesthetic risks, risk of infection, postoperative adhesions, a very small risk of uterine rupture, the increased likelihood that a Cesarean section will be used for delivery, and the expense of surgery plus the discomfort and time for recovery. Therefore, until intramural myomas are shown to decrease and myomectomy to increase fertility rates, surgery should be undertaken with reluctance. Randomized studies are needed to clarify these important issues.

MYOMAS AND PREGNANCY

Incidence of Myomas during Pregnancy

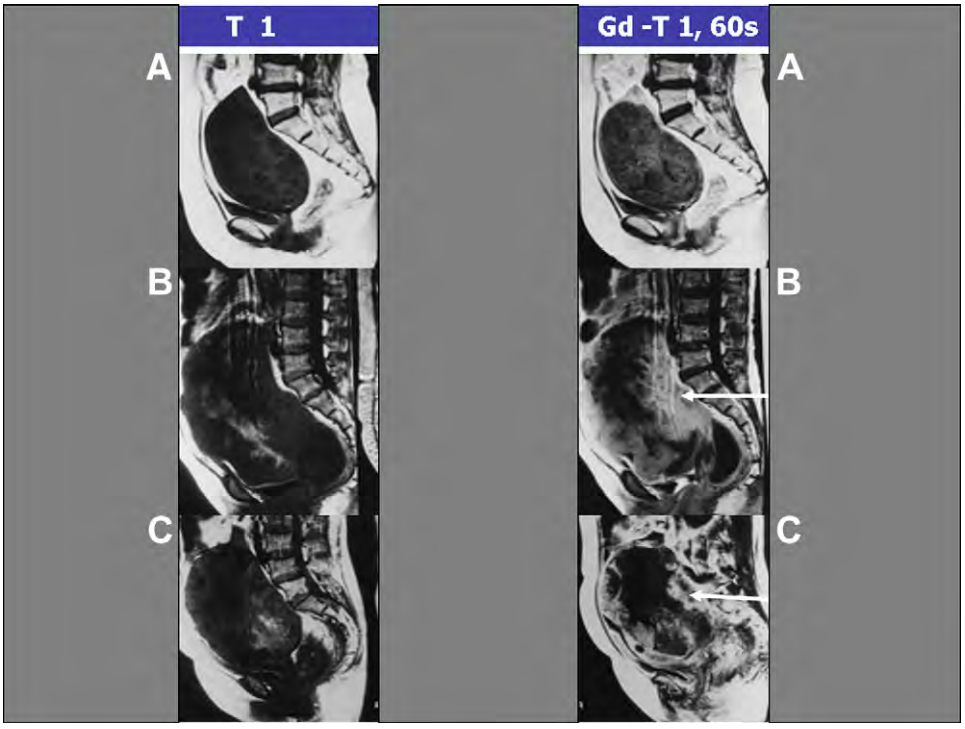
During pregnancy, the incidence of sonographically detected myomas is low (74). Of 12,600 women attending a prenatal clinic, routine second trimester sonography identified myomas in 183 women (mean age: 33 years), for an incidence of 1.5%. Only 30% of the 183 women were suspected of having myomas on pelvic examination (75). Clinical examination has been reported to detect 42% of myomas greater than 5 cm during pregnancy, but only 12.5% when they are less than 5 cm (76).

Effect of Pregnancy on Myomas

Pregnancy has a variable and unpredictable effect on myoma growth, likely dependent on individual differences in genetics, circulating growth factors, and myoma-localized receptors. However, most myomas do not increase in size during pregnancy. A prospective study of 36 pregnant women who had a single myoma found during routine first-trimester

FIGURE 4

MR images of degenerating myoma and leiomyosarcoma. (**A**) Degenerating myoma shows no enhancement after gadolinium. (**B**) Leiomyosarcoma enhanced with Gd-DPTA at 60 seconds after administration. (**C**) Leiomyosarcoma enhanced with Gd-DPTA at 60 seconds after administration. (Reprinted from Goto A, Takeuchi S, Sugimura K, Maruo T. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer 2002;12:354–61. Copyright 2002 Blackwell Publishing, with permission.)



Parker. Uterine myomas. Fertil Steril 2007.

sonographic screening who were then examined by sonography at 2 to 4 week intervals found that 69% of the women had no increase in volume throughout pregnancy. In the 31% of women noted to have an increase in myoma volume, the greatest increase occurred before the 10th week of gestation. There was no relationship between initial myoma volume and myoma growth during gestational periods. A reduction in myoma size was observed 4 weeks after delivery (77).

Myoma Degeneration during Pregnancy

In women noted to have myomas during pregnancy, clinical symptoms and sonographic evidence of myoma degeneration occur in about 5% (75, 78). One theory proposes that as the uterus grows a myoma may change orientation to supplying blood vessels with subsequent obstruction of the vessels. Among 113 women followed during pregnancy with serial sonography, 10 (9%) developed anechoic spaces or coarse heterogenous patterns in the myomas consistent with degeneration. Seven of those 10 (70%) also had severe abdominal pain consistent with clinical symptoms of degeneration and required hospitalization. Four women had symptoms for 7 days, and three women had recurrence of symptoms during the remainder of pregnancy. No sonographic changes were noted in the other 103 women, and only 11.7% had similar abdominal pain ($P<.001$) (78). A small study of women with pain during pregnancy from presumed myomas found ibuprofen to shorten the hospital stay and decrease the rate of readmission (79).

Influence of Myomas on Pregnancy

Very rarely does the presence of a myoma during pregnancy lead to an unfavorable outcome. Many problems exist with the current literature regarding the effect of myomas on pregnancy; the most significant is the problem of selection bias. However, two studies reported on large populations of pregnant women examined with routine second-trimester sonography with follow-up and delivery at the same institution.

In one study, 12,600 pregnant women were evaluated, and the outcomes of 167 women with myomas were compared with women without myomas. There were no significant differences, despite similar clinical management, in the incidence of preterm delivery, premature rupture of

membranes, fetal growth restriction, placenta previa, placental abruption, postpartum hemorrhage, or retained placenta. Only cesarean section was more common among women with myomas (23% vs 12%, $P<.001$) (75).

The other study reviewed 15,104 pregnancies and compared 401 women found to have myomas to the remaining women without myomas. Although the presence of myomas did not increase the risk of premature rupture of membranes, operative vaginal delivery, chorioamnionitis or endomyometritis, there was increased risk of preterm delivery (19.2% vs 12.7%), placenta previa (3.5% vs 1.8%), and postpartum hemorrhage (8.3% vs 2.9%). Cesarean section was again more common (49.1% vs 21.4%) (80).

Lower uterine segment myomas appear to increase the cesarean section rate when compared with myomas in the uterine body (53% vs 30.8%). The presence of submucous myomas and multiple myomas may also increase the cesarean section rate (75, 81). However, the recent study evaluated size, number, and position of myomas and found that myoma size >10 cm was associated with malposition but not cesarean section rate. An increased number of myomas was not associated with outcomes, and there were insufficient data to evaluate the influence of myoma position (80).

Fetal injury attributed to mechanical compression by myomas has been reported to occur very infrequently. A review of the literature from 1980 to 2005 revealed one case of fetal head anomalies with fetal growth restriction, one case of a postural deformity, one case of a limb reduction, and one case of fetal head deformation with torticollis (82–85).

No data are available comparing pregnancy outcomes following myomectomy with pregnancy outcomes in women with untreated myomas. Any decision to perform myomectomy should take into account the risks of surgery, anesthesia, postoperative adhesions, likelihood of subsequent cesarean delivery, and concerns about discomfort, expense, and time away from work or family.

Rupture of Myomectomy Scar during Pregnancy

Uterine rupture during pregnancy or delivery as a consequence of abdominal myomectomy appears to be extremely rare. A report of 98,872 deliveries over 30 years found 76 cases of uterine rupture in the third trimester, but only one of these women had a prior myomectomy, and 16 women had had no prior uterine incisions (86).

Review of 137,582 pregnancies found 133 cases of uterine rupture after the 28th week of pregnancy, of which three followed abdominal myomectomies (87). The number of women who had had a previous myomectomy in these two studies is unknown, so the incidence of rupture cannot be calculated. Eighty-three women during the same period (1958 to 1960) had elective cesarean section for previous myomectomy scars, and none had uterine rupture during pregnancy.

There are 11 reports of uterine rupture following laparoscopic myomectomy (88–98). The seemingly high number of events, particularly as laparoscopic myomectomy is uncommonly performed, brings up the question as to whether the procedure has more risk of subsequent rupture, or whether rupture is being more completely reported because laparoscopic myomectomy has been recently developed and the question is of academic interest.

SUMMARY

1. Myomas are remarkably common. Fine serial sectioning of uteri from 100 consecutive women who underwent to hysterectomy found myomas in 77%.
2. Myomas are monoclonal, and about 40% are chromosomally abnormal; the remaining 60% may have undetected mutations.
3. Genetic differences between myomas and leiomyosarcomas indicate that they most likely have distinct origins and that leiomyosarcomas do not result from malignant degeneration of myomas.
4. Both estrogen and progesterone appear to promote the development of myomas. Growth factors produced by smooth muscle cells and fibroblasts control proliferation and stimulate myoma growth.
5. First-degree relatives of women with myomas have a 2.5 times increased risk of developing myomas. African-American women had a 2.9 times greater risk of having myomas, have myomas present at a younger age, and have more numerous, larger and more symptomatic myomas than Caucasian women.
6. There is no definite relationship between oral contraceptives and the presence or growth of myomas, and hormone therapy will not stimulate myoma growth in the majority of postmenopausal women.
7. The association of myomas with menorrhagia has not been clearly established. Other possible causes, including coagulopathies such as von Willebrand disease, should be considered. Women with myomas are only slightly more likely to experience pelvic pain than women without myomas.
8. In premenopausal women, "rapid uterine growth" almost never indicates the presence of uterine sarcoma. The preoperative diagnosis of leiomyosarcoma in premenopausal and postmenopausal women may be possible using total serum lactic acid dehydrogenase (LDH), LDH isoenzyme 3, and gadolinium-enhanced dynamic MRI (Gd-DTPA).
9. The presence of submucous myomas decreases fertility, and their removal increases fertility to baseline rates. Neither intramural nor subserosal myomas appear to affect fertility rates, and removal has not been shown to increase fertility.
10. Pregnancy has a variable and unpredictable effect on myoma growth, but most myomas do not increase in size during pregnancy. Very rarely does the presence of a myoma during pregnancy lead to an unfavorable outcome. Uterine rupture during pregnancy or delivery as a consequence of abdominal myomectomy appears to be extremely rare.

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