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Biomarkers in uterine leiomyoma

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Abstract

Biomarkers are biologic compounds that are easily accessible and reflect normal physiology or pathology. They are useful in a variety of clinical situations that involve detection of subclinical disease, risk stratification, preoperative planning, and monitoring treatment. A useful intervention needs to exist for a biomarker to be an effective tool. Many compounds have been investigated as potential biomarkers for the diagnosis and surveillance of uterine leiomyomas. Most of these compounds demonstrate subtle differences among patients when leiomyomas are compared with controls. The compounds investigated lack the diagnostic accuracy necessary to add any benefit to the current available modalities used to diagnose and monitor uterine leiomyomas.

Keywords

Leiomyoma; fibroids; biomarker

Uterine leiomyomas are benign tumors (1, 2) afflicting up to 60% to 80% of reproductive-aged women (3). The majority of leiomyomas are asymptomatic, however up to 20% cause menorrhagia, pelvic pain, and genitourinary symptoms (4). Leiomyomas grow in the presence of gonadal steroids, disproportionately afflict women of African descent (5, 6), and are associated with 10% of infertility cases (7). The diagnosis of uterine fibroids is usually achieved through radiographic modalities or surgical procedures (8). The sensitivities and specificities of available diagnostic tools vary; currently, they range from 50% and 20% for hysterosalpingogram (HSG) (9), 90% and 87% for transvaginal ultrasound (10, 11), and approach 100% for magnetic resonance imaging (MRI) (12).

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Biomarkers, biologic compounds that can be obtained from the serum or other easily accessible tissue, are a reflection of normal physiology or a pathologic process (13). They are useful in a variety of clinical situations that involve detection of subclinical disease, risk stratification, preoperative planning, treatment monitoring, and diagnosis (13, 14). Serum biomarkers for uterine leiomyomas that accurately diagnose, differentiate, or monitor response to therapy are currently absent from the clinician's arsenal.

Biomarkers have been used previously in gynecologic disease and recent successes have validated the usefulness of biomarkers in clinical medicine (15, 16). For a biomarker to be an effective clinical tool, its sensitivity should be >75% and specificity >99.6% (17, 18). Recently, the introduction of OVA1, the first assay of multiple protein biomarkers approved for clinical use, has revolutionized the detection and surveillance of epithelial ovarian cancer, improving sensitivity from 72% to 91% over physician assessment with prior clinical tools (15). However, for a disease as prevalent as uterine fibroids, such low sensitivity would translate into an unacceptably high false-negative rate. For example, if up to 80% of women will be affected by uterine leiomyomas in their reproductive years (3) a biomarker with 75% sensitivity would miss up to 20% of affected women, and as only a fraction of these tumors are symptomatic and require intervention, early detection with a biomarker is of limited value. Furthermore, physical examination and pelvic ultrasound are excellent tools for diagnosis and surveillance of uterine fibroids (8), so the addition of serum biomarkers is of questionable benefit. Thus, improvements in the diagnostic accuracy of a serum biomarker capable of assisting in the diagnosis and monitoring of uterine leiomyomas are needed for it to be implemented in clinical practice.

In this article, we investigate the use of biomarkers in patients with uterine leiomyoma (Table 1). Our goal is to review the biomarkers previously evaluated, describe their clinical utility, and provide future directions in the field of biomarkers for the diagnosis and monitoring of uterine leiomyoma.

POTENTIAL BIOMARKERS

Prolactin

Prolactin is a protein hormone involved in a variety of mammalian physiologic actions such as lactogenesis. Prolactin mediates its function by interacting with type-1 cytokine receptors, and signals through Janus kinase, signal transducers, and activators of transcription (JAK/STAT) pathways (19). Although isolated as a pituitary hormone, prolactin is expressed in other tissues including uterine leiomyomas (20).

A study found that serum prolactin in patients with uterine fibroids before myomectomy or hysterectomy was elevated (169.64 ± 133.1 ng/mL) compared with postoperative levels (19.69 ± 9.54) ($P < .05$) and controls (21). The investigators considered a prolactin level >35 ng/mL to be elevated; despite having 84% of patients with uterine leiomyomas meet this criteria, they did not evaluate any other etiologies of hyperprolactinemia. The control group of fibroid-free patients demonstrated a normal mean prolactin level (18.93 ± 5.16 ng/mL). In this study, serum prolactin levels correlated with fibroid number, independent of size or location (21). Although a statistically significant association with fibroids and serum

prolactin was demonstrated in this study of 32 patients, further studies with larger sample sizes are needed to confirm this finding. The association of prolactinemia with pituitary prolactinomas and other pathology will likely limit prolactin as a useful biomarker for uterine leiomyomas, even if an association is confirmed. As this study was limited by its small sample size, observational nature, and a lack of control for other causes of hyperprolactinemia, the findings presented need to be interpreted with caution.

Total Protein

The total protein serum test measures the total amount of albumin and globulin in the blood. Values below the normal threshold usually are associated with nutritional deficiency, liver and kidney disease, or prolonged hemorrhage or anemia. Elevated total protein values can be a marker of chronic inflammation or malignancies such as multiple myeloma. In a prospective trial examining total protein as a biomarker for uterine leiomyomas, the serum total protein level was lower in patients with uterine fibroids before they underwent hysterectomy for leiomyomas or myomectomy. The preoperative serum total protein levels were statistically significantly lower in patients with fibroids (5.56 ± 9.66 g/dL) and returned to levels similar to fibroid-free controls 3 weeks after surgery (6.83 ± 0.9 g/dL) (21). However, as patients with fibroids are predisposed to abnormal uterine bleeding and menorrhagia (2), it is possible that the reduced serum total protein demonstrated in patients with leiomyoma was a result of abnormal, heavier uterine bleeding versus the fibroids themselves.

Soluble Serum HLA-G

Human leukocyte antigen G (HLA-G) is a regulatory antigen of the immune system. Expressed in the uterus and originally demonstrated in the cytotrophoblast (22), HLA-G has been demonstrated to be elevated in ovarian carcinoma and other cancers such as melanoma and breast carcinoma (23), in addition to peritoneal inflammatory conditions such as endometriosis (24). Basta et al. (25) evaluated serum samples in 48 women who had undergone myomectomy or hysterectomy for symptomatic uterine leiomyomas. The controls consisted of healthy volunteers or surgical patients who had undergone diagnostic laparoscopy for unexplained infertility without peritoneal pathology. Patients with leiomyomas demonstrated statistically significantly higher HLA-G serum levels than the controls (9.01 vs. 3.31; $P=.04$) (25). However, there was significant overlap in serum values between the control patients and leiomyoma patients. In addition, no postoperative assessment was conducted for the HLA-G association with removal of fibroid tissue, preventing its current use as a biomarker for uterine leiomyoma.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is an angiogenic peptide that has been shown to be critical for the growth of numerous tumors (26–28). Chen et al. (31) evaluated serum VEGF levels in women with uterine leiomyomas as a prospective biomarker. Expression of VEGF was increased in uterine fibroids compared with adjacent myometrium. The investigators conducted a prospective trial evaluating VEGF in 80 women before and after hysterectomy for symptomatic fibroids. The serum VEGF levels did not correlate with uterine weight, which was used as a surrogate marker of fibroid burden, or the number of

fibroids. However, serum VEGF levels declined after hysterectomy from 716.31 ± 457.99 to 581.81 ± 403.32 ($P < .05$). This, however, was not a novel finding, as it was previously demonstrated that the uterus itself is an important source of VEGF production (29, 30). The investigators concluded rightly that serum VEGF levels did not predict uterine fibroid development, and it is not an effective biomarker for uterine leiomyoma (31).

Ghrelin and Obestatin

Ghrelin is a 28 amino acid peptide, secreted mainly in the stomach, which primarily functions in control of energy homeostasis (32). To be active, ghrelin requires N-octanoylation at serine 3 (33). Ghrelin and its receptors have been expressed in hormone-dependent tumors, uteri, and many other organs. In addition, ghrelin has been shown to be involved in steroidogenesis and cellular leiomyomas (34–36). Obestatin originates from the ghrelin prohormone and is secreted by the stomach. In contrast to ghrelin, obestatin acts as an anorectic hormone, has been implicated in cellular proliferation, and exhibits other proliferative effects, such as increasing phosphorylation of certain response elements and activation of growth factors (37–39).

In a study of 39 women undergoing surgery for symptomatic uterine fibroids (40), serum concentrations of active ghrelin were statistically significantly higher in women with leiomyomas compared with controls matched for body mass index (BMI) (86 ± 3 vs. 56 ± 9 pg/mL, $P < .05$). However, the serum concentrations of total ghrelin and obestatin in women with leiomyomas did not differ from the fibroid-free controls. In the control group, the ratio of active ghrelin to total ghrelin was 0.62 whereas in women with uterine fibroids the ratio was 0.95, indicating an increased prevalence of active form of ghrelin. Although there was an increase in the active ghrelin levels in women with uterine leiomyomas, a more interesting finding was the increased ratio of active to total ghrelin. This indicates that a mechanism other than elevated production and release is likely responsible for the increased active form of the hormone in the cohort studied. However, this study failed to control for many factors that can alter ghrelin levels, such as thyroid disease, eating disorders, and anemia. As with other biomarkers, there was considerable overlap between the control group and leiomyomatous women, making ghrelin and obestatin unlikely candidates for leiomyoma biomarkers.

Lactate Dehydrogenase A (LDHA)

Lactate dehydrogenase A (LDHA), which is involved in anaerobic glycolysis, converts pyruvate to lactate under anaerobic conditions (41). Its serum levels are often increased in cancer patients. The gene of LDHA is often up-regulated and has been linked to poor prognosis in various cancers (42, 43). When evaluating 24 patients with leiomyomas compared with controls, Koukourakis et al. (41) demonstrated that the patients with fibroids had statistically significantly higher serum LDHA levels (310 ± 81 vs. 256 ± 68 ; $P = .05$). However, this analysis was conducted along with endometrial cancer patients, and their LDHA levels were found to be almost identical with those of the patients with leiomyomas. Furthermore, the levels were similar to those of the patients with other malignant gynecologic pathologies such as ovarian cancer, making this a poor differentiator of leiomyoma from coexisting malignancy. In addition, LDH is a marker of anaerobic

metabolism and will be influenced by a variety of benign and malignant conditions that influence metabolic conditions, making it unusable in the diagnosis and follow-up observation of uterine leiomyoma.

Hypermethylated Death-Associated Protein Kinase (DAPK)

Aberrant DNA methylation has been previously found in uterine leiomyomas when compared with matched myometrium (44). Hafner et al. (45) evaluated hypermethylated death-associated protein kinase (DAPK) as a biomarker of uterine leiomyoma. Methylation-specific polymerase chain reaction (PCR) was used to detect DAPK methylation in 17 patients with uterine leiomyomas, and the results were confirmed by sequencing analysis of cloned PCR products. The investigators confirmed DAPK methylation in 35.5% of primary tissue and 23.8% of serum samples from patients with uterine leiomyoma. The primary aim of this study was to evaluate the amount of aberrant DNA methylation in ovarian cancer; and the examination of uterine leiomyoma was used as the comparison group of patients with gynecologic pathology. Unfortunately, the findings were neither sensitive nor specific for uterine leiomyoma.

Cancer Antigen-125

Cancer antigen 125 (CA125) is a marker of nonspecific peritoneal conditions and is not specific to ovarian malignancy (46). In a study of 55 patients with leiomyomas or adenomyosis, Zhou et al. (47) found that median CA125 levels were 102.1 kIU/L, 34.6 kIU/L, and 33.1 kIU/L in adenomyosis, leiomyomas, and controls, respectively. The CA125-positive rates (defined as >50 kIU/L) were 80%, 10%, and 5%, respectively. In a study of tumor markers, Tsao et al. (48) found that 92% of women with leiomyomas demonstrated elevated tumor markers such as elevated CA125 or CA19-9 (>40 IU/mL).

Studies have assessed CA125 for its utility in preoperative diagnosis of uterine sarcoma. In a retrospective study of 2,382 patients undergoing surgery for uterine leiomyoma, 26 patients were diagnosed with sarcoma. The preoperative CA125 levels were not predictive of sarcoma (49). Another study assessed the potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and leiomyosarcoma in 42 patients and 84 controls with benign pathology (50). The investigators found that values of preoperative CA125 in patients with leiomyosarcomas were statistically significantly higher, but there was significant overlap between the early-stage sarcoma and leiomyoma groups. The investigators developed optimal cutoff values for differentiation via receiver operating characteristic (ROC) curves of 162 IU/mL and 75 IU/mL in premenopausal and postmenopausal patients, respectively, to use CA125 as a biomarker to differentiate leiomyosarcoma from leiomyoma (50). This cutoff is not particularly useful, as CA125 is routinely elevated in patients with a variety of benign intraperitoneal pathologies that can accompany uterine leiomyomas and leiomyosarcomas. For example CA125 can be elevated past these levels in endometriosis, pelvic inflammatory disease, and nongynecologic conditions such as liver disease (51). Given the prevalence of uterine leiomyosarcomas, it seems unlikely that a biomarker will be developed to distinguish sarcomas from leiomyomas: the test would have to have 100% negative predictive value to be clinically useful.

Attempts to differentiate between leiomyomas and adenomyosis have also been made with measurements of CA125. Developing an assay that could distinguish fibroids from adenomyosis would be clinically useful. Adenomyosis requires a hysterectomy for definitive management, which prevents future childbearing, but some leiomyoma may be managed via fertility-sparing interventions. Furthermore, current diagnostic modalities are rather poor at detecting adenomyosis (52). Takahashi et al. (53) evaluated 19 women before and after surgery and found that patients with leiomyomas had lower serum levels of CA125 compared with patients with pathologic diagnosis of adenomyosis (18.3 ± 6.1 vs. 93.3 ± 49.4 IU/mL; $P < .01$). In all patients with adenomyosis, the serum levels of CA125 were over 35 IU/mL and decreased postoperatively to below 35 IU/mL within 30 days. However, other studies have failed to corroborate these findings. In a study of 22 women, CA125 levels were not found to be different before and after surgery in patients with leiomyomas or adenomyosis (54).

Posttreatment monitoring—In cases where CA125 was elevated, monitoring CA125 levels in patients on gonadotropin-releasing hormone (GnRH) therapy was a good indirect measurement of decreased tumor burden (55). However, in another study this finding was not corroborated in either pretreatment levels or correlation with tumor size after initiation of treatment with GnRH agonists (56). Currently, there is conflicting literature regarding the use of CA125 in the diagnosis, differentiation, and surveillance of uterine fibroids, so using CA125 as a biomarker for fibroids currently cannot be recommended.

Hematopoietic Growth Factors

Hematopoietic growth factors—macrophage colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF)—were investigated as serum markers in patients with endometrial cancer ($n = 55$), women with uterine myomas ($n = 30$), and healthy controls (20). Both were noted to be higher in women with leiomyomas when compared with the control group. The investigators suggested that M-CSF could be particularly useful in distinguishing endometrial cancer and leiomyomas. However, the sensitivity of hematopoietic growth factors for recognition of uterine leiomyomas was poor at only 51%. When CA125 was included as an additional marker, the specificity approached 93%.

Human Epididymis Protein 4 (HE4)

Human epididymis protein 4 (HE4) has been shown to be a promising biomarker in ovarian cancer, with improved sensitivity and specificity over CA125 in recognition of malignant pelvic masses (57). It is a protein initially isolated from epithelial cells in the human epididymis and is expressed throughout the body, including in the female reproductive organs (58). Moore et al. (59) evaluated serum levels of HE4 and CA125 in over 1,000 premenopausal and postmenopausal women with benign pelvic disease. Of 61 patients with leiomyomas, only three patients (5%) had an HE4 level greater than the 95th percentile. Comparatively, 26% of patients with fibroids were found to have an elevated serum CA125. This study concluded that HE4 is elevated less frequently than CA125 in benign gynecologic diseases, including uterine leiomyomas (59), which provides the basis for its use as a biomarker for ovarian neoplasia.

Proteomics

Initial work in proteomics has been performed to identify plasma proteins as biomarkers for diagnosing uterine fibroids. Lin et al. (60) used two-dimensional differential gel electrophoresis to identify differentially expressed proteins in the plasma of patients with and without uterine leiomyomas. The differentially expressed proteins were then identified by matrix-assisted laser ionization mass spectrometry. The results yielded 20 differentially expressed plasma proteins, the majority belonging to either coagulation or transportation groups with cytoskeleton, inflammatory cascade, and signal transduction proteins also being differentially expressed. The serum proteins with the highest differential expression ratios were actin, fibrinogen, gelsolin, and serotransferrin. Gelsolin is a regulator of actin assembly. Actin, an intracellular protein that is ubiquitous in the majority of eukaryotic cells, is involved in cellular motility and division. The investigators presented a proteomic approach for the identification of plasma biomarkers for uterine leiomyomas. However, investigation into the clinical utility or the use of the identified proteins in diagnosis and surveillance of uterine leiomyomas has yet to be performed.

Gonadal Hormones and Growth Factors

There is evidence to support that gonadal hormones and growth factors are responsible for leiomyoma growth (61). To evaluate whether women with fibroids demonstrate higher steroid hormone and growth factor serum levels, 51 women with leiomyomas of >14 weeks' size were compared with 30 control fibroid-free patients. The levels of plasma insulin-like growth factor I (IGF-I) in women with leiomyomas during the follicular and luteal phases were almost identical to those of fibroid-free women. Furthermore, estrone, estradiol, and progesterone were measured repeatedly in each group during both the follicular and luteal phases of the menstrual cycle and were similar in both groups (62).

UTERINE LEIOMYOMAS AND EFFECT ON BIOCHEMICAL SCREENING IN PREGNANCY

Uterine fibroids may change the concentrations of serum markers and alter risk calculations for fetal chromosomal abnormalities. In a pilot study, Sieroszewski et al. (63) evaluated 127 women with singleton pregnancies between 11 and 20 weeks. All patients were diagnosed with intramural leiomyomas greater than 20 mm in diameter. Seventy-seven patients underwent a first-trimester screening with measurement of pregnancy-associated plasma protein A (PAPP-A) and β -human chorionic gonadotropin (β -hCG) levels, and 50 patients underwent a second-trimester triple screen. The controls consisted of 1,020 pregnant women between 11 to 20 weeks without myomas. No difference was observed in the markers except for higher values in β -hCG in first (1.43 MoM) and second trimester (2.01 MoM), which may potentially lead to an increased rate of false-positive results during prenatal testing, specifically the triple screen (63, 64).

Is a Biomarker Necessary for the Care of Uterine Leiomyomas?

As evidenced by this review, the current literature investigating the use of biomarkers in uterine leiomyomas is not encouraging (Table 1). However, the question that arises is

whether we really need biomarkers in the diagnosis and surveillance of uterine leiomyomas. Currently, patients either present for evaluation due to gynecologic symptoms associated with uterine fibroids, such as pelvic pain, heavy bleeding, or urinary frequency (2), or they may be diagnosed during an evaluation for infertility or a through incidental radiologic identification during diagnostic evaluation of other pathology. The current methods of diagnosis are adequate to identify and treat symptomatic disease. For example, transvaginal ultrasonography with and without the addition of sonohysterography been shown to have a sensitivity and specificity in the range of 90% to 100% and 87% to 98%, respectively (10, 11). Ultrasound is relatively inexpensive, risk free, and can be performed at the bedside during a routine gynecologic evaluation, providing immediate diagnostic information; this makes the addition of a biomarker for diagnosis unnecessary.

As a tool of leiomyoma surveillance, a biomarker may be useful in charting the response to medical therapy. However, the only medical therapy approved in the United States is leuprolide acetate, and it is used as a perioperative adjunct for 3 to 6 months to improve preoperative hemodynamic parameters and diminish fibroid size to decrease the technical difficulties associated with operating on large fibroids.

Consequently, in the present environment, no long-term surveillance to monitor chronic medical management is necessary, as no long-term medical therapy currently exists. However, just as CA125 is not the only piece of clinical information used to guide ovarian cancer surgical decision making, gynecologic surgeons would likely prefer additional information, and images are more informative than biomarker laboratory values in guiding surgical decision making. For patients in whom ultrasound is not sufficient, magnetic resonance imaging (MRI) provides excellent sensitivity and specificity for evaluation of uterine fibroids. Although MRI is significantly more expensive, it is required for accurate diagnosis in a small minority of patients and accurately describes even small leiomyomas (65).

Currently, the primary mode of therapy for uterine fibroids is surgery, and postoperative outcomes are usually monitored through subjective assessment of symptoms and radiographic imaging (65). Certainly, a biomarker that is indicative of a recurrence, such as CA125 in ovarian cancer, could be useful, but patients with a benign disorder should not undergo repeated surgical procedures with consequent morbidity simply on account of a rising serum level; recurrent symptoms should be present before further intervention is considered.

CONCLUSION

Biomarkers are sought to provide diagnostic as well as prognostic information. Ideally, a good biomarker must be both reliable and reproducible. They must be easily measured in peripheral tissues or bodily fluids. A biomarker should be sensitive and specific; it should be cheap, and should detect a potentially morbid disease for which there is a useful intervention. The development of biomarkers for uterine leiomyomas would provide substantial cost savings, as they are easily accessible from the peripheral vasculature. This would decrease the amount of expensive ultrasounds and MRI scans ordered for the

diagnosis and surveillance of this prevalent disease. Furthermore, it would improve patient satisfaction, as invasive diagnostic modalities such as transvaginal ultrasounds would be reduced.

It is possible that multiple biomarkers could markedly improve specificity and sensitivity, as is the case of the in vitro diagnostic multivariate index assay (IVDMIA) for ovarian cancer. Novel technology has been improving the likelihood that biomarkers will become an increasingly important tool in the physician's armamentarium. However, the hormones, proteins, and cytokines that have been investigated as potential biomarkers for uterine leiomyomas are not reliable, reproducible, sensitive, or specific; currently, they are not complementary to the available diagnostic and surveillance methods, and they do not provide any additional clinical utility.

For diseases such as ovarian cancer where early intervention before the onset of clinical symptoms helps improve survival, biomarkers are extremely beneficial; recurrence may be diagnosed, and intervention may initiated based on biomarkers alone (66). Uterine fibroids, although symptomatic and potentially debilitating, are benign, and gynecologic surgery even when undertaken through the minimally invasive approach may carry substantial morbidity (67, 68). Thus, in a hypothetical situation with a rising serum biomarker level along with an asymptomatic patient, surgical intervention would not be warranted. On the other hand, in a situation when a low-risk prophylactic agent is available, the physician may initiate this after the initial identification of biomarker elevation. Another example where a biomarker would be useful in uterine fibroids is in differentiating benign uterine fibroids from uterine sarcomas because they have a similar appearance on radiologic imaging. Although uterine sarcomas do have characteristic MRI findings and typically present later in life than uterine fibroids, a significant number are still diagnosed after routine myomectomy for presumed, benign uterine leiomyomas (69–71). Consequently if further work proves that specific serum biomarkers help differentiate fibroids from uterine sarcoma, this would potentially improve referral to gynecologic oncologists for the initial surgery of uterine myometrial cancers and decrease the number of secondary staging procedures, as initial aggressive surgical cytoreduction likely prolongs survival (72).

The search for a reliable biomarker in uterine leiomyomas continues. However, the current evidence suggests that this may not be an appropriate disease process in which biomarkers would be beneficial for diagnosis.

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TABLE 1

Summary table of selected biomarkers studies in women with leiomyomas.

Biomarker evaluated	Study size (n)	Results	Comments
Prolactin	32	84% elevated (>35 ng/mL) Correlate with size and number Normalized with surgery	No cutoff identified associated with disease Associated with other pathology
Soluble human leukocyte antigen G	48	Significantly higher in patients with leiomyoma	Varies across the menstrual cycle and menopausal status No cutoff identified Healthy control group Elevated with other gynecologic pathology
Vascular endothelial growth factor	80	Serum levels higher in women with leiomyoma Levels significantly declined after myomectomy	Uterine weight used as surrogate for fibroid burden Serum levels did not correlate with uterine weight
Ghrelin/Obestatin	39	Active ghrelin higher in women with leiomyomas	Not controlled for physiology and pathology affecting ghrelin/obestatin Total serum levels did not differ from fibroid-free controls
Lactate dehydrogenase	24	Serum levels higher than fibroid free controls	Levels similar to patients with gynecologic cancer Affected by changes in anaerobic metabolism
Cancer antigen 125 (CA125)	25	10% of patients with leiomyoma >50 IU/L 92% of patients with leiomyoma with CA 125 >25 IU/L	Serum levels were similar to normal controls and adenomyosis patients
	2,282 126	Preoperative differentiation between leiomyoma and sarcoma Optimal cutoffs of 162 IU/mL and 75 IU/mL for premenopausal and postmenopausal patients	Preoperative CA125 levels were not predictive of uterine sarcoma Serum values are influenced by variety of intraperitoneal pathology
Hematopoietic growth factors	30	Significantly higher than fibroid-free controls Possible potential in distinguishing from endometrial cancer	No distinguishing cutoff identified Poor sensitivity
Human epididymis protein 4	1,000	More specific for gynecologic malignancy	Elevated in <5% of patients with fibroids Not suitable as a leiomyoma biomarker

Levy. Biomarkers in uterine leiomyoma. Fertil Steril 2013.