1991

Correlation of the signs and symptoms of uterine leiomyomas with the findings on magnetic resonance imaging studies

Symphorosa Magdaleine Williams
Yale University

CORRELATION OF THE SIGNS AND SYMPTOMS OF UTERINE LEIOMYOMAS WITH THE FINDINGS ON MAGNETIC RESONANCE IMAGING STUDIES

SYMPHOROSA MAGDALEINE WILLIAMS

1991

Permission for photocoping or microfilming of " Correlation of the & Symptoms Associated with Uterine Leiomyomas, with the Radiological g on MRI Studies."

(Title of thesis)

for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

S A Williams

Signature of Author

3/30/91

Date

CORRELATION OF THE SIGNS AND SYMPTOMS OF UTERINE LEIOMYOMAS WITH THE FINDINGS ON MAGNETIC RESONANCE IMAGING STUDIES.

A THESIS SUBMITTED TO THE YALE UNIVERSITY SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF MEDICINE.

BY
SYMPHOROSA MAGDALEINE WILLIAMS
1991

This thesis is dedicated with love to my husband, Nee, who has been incredibly tolerant and supportive during my medical school years. It is also dedicated to my parents, Edward and Teresa Williams who have encouraged and believed in me ever since my birth, and to my brothers and sisters, Eddie, Kate, Justin, Agatha, Germain, Gregory and Bernard.

Acknowledgements

I would like to thank my advisors, Dr Shirley McCarthy and Dr Florence Comite for all the help and advice they gave me, and for taking the time to assist me despite their hectic schedules. I would also like to thank Dr Edith Budik and Dr Robert Lange for the invaluable assistance I received from them while performing this thesis requirement. Without their help, this thesis would never have been completed. I also thank Jean Vulte and Ann De Roode for their help with my clinical research.

ABSTRACT

CORRELATION OF THE SIGNS AND SYMPTOMS OF UTERINE LEIOMYOMAS WITH THE FINDINGS ON MAGNETIC RESONANCE IMAGING STUDIES.

Symphorosa Magdaleine Williams

1991

This study was designed to investigate any correlation between the symptoms and signs of uterine leiomyomas and magnetic resonance imaging (MRI) findings. The symptoms and signs reported at each visit were recorded from a review of the clinical charts of 45 patients. 114 MRI studies, 98 of which were performed within 0-30 days, and 16 of which were performed within 30-51 days of the corresponding clinical visit, were reviewed by an investigator, blinded to the clinical data. Total uterine volume, total leiomyoma volume, and the uterine and leiomyoma MRI characteristics were assessed. Thirty-one patients, with a total of 47 MRI studies, received leuprolide acetate (LA) during the period of review. These were examined as a separate group, and compared with the "no drug" group. Junctional zone (JZ) disruption did not correlate with the presence of menorrhagia or metrorrhagia ($p > 0.05$) in either patient group. LA decreased the incidence of menorrhagia ($p < 0.0005$), but had no effect on metrorrhagia ($p > 0.05$). JZ disruption did not correlate with spontaneous abortion or infertility ($p > 0.1$). The leiomyoma location (uterine body, fundus, cervix, broad ligament, multiple) did not affect the incidence of pressure ($p > 0.1$), abdominal/pelvic

(A/P) pain ($p > 0.1$), back pain ($p > 0.1$), or infertility ($p > 0.5$). LA decreased the incidence of pressure only in patients with leiomyomas in the uterine body ($p < 0.05$). The leiomyoma type (submucosal, intramural, subserosal) did not affect the incidence of infertility ($p > 0.05$) or spontaneous abortion ($p > 0.5$). It did not affect dysmenorrhea in LA treated patients ($p > 0.5$), but intramural leiomyomas were associated with dysmenorrhea in the no drug group ($p < 0.005$). Submucosal and intramural tumors in patients with no drug treatment were also associated with dysmenorrhea, when compared with LA treated patients ($p < 0.005$). Leiomyoma degeneration was dependent on the tumor volume. Smaller tumors had less degeneration while the larger tumors had more carneous and non-specific degenerative changes ($p < 0.005$). LA had no effect on the incidence of degeneration. A/P pain was associated with carneous leiomyomas in patients with no drug treatment ($p < 0.05$). There was no association between A/P pain or pressure and total uterine volume ($p > 0.1$), but LA decreased the incidence of pain in patients with uterine volumes less than 600 cc ($p < 0.005$). Uterine non-leiomyoma volumes were not associated with spontaneous abortion or infertility ($p > 0.5$). We conclude that most symptoms that have always been attributed to individual characteristics of the leiomyomas cannot be directly explained by them. The only statistically significant relationships occurred between degeneration and tumor size, and dysmenorrhea and intramural tumors. The effect of LA in alleviating patient symptoms is again confirmed.

TABLE OF CONTENTS

1. INTRODUCTION

I. UTERINE LEIOMYOMAS

A. Epidemiology & Etiology

Uterine leiomyomas, also known as fibroids, fibromas, or fibromyomas (42), are benign smooth muscle tumors of the uterus.They are the most common pelvic tumors in women, occurring in one out of four to five women of reproductive age (9). They occur more frequently in women over thirty-five years of age (42), and they are responsible for at least one-third of all gynecological admissions (50). Leiomyomas are also more common in Black women than in White women (42). The reason for this racial difference in incidence is not known.

The etiology of these tumors is still not clearly understood. Various theories include the probability that i. they arise from groups of persistent embryonic cells (42), ii. they arise from the smooth muscle layers of blood vessels in the myometrium (42), iii. they arise from a single neoplastic parent smooth muscle cell in the myometrium (9). This latter theory is supported by the evidence presented by Townsend et al. who found that cells in each individual leiomyoma had identical glucose-6-phosphate dehydrogenase (electrophoretically), although this enzyme was different in other leiomyomas within the same uterus (58). Although the initial etiology of these tumors is not clearly defined, one generally accepted factor in the growth of leiomyomas is the effect of estrogen. Leiomyomas tend to occur in women of reproductive age; they rarely occur

before menarche, and usually regress after menopause. They also proliferate during pregnancy, and with the use of birth-control pills, when serum estrogen levels are high. (42). Wilson et al. and Tamaya et al., in separate studies, demonstrated a higher concentration of estrogen receptors in leiomyomatous tissue than in adjoining myometrium in the same patient (60, 56). Other hormones, such as growth hormone and human placental lactogen have been implicated in a probable synergistic effect with estrogen on the tumor proliferation (9). This may explain the increased sensitivity of leiomyomatous tissue to estrogen, and the rapid growth observed in hyperestrogenic states. There are, however, several other factors, currently unknown, which contribute to the varying rates of growth of leiomyomas in different women. Additional studies will be needed to further clarify the etiology and development of leiomyomas.

B. Histopathology

Leiomyomas have three main classifications, depending on the layer of the uterus they originate in. They are called subserosal when they arise from the myometrium and grow directly beneath the uterine serosa, projecting into the pelvic cavity (42). Subserosal leiomyomas can become pedunculated with increased growth and form a migratory leiomyoma (50). They may remain attached to the uterus by a pedicle, or may attach to adjacent viscera, peritoneum, or omentum. In the latter case, the subserosal leiomyoma may lose its primary blood supply from the uterus, develop a secondary blood supply from its new attachment, and is then classified as a parasitic leiomyoma. Intraligamentous leiomyomas occur

when the subserosal leiomyoma grows into the broad ligament. Intramural leiomyomas, the most frequent type of leiomyomas, originate in the myometrium, and while they may impinge on the uterine serosa or mucosa, the bulk of the leiomyoma remains in the myometrium. These can also enlarge, and distort the uterine cavity or the outer uterine surface. Submucosal leiomyomas arise in the myometrium directly beneath the endometrium. These may also distort the uterine cavity. They also occasionally become pedunculated, and can then protrude into the cervix and vaginal canal where they are prone to infection (42).

Leiomyomas occur most frequently within the uterine corpus (42, 50). They less frequently occur in the lower uterine segment, the cervical region (50), the isthmus and the cornual regions of the uterus. They can occur singly, but are often multiple, ranging in size from barely visible "seedlings" of one centimeter or less, to large masses (42, 50), weighing as much as 147 lbs (42). They are firm masses, distinct from the surrounding myometrium. The leiomyomas do not have true capsules, but are covered by a pseudocapsule, formed by compression of the surrounding myometrium (42). Gross pathological inspection shows a characteristic whorled pattern of smooth muscle bundles (42, 50). Histologically, the smooth muscle cells of the leiomyomas resemble those of the normal myometrium, without increased mitotic figures or anaplastic changes (50). There is fibrous connective tissue interspersed between the smooth muscle bundles with one or more blood vessels providing nutrients to the tumors.

Leiomyomas may undergo various degenerative changes. These are often associated with a relative decrease in blood supply, which usually occurs with a rapid increase in the growth of the tumors, particularly in

pregnancy, when there is mechanical disruption of the blood vessels, or degenerative changes may occur with menopause. (42). These changes consist of hyaline, cystic, fatty, carneous, or calcific degeneration. Hyaline degeneration is the most common type of degenerative change, and occurs in even small leiomyomas (42). Persaud et al. found hyaline degeneration in 63% of the 195 leiomyomas that had degenerative changes (45). The consistency of the tumor changes and becomes softer. On gross examination, the degenerated areas are pale, homogeneous, and lack the characteristic whorled appearance. Microscopically, hyaline connective tissue replaces the smooth muscle cells, and the affected regions appear amorphous and pinkish-red (45). Hyalinization can further degenerate into liquefied areas (42,45), which are also visible grossly - cystic degeneration. These cysts lack an epithelium, and may contain colorless or bloodstained fluid. Myxomatous and mucoid changes can also result in cystic degeneration. Fatty degeneration occurs rarely, and is also associated with hyaline changes. It is characterized by small vacuolated fat-containing cells within the tumors (45). Carneous (red) degeneration is believed to occur in about 8% of leiomyomas complicating pregnancy. Aseptic necrosis occurs, followed by hemorrhage into the leiomyoma (42). The tumor becomes mottled, beefy-red and soft, and microscopically a patchy necrosis associated with hemorrhagic muscle fibers is seen (42, 45). Calcification tends to occur in postmenopausal women, with diffuse or focal changes within the leiomyoma (42). In extreme cases, the entire tumor may be converted into a calcified mass (43). Finally sarcomatous transformation is said to occur in leiomyomas, but this is very rare, less than 0.5-1% (42, 29). This is not considered to be the natural progression of leiomyomas, since the incidence of leiomyomas, which is relatively

high, does not correlate with the incidence of uterine sarcomas which is low.

C. Signs, Symptoms & Complications

Uterine leiomyomas may produce several different signs and symptoms, or may remain totally asymptomatic. Between 20-50% of all leiomyomas are symptomatic (9, 29). Abnormal uterine bleeding is the most prevalent symptom, occurring in about 30% of patients (9, 29). It is usually manifested as menorrhagia, with heavy extended periods of menstrual bleeding associated with perimenstrual spotting. Metrorrhagia also frequently occurs in these patients. This abnormal uterine bleeding has been attributed to the presence of submucosal leiomyomas causing thinning and ulceration of the overlying endometrial mucosa (9, 29, 42). In a study by Fraser et al., submucosal and intrauterine pedunculated leiomyomas were found most frequently in patients with excessive bleeding (18). However, the incidence of submucosal leiomyomas is not high enough to account for the frequency of the abnormal uterine bleeding. Farber-Brown et al. have demonstrated compression of the venous plexi in the endometrium and myometrium by all three types of leiomyomas. This causes engorgement and dilation of the vessels, and predisposes the patient to excessive bleeding during menstruation (15, 16). It is also believed that the increased endometrial surface area due to protruding submucosal leiomyomas, and an impairment of uterine contractility by intramural leiomyomas may contribute to the menorrhagia (42). Patients may present with an iron deficiency anemia refractory to iron replacement

therapy, or in a hypovolemic state due to excessive and rapid blood loss. These conditions can require surgical intervention.

Pressure and pain were the presenting symptoms in 34% of patients with uterine leiomyomas in a review by Buttram et al. (9). Large tumors may impinge on the urinary bladder, causing urinary retention, incontinence, or frequency; compression of the ureters can cause hydroureters or hydronephrosis; compression of the pelvic vessels may cause lower extremity edema or varicosities. Pressure on the rectum or intestines may cause constipation and intestinal obstruction (29, 42). Patients may also complain of a general heaviness in the pelvic region. Pain often occurs with infection or carneous degeneration of a leiomyoma. Tumors may impinge on adjacent abdominal and pelvic viscera and nerves, causing pain that can radiate into the lower extremities (29). Pedunculated leiomyomas can undergo torsion, infarcting and producing acute pain (29, 42). Patients may also experience increased dysmenorrhea, which may be due to cramping caused by submucosal and intramural leiomyomas (42). Dyspareunia can also be associated with cervical leiomyomas (29).

25-35% of patients with uterine leiomyomas are estimated to have infertility problems (43). Infertility is defined as the inability to conceive after one year of unprotected intercourse (54). Only about 2-10% of all cases of infertility can be solely attributed to these tumors (9, 29). There are usually other associated factors, such as pelvic inflammatory disease, endometriosis, anovulatory cycles, abnormal tubal and uterine motility, and various male partner factors (29). Uterine leiomyomas can cause infertility in several ways. Cervical and cornual tumors can impinge on the uterine and tubal lumens, obstructing the passage of sperm (9).

Submucosal and intramural leiomyomas may cause distortion of the uterine cavity, which may interfere with sperm passage or implantation of the fertilized ovum. Submucosal leiomyomas can also cause atrophy and ulceration of the overlying endometrium, producing an inappropriate milieu for the implantation and development of the embryo (9). This can also predispose the patient to spontaneous abortions. The occurrence of spontaneous abortions in pregnant women with uterine leiomyomas was found to be as high as 41% by Buttram et al., compared with an incidence rate of 10% in the general population. The rate of spontaneous abortions in women after myomectomies decreased to 19% (9), which is much closer to that of the general population. Multiple submucosal and intramural leiomyomas can distort the uterine cavity, and decrease the uterine volume available for normal development of the fetus, increasing the chances of a spontaneous abortion.

Once a patient with uterine leiomyomas becomes pregnant, she may face further problems associated with the tumors. Leiomyomas are associated with 0.3-7.2% of all pregnancies (42). The leiomyomas are usually present, and may be asymptomatic before pregnancy, but they tend to increase in size due to edema, hemorrhage into the tumor (29), and response to the increased estrogen levels. About 50% of leiomyomas that are present prior to pregnancy increase in size during the gestational period. The timing of the growth of the tumors varies depending on the original tumor size. Smaller leiomyomas tend to grow in the first and second trimesters, and regress thereafter. Larger tumors grow only during the first trimester, and regress in the second and third trimesters (32). The growth of the leiomyomas outstrips the blood supply to the tumors resulting in infarction, carneous degeneration and pain. Leiomyomas can

further complicate pregnancy by causing premature delivery, fetal malpresentation, and dystocia due to cervical tumors causing obstruction. This could necessitate a cesarean section for safe delivery of the baby (29). Postpartum hemorrhage is also more frequent in a myomatous uterus (42), because of the inability of the uterus to contract and involute completely, producing inadequate hemostasis. Despite all these possible complications, several patients with large leiomyomas remain fertile, become pregnant, and carry their fetus to term (9, 42).

D. Diagnosis

In asymptomatic patients, a leiomyoma might be detected as an incidental finding during a gynecological exam, ultrasound, magnetic resonance imaging (MRI) study, or on an abdominal x-ray, if calcification has occurred. Some observant patients may notice an increase in abdominal girth. Some previously asymptomatic leiomyomas may enlarge during pregnancy, or with the use of exogenous estrogens, producing symptoms leading to their detection. In patients with symptoms such as abnormal uterine bleeding and pelvic pain or pressure (29), the clinical suspicion of leiomyomas would be very high. This can be initially evaluated with a pelvic exam, during which a uterine mass or nodularity may be palpated.

Diagnostic imaging procedures are used for additional non-invasive work up. Ultrasonography (US) is usually the first imaging modality used in the evaluation of uterine leiomyomas. Computed tomography (CT), hysterosalpingography (HSG), and MRI are also used to evaluate leiomyomatous uteri. US is inexpensive, fast, and readily available (1) of

the imaging modalities. The ultrasonographic criteria used to diagnose leiomyomas include altered echo texture with inhomogeneity within the uterus, and an enlarged uterus with an irregular contour (22, 38). US can be used to distinguish between cystic and solid structures, and can, sometimes, give a reasonable estimation of the location of a leiomyoma (1). However, the quality of the US scan is highly dependent on the operator's expertise and the patient's habitus (26). Patients should have a full bladder to facilitate scanning (1), and excessive bowel gas (52) can block effective scanning. An enlarged uterus can also obscure adnexal pathology (1, 38). Leiomyomas are frequently misdiagnosed with US. Retroflexed uteri and uteri with developmental anomalies can cause contour irregularities that can mask leiomyomas (22, 24). Degenerating leiomyomas have been mistaken for fetal tissue (5). In one study, cystic degeneration of leiomyomas were misdiagnosed as an abnormal gestational sac - intrauterine location, and as an ectopic pregnancy - extrauterine location (3). US is also relatively inaccurate in distinguishing between subserosal pedunculated leiomyomas and extrauterine adnexal masses (22, 38) or posterior subserosal tumors and masses in the cul-de-sac (5). With the advent of transvaginal ultrasonography (TVUS), imaging resolution and detail has been greatly improved, and the limitations of the patient's habitus and bladder volume have been eliminated. However, the field of view is very limited, so uterine enlargement and volume cannot be adequately assessed (41, 52). It also has a limited utility in children and postmenopausal women due to the smaller vaginal size in these patients (52). Although transabdominal US has inferior resolution when compared with TVUS, it is usually considered adequate for diagnosis and follow up of patients for whom no surgical intervention is planned.

CT scanning has very limited utility in the evaluation of uterine leiomyomas. It provides relatively poor tissue contrast, so uterine anatomy can not be clearly defined, and leiomyomas usually can not be accurately localized (38, 52). In addition to these disadvantages, ionizing radiation and intravenous contrast are used (38, 52). MRI is currently the optimal diagnostic modality for obtaining definitive information about uterine leiomyomas, especially when US is indeterminate, or if surgery is planned (13, 52, 61). MRI uses no ionizing radiation, and it is not as operator dependent as US. It is noninvasive, and is only limited by patient habitus when the patient is morbidly obese and cannot fit into the MRI scanner. It provides excellent tissue contrast and uterine anatomic detail (25, 36), and can be used to gain valuable information on the number, location, classification, vascularity and degeneration of leiomyomas (38). Three dimensional measurements can be obtained with ease, for use in calculating uterine and tumor volumes (6, 36). Excellent resolution is obtained with MRI, and tumors as small as 0.8 cm in diameter can be confidently identified, compared with minimum tumor diameters of 1.1 cm on US (61). MRI also has a wider field of view than US facilitating the evaluation of massively enlarged uteri. Zawin et al. found that enlarged uteri with volumes of 1429 cc could be measured with MRI, while the maximum volume US could accurately measure was 140 cc (61). Dudiak et al. determined that MRI was better at detecting small tumors than US and HSG (13). In one group of patients, MRI had a sensitivity of 91%, compared with 18% for HSG, in detecting abnormal uterine segments. In the same study, when compared to US, MRI sensitivity was 85%, while US sensitivity was 69% (13). MRI is also effective in distinguishing leiomyomas from other solid tumors when US is indeterminate (52, 59).

MRI, however, does have some disadvantages. It is an expensive procedure. It is also susceptible to image degradation due to patient motion (6, 8). CT and US are less susceptible to this type of image degradation. Claustrophobic patients cannot undergo MRI scanning (52). Cardiac pacemakers, intracranial vascular clips (52), and any metallic ferromagnetic implants that could harm patients, by moving or malfunctioning under the magnetic force of the scanner, are major contraindications to MRI scanning. Despite these drawbacks, MRI is still the modality of choice for evaluating leiomyomas during hormonal therapy (61), infertility work ups (37), and prior to surgery (13). US can be used to screen and follow up patients when no definitive treatment is planned (mr6, 52).

E. Treatment

Treatment of uterine leiomyomas depends on the patient's menstrual status, the tumor size, the patient's wishes regarding fertility, and whether or not the patient is symptomatic (9). Until recently, the only options available were observation, with follow up, and surgery - either a hysterectomy or a myomectomy. The current use of gonadotropin-releasing hormone (GnRH) agonists provides a temporizing method for women who wish to postpone, or avoid surgery. Patients who are asymptomatic, or have only minor tolerable symptoms, with uterine size less than 10-12 weeks gestation can be followed every 3-6 months with pelvic exams and US. This is usually adequate to monitor for rapid growth and complications (9, 42). These patients rarely have infertility problems due to the

leiomyomas (9). Surgery is usually recommended for symptomatic patients, for patients with uteri larger than 10-12 weeks (9), and for patients whose adnexae can not be thoroughly evaluated because of the enlarged uterus. Surgery is required for patients with rapid, unaccountable growth of their leiomyomas, especially in postmenopausal women (9), in whom the risk of malignancy is higher. A dilatation and curettage should be followed by a hysterectomy in patients with abnormal uterine bleeding (9, 42) and anemia which is refractory to iron replacement and hormonal therapy. The definitive treatment for uterine leiomyomas is a hysterectomy (19). Many patients are resistant to having hysterectomies for various reasons, including the desire to preserve fertility (9), menstrual function (42), and other personal and psychological reasons. Myomectomies are also performed, but have the disadvantage of a 15-30% leiomyoma recurrence rate (9, 19). Both procedures also have the possibility of major blood loss (9, 42), which could make blood transfusions necessary. This increases the patient's risk of infection with the hepatitis or human immunodeficiency viruses. Postoperative adhesions can cause further complications of bowel obstruction and pain.

GnRH agonists, such as leuprolide acetate have been shown to decrease uterine and leiomyoma size, usually within 3-6 months of treatment (11, 19, 51, 62). Symptoms associated with the leiomyomas, such as pelvic pressure, pain, and menorrhagia were relieved (11, 19, 51), and the vascularity of the tumors decreased (62). Friedman et al. found that patients with large uteri who received preoperative therapy with leuprolide acetate had decreased intraoperative blood loss when compared to those who received placebo (20). The main disadvantage of treatment with leuprolide acetate is that the uterus returns to the pretreatment size

within about 3-6 months after treatment is stopped (19, 51), although the patients may remain symptom-free for several months longer (51). This rapid regrowth may be due to an increased number of estrogen receptors induced in the leiomyomatous tissues due to the hypoestrogenic action of leuprolide acetate (48). It also has many side effects, including hot flashes, mood changes, vaginal dryness and spotting, which are due to the decreased estrogen levels (20, 51). These effects are uncomfortable, may be tolerated (20, 51), but can be severe enough to cause premature cessation of therapy (21). Since the decrease in uterine size is not permanent, and growth recurs once the leuprolide acetate has been withdrawn, the drug is currently used as an adjunct to surgery. It decreases the leiomyoma size and vascularity, facilitating the surgical removal and minimizing blood loss (11, 19, 20). The induced amenorrhea reverses the anemia in patients with menorrhagia prior to treatment, also decreasing the need for intraoperative blood transfusions (11, 19). It can be used as a temporizing method for perimenopausal women, since leiomyomas tend to regress after menopause (19, 51). It can also be used in patients who are poor surgical risks (19), and in women who wish to shrink their leiomyomas, and undergo a trial of conception before any surgical intervention.

It is unfortunate that the only known cure for uterine leiomyomas is a hysterectomy (19), however, each patient's treatment can be modified, depending on their presenting symptoms, age, and personal concerns to enable them to maintain a relatively normal lifestyle.

II. MAGNETIC RESONANCE IMAGING

A. History

The phenomenon of nuclear magnetic resonance (NMR) was first demonstrated by Bloch et al. (4), and Purcell et al. (47) working separately. They called it "nuclear induction" (4, 47). Further studies continued, with Odeblad and Lindstrom publishing a report on the first use of NMR on living animal tissues in 1955 (44). In 1973, Lauterbur published the first account of an image obtained with NMR (30). He produced an image of two containers of water (30). In 1976, the first image of human tissue, a finger, was produced by Mansfield and Maudsley (35). The field of NMR imaging (NMRI), frequently referred to as MRI, continued to develop rapidly, with increased utilization in humans. Extremely sophisticated and powerful scanners have been built, with advanced and innovative imaging techniques constantly being developed.

B. Basic Principles

The phenomenon of MRI is dependent on the magnetic qualities of atomic nuclei (14). When nuclei have unpaired protons or neutrons, they possess an intrinsic spin, and a magnetic moment (14, 53). In the absence of an external magnetic field, the magnetic moments of the nuclei are randomly oriented. However, when an external magnetic field is applied, the nuclei become aligned with the direction of the field, because of their magnetic moments (14, 46, 53). At equilibrium, this forms a net magnetic moment of all the nuclei (14, 46). The nuclei then rotate at a "precessional" or "resonant" frequency about the axis of the external field,

the "z-axis" (14, 46), This frequency is determined by the type of nuclei, and the strength of the magnetic field applied (14, 46, 53). These are related by the Larmor equation:

$$v = {}^{\gamma}/_{2\pi} \cdot B_0 ,$$

where v is the precessional frequency; ${}^{\gamma}/_{2\pi}$ is the gyromagnetic ratio, which is a constant that differs for each nucleus; and B_0 is the magnetic field strength.

Hydrogen is the most frequently used atom in MR imaging today (14, 53). It is a stable atom with a single proton, and is ubiquitous as a component of water in the human body, except in compact bone where it is present in decreased concentrations (34, 53). For these reasons, the remaining discussion will focus on the use of the hydrogen nucleus (proton) in medical imaging. The gyromagnetic ratio for hydrogen is 42.577 megahertz (MHz) at 1 Tesla (T) of field strength (46). The magnetic field strength of most scanners used for medical imaging ranges from 0.02-2.0 T (46) These produce precessional frequencies in hydrogen of 0.2-84 MHz. When a static magnetic field is generated in the scanner, the hydrogen nuclei become oriented both parallel and antiparallel (53) to the z-axis and this produces a large z-component of the net magnetization vector, $\bar{M}$ (14). The x and y components are zero, because although all the protons rotate at the same frequency, they are out of phase and therefore cancel each other out. When radiofrequency (RF) waves at the precessional frequency are directed at the nuclei in the x,y plane, the protons absorb energy, and are rotated from the z-axis (14, 46) This process is called excitation. These RF waves form excitation pulses which are characterized by the amount of rotation from the z-axis they produce - a 90º pulse rotates $\bar{M}$ from the z-axis onto the x,y plane. This makes the $\bar{M}_z$ component

zero, while the $\bar{M}_{xy}$ component increases (14). The resumption of the equilibrium state from the excited state is called relaxation (14). It consists of two components: the reconstitution of the $\bar{M}_z$ component, also known as the spin-lattice relaxation, with a time constant T1; and the loss of the $\bar{M}_{xy}$ component, also called the spin-spin relaxation, with a time constant T2 (14). During relaxation the protons emit the RF energy they previously absorbed, and this is received as the MR signal (53). This emission is the $\bar{M}_{xy}$ component of $\bar{M}$ (14). Three magnetic field gradients, oriented perpendicular to each other, are superimposed on the static magnetic field to provide spatial localization of the MR signal (33, 46, 53). The magnitude of the MR signal is directly proportional to the proton density in the tissue being scanned (53). The MR signal measured is always less than the original amplitude absorbed, because of losses during T1 and T2 relaxation (53). T1 relaxation is dependent on the environment surrounding the nucleus. As the excited nuclei return to equlibrium, they dissipate some of the absorbed RF energy to the environment. T1 measures this factor, and is the time, in milliseconds, for the recovery of 63% of the $\bar{M}_z$ component (53). It varies with the static magnetic field of the scanner (53). The T2 relaxation is due to variable inhomogeneity in the magnetic field caused by identical adjacent nuclei interacting. It is the time, in milliseconds, required for the $\bar{M}_{xy}$ component to be reduced by 37% of the excitation level (53). T2 is independent of the magnetic field strength, but is dependent on the chemical properties of the protons (53). The difference between the T1 and T2 values of various tissues is an essential factor in the production of image contrast (14).

Pulse sequences consist of specific patterns of excitations and listening times (14). Spin echo sequences are frequently used, and consist

of an initial 90^0 excitation pulse, followed by a pause, then a 180^0 excitation pulse is delivered. This serves to correct any inhomogeneity in the magnetic field. The 180^0 pulse is followed by another pause, and then there is a listening period (14, 33, 46). The sequence is repeated after the listening period. The echo time, TE, is the time (milliseconds) between the first pulse (90^0) and the listening period. The repetition time, TR, is the duration (milliseconds) of the entire pulse sequence before it is repeated (14). Variations of the spin echo sequence, such as the inversion recovery, IR, pulse sequence are also utilized. The IR pulse sequence consists of an initial 180^0 pulse, followed by a pause, then a 90^0 pulse, then a pause, another 180^0 pulse and finally, the listening period (14). Varying the pulse sequences used will produce differences in the extent of the T1 or T2 weighting of the images obtained. The $\bar{M}_{xy}$ component is dependent on TE and TR during excitation and relaxation (14). If the TE is prolonged, during the listening period, there will be less $\bar{M}_{xy}$ and more $\bar{M}_z$ component. Therefore, the T1 dependence is decreased, and T2 dependence is increased (14). Increasing the TR (> 1500 msec), and the TE (> 60 msec) produces a T2 weighted image. Shorter TR (< 800 msec) and TE values (< 40 msec) produce T1 weighted images (14). Proton density dependent images have a short TE, similar to T1 weighted images, but have a long TR, similar to the T2 weighted images. The TE and TR parameters chosen, therefore, influence the MR signal intensity, because they determine how much signal is received after excitation. The MR signal intensity is therefore dependent on T1, T2, the proton density of the tissue, and the pulse sequence being utilized.

C. Image Production

Two dimensional MR images are produced for most medical purposes. MR scanners use the two dimensional Fourier transformation method (33). This involves the use of three weak magnetic gradients superimposed on the static magnetic field. These are oriented in orthogonal directions. One gradient, turned on during the 90^0 excitation pulse, is called the slice select gradient (33). The RF pulse excites a certain predetermined volume of protons, and in this way, the thickness of the slice is determined (33). The second gradient is the phase encoding gradient. This enables the location of the protons to be spatially encoded, due to changes in their spin frequencies that occur under the effect of the gradient. These changes cause the protons to fall out of the excitation phase induced by the 90^0 pulse. The changed phase angles can be recorded and analyzed to determine the location of the protons (33). The third gradient is called the frequency encoding or readout gradient. This is activated during the echo reception (listening period), and also causes changes in the proton frequencies. The location of the protons along the gradient can then be determined by the gradient strength, and the difference between the resonant frequency of the static magnetic field and the new proton frequencies (33). Each slice of tissue produces MR signal which is displayed in a map with the use of pixels and voxels (14, 33). Each volume of tissue sampled forms a volume element, or voxel. The length of the voxel corresponds to the slice thickness. One surface of the voxel forms the picture element, or pixel (33), and the signal from the entire voxel determines the signal intensity of the image (14, 33). Each voxel corresponds to a specific pixel, several of which are combined to form a signal intensity map in black and white (14, 33), while the phase frequency information maps out spatial location

(33). Several projections ranging from 128 to 512 are obtained, repeated and averaged to decrease data variation,and improve image resolution (14, 33). Spatial resolution depends on the number of pixels (the image matrix size). The pixel size is affected by the size of the field of view (FOV), such that the pixel size = FOV/matrix size (33). Since smaller pixel sizes increase the spatial resolution, resolution can be improved by increasing matrix size without changing the FOV (33). This will, however, increase scanning time. Another alternative is to decrease the fov while maintaining the matrix size. This has the disadvantage of introducing imaging artifacts and decreasing the signal to noise ratio, SNR (33). The SNR reflects the ratio of MR signal to background noise. This can be improved with signal averaging, and the use of body surface coils. This produces shortened scan times, and better spatial and contrast resolution (33).

One major disadvantage of MRI is the amount of scanning time required. Scan time is the product of TR, the number of repetitions or excitations performed, and the number of the views obtained (14, 33), and can range from a few minutes to a few hours. It can be shortened by decreasing TR, or cutting down the number of views and excitations. However, each alternative has disadvantages such as decreased image SNR (33) Techniques such as zero filling, echo planar and hybrid imaging, are methods of decreasing the number of views in scanning. Driven equilibrium and magnetic field gradient echo techniques are methods of decreasing TR, but in addition to the decreased SNR, the images produced are also more T1 weighted (33). Most modern MR scanners have body surface coils, and other adaptations that increase the SNR (33). This is making it possible for several of the techniques mentioned above to be used to cut scan times

without significant image degradation.

Artifacts can be introduced into MRI in several ways. External objects emitting RF waves, ferromagnetic objects on, or in the patient and voluntary or involuntary (cardiovascular, respiratory) patient motion can all produce image artifacts (33, 53). These can be minimized by signal averaging and gating techniques (33). Chemical shift and flow void artifacts which are due to characteristics or rapid motion of the protons being scanned also occur (33). Chemical shift artifacts can be decreased by using special pulse sequences and steeper magnetic gradients (33). With an understanding of how MR images are generated, it should be possible to anticipate artifacts, and minimize them by adjusting imaging techniques.

D. Instrumentation

MRI scanners consist of a large main magnet, which may be either a permanent magnet, an air core or iron core resistive magnet, or a superconductive magnet (33). This produces the static magnetic field which surrounds the patient. The three orthogonally oriented weaker magnetic gradients are produced by three coaxial electromagnet coils (33, 46) that superimpose their fields on the static magnetic field. The RF coils are planar or solenoidal coils which usually serve as both the transmitter and receiver of the RF waves (33, 46) . The RF pulses received are then transmitted through a spectrometer to a computer where the image is generated (46).

E. Patient Safety Concerns

There are three main components of medical MRI which are being investigated for possible adverse effects on humans with frequent and prolonged exposure. These are the static magnetic fields (SMF), the extremely low frequency magnetic fields (ELFMF), and the RF waves used in imaging (46). There have been reports of patients with dental fillings experiencing strange taste and pain sensations when exposed to SMF up to 1,5-2 T (46). There are, however, no reports of other detrimental effects directly attributable to SMF exposure (7, 46). There is evidence that neuronal stimulation or ventricular fibrillation can occur in some patients exposed to the rapidly changing ELFMF generated by the gradient coils (46). The RF waves generate heat in the patients' tissues, but this is usually easily dissipated through the skin (46). Another problem associated with the RF waves is interference with cardiac pacemaker functioning (46). This problem can be avoided by careful patient screening and with new developments in the manufacture of the pacemakers. Apart from these cases, there is no evidence of increased morbidity or mortality with low level exposure to RF waves (46, 49).

Other safety hazards in MR imaging include the previously discussed effects of the magnetic fields on ferromagnetic objects, such as aneurysmal clips and pacemakers which could rotate and harm the patient. It is also difficult to monitor critically ill patients in the MRI areas, because of the limited space in the scanner, and the use of metal in most monitoring devices (46).

Despite some valid safety concerns with MRI, most patients prefer this imaging modality to CT scanning, because of the lack of ionizing radiation and IV or oral contrast (46).

F. MRI of the Female Pelvis

MRI is particularly well suited to the study of the female pelvis. Multiple planes can be imaged without difficulty, it is noninvasive, and does not involve the use of ionizing radiation. This eliminates concerns about radiation effects on the female reproductive organs. Imaging of the female pelvis is often done to distinguish between uterine and ovarian pathology, and to obtain specific information about the location and type of lesion in the uterus. By altering the TE and TR parameters, T1 or T2 weighted images can be obtained, producing excellent depictions of anatomy and soft tissue differentiation. T1 weighted images are excellent for differentiating between fat and smooth muscle (38), while T2 weighted images provide anatomic detail and contrast between soft tissues. Tissues with short T1 values include fat, iron containing tissues as occur in a subacute hemorrhage, and some proteinaceous fluids appear bright on T1 weighted images (53). Tissues with long T1 values, such as ligaments, tendons, cerebrospinal fluid, urine and cortical bone appear darker on T1 weighted images (53). Muscle, inflammatory and neoplastic tissue have an intermediate signal on T1 weighted images. Cortical bone, ligaments and tendons also have short T2 values, and have a low signal intensity on T2 weighted images, while iron containing tissues, inflammation, fluids, and neoplastic tissues appear bright, due to their long T2 values (33, 53). Fat has an intermediate signal intensity on T2 images (33).

The uterus in MR images appears as an organ with three intrinsic layers - the endometrium, myometrium, and the junctional zone, which is a

low intensity layer only visualized with MRI (fig. 1). The T1 values of endometrium and myometrium are similar, so there is not much tissue contrast on T1 weighted images (36). However, endometrium has a longer T2 than myometrium, so it emits a brighter signal than the myometrium on T2 weighted images. It is referred to as the endometrial stripe. MRI has been used to study the uterus during the menstrual cycle, and the endometrial stripe was observed to increase in thickness during the follicular and secretory phases, corresponding appropriately with the proliferative stage (28, 40). The changes in the endometrium under the influence of oral contraceptives (12) and GnRH analogs (40) have also been studied with MRI.

The myometrium is a region of intermediate intensity on T2 weighted images. There is a thin layer of low intensity between the endometrium and the myometrium called the junctional zone. Earlier studies defined this region as either the stratum basale, vasculature (12, 25), or an area of flow void (31). However, a recent study by McCarthy et al. has demonstrated that the junctional zone is probably a tissue layer, within the myometrium, with a decreased water content, and low T2 values (39) (hence the low signal intensity on T2 weighted scans).

The cervix is usually visualized as a two layer region, with a intermediate intensity signal obtained from the external fibrous stroma, and a bright central signal from the cervical mucus. There are venous plexi around the cervix and upper vagina which emit a bright signal (37). The vagina is also easily seen on T2 weighted images as a central bright signal, due to mucus, surrounded by an intermediate signal from the fibromuscular walls. It is clearly distinct from the urethra (38). The ovaries are easily identifiable on T2 weighted images, because of the

bright signal produced by the follicles (37).

Because of the excellent resolution and soft tissue contrast obtained with MRI, it is possible to identify and accurately localize pathologic lesions within the pelvis, and to differentiate between ovarian, cul-de-sac, and uterine masses. It is also the technique of choice in evaluating the uterus, enabling definitive diagnoses which are essential for the appropriate management of uterine leiomyomatous disease, differentiating it from adenomyosis (57).

Although supported by little data, it has always been generally accepted that certain characteristics of a leiomyomatous uterus, such as tumor size, type, degeneration and location correlate with clinical symptoms such as pain, infertility, and spontaneous abortions. More recently, Hricak et al. performed a study of 23 patients, which linked disruption of the junctional zone, observed on MRI, with hypermenorrhea (27). Their study, however, did not examine other MRI features of uterine leiomyoma disease for correlation with clinical symptoms other than hypermenorrhea. The purpose of this study is to use the excellent diagnostic capabilities of MRI, combined with patients' clinical histories, to examine any possible correlation between leiomyoma characteristics and patient symptoms and signs, such as menorrhagia, metrorrhagia, abdominal/pelvic pain, back pain, dysmenorrhea, dyspareunia, infertility, and spontaneous abortion.

2. METHODS

I. PATIENT SELECTION

The study subjects were selected from a group of women who were evaluated for uterine fibroid disease at the Yale Obstetrics and Gynecology Infertility and Endocrine Clinic between October 1986 and December 1990. 45 patients were selected based on the following criteria:

Definite evidence of uterine leiomyomas on MR imaging - presence of discrete rounded hypointense masses within the uterus.

A record of a clinical evaluation and an MRI study performed within 0-60 days of each other.

The patients' age range was 25-54 years, with a mean age of 36.8 years. A total of 114 clinical visits associated with concurrent MRI studies were reviewed.

II. CLINICAL DATA COLLECTION

All the patients' charts were reviewed, and the following clinical data were recorded from the histories obtained at the clinical visit:

The presence or absence of symptoms

The presence or absence of pain

The anatomic location of pain: abdominal/pelvic or back pain

The presence or absence of pressure

The presence or absence of 2º dysmenorrhea, or an increase in the

severity of 1º dysmenorrhea

The presence or absence of dyspareunia

The presence or absence of menorrhagia

The presence or absence of metrorrhagia

History of infertility

History of spontaneous abortion

Uterine size in gestational weeks from a bimanual exam

This data was then tabulated for subsequent analysis.

III. IMAGING TECHNIQUES

A total of 114 MRI studies performed between October 1986 and December 1990 were reviewed. MR imaging was performed with a 1.5 T Signa scanner (General Electric Medical Systems, Milwaukee). Spin echo axial and sagittal images were obtained with two excitations, 28 cm FOV, and a 128 × 256 matrix. T1 weighted images were produced with a TR of 400-800 msec, and a TE of 20-40 msec with 5-10 millimeter (mm) thick slices with 2.5-5.0 mm gaps. Intermediate and T2 weighted images were obtained with a TR of 1500-2200 msec and a TE of 20/80 msec, using 5 mm thick slices, and 2.0-5.0 mm gaps. All the MRI studies obtained were reviewed by a blinded investigator, (E.B.) who had no knowledge of the patients' clinical data.

IV. MAGNETIC RESONANCE IMAGING DATA COLLECTION

The pelvic images were evaluated for total uterine volume, (TUV), the presence of uterine leiomyomas, and various characteristics to be described. All dimensions were measured manually with calipers. The following information was amassed:

Three uterine dimensions, consisting of the anterior-posterior diameter (AP), which was measured on sagittal images as the widest AP thickness of the mid-corpus, the cranio-caudad height (CC), which was obtained from sagittal views as the greatest length from (and including) the cervix to the top of the fundus, and the transaxial width (TR) which was obtained from transaxial views as the widest measurement of the uterine corpus. Subserosal leiomyomas projecting from, and distorting the uterine contour were included in the maximum diameters. (Fig 2).

The dimensions, (AP,CC,TR) of the discrete countable leiomyomas were obtained in the same planes as the uterine dimensions.If a leiomyoma was spherical, and was measured in one image plane, but was absent in the other planes due to scanning gaps, the single dimension obtained was used in the volume calculations.

The locations of the leiomyomas within the uterus were recorded as follows: body, fundus, cervix, broad ligament, and cornual. The category of "multiple" was used when the leiomyomas were too many, and too small to identify and measure with certainty.

The junctional zone appearance was categorized as present, intact or disrupted.

The type of leiomyoma was noted as follows: submucosal leiomyomas had the tumor epicenter in the submucosa, and were noted to

disrupt the contiguous junctional zone (figs. 3 & 4); intramural leiomyomas had the epicenter in the myometrium, and did not disrupt the junctional zone (figs. 5 & 6); subserosal leiomyomas had the epicenter in the myometrium directly beneath the subserosa, with the bulk of the tumor bulging into the subserosal layer (figs. 2 & 6).

Finally, the types of degenerative changes in the leiomyomas were noted based on the tumors' internal signal. The degeneration was categorized as "non-specific", when the tumor had some signal increase and inhomogeneity, which could not be definitely classified as fatty or carneous (figs. 2 - 6). Although this probably represented hyaline degenerative change, we did not classify it as such, since there are only a few conclusive reports of a characteristic MR appearance for this type of degeneration (27, 31), and we did not have histopathologic correlation available. Carneous degeneration was diagnosed when there was a bright signal within a tumor on T2 images, and an intermediate to bright signal on T1 images, signifying a probable subacute hemorrhage (10, 23, 33, 55). Fatty degeneration was identified when the tumor's internal signal was of the same intensity as the subcutaneous fatty tissue. The category of "no degeneration" was used when the leiomyoma had a homogeneous signal.

V. PATIENT/MRI SCAN PROFILE

The number of visit days per patient ranged from 1-6 days. The mean time between the 114 MRI studies and clinical visits was 14 days (range of 0-51 days). Twenty-nine scans were performed on the same day as the clinical visit, 30 scans were performed within 1-10 days of the clinical visit, 29 scans were performed within 11-20 days of the clinical visit, 10

scans were performed within 21-30 days of the clinical visit, 10 scans were performed within 31-40 days of the clinical visit, 5 scans were performed within 41-50 days of the clinical visit, and 1 scan was performed within 51 days of the clinical visit. Since the patients' symptoms varied during their clinical evaluations, the MRI results were re-evaluated for each consecutive scan, yielding a total of 317 MRI-clinical data correlations. Twenty-nine out of the 45 patients in this study were on leuprolide acetate for a portion of their clinical course; 5 of these 29 patients were initially on placebo, and then elected to undergo treatment with the drug after the study ended. Two patients received placebo, but did not subsequently receive leuprolide acetate. (All the 31 patients described above were subjects in previous studies unrelated to this current study). Fourteen patients did not receive any drug treatment. A total of 47 scans were performed while patients were on leuprolide acetate, and the remaining 67 scans comprised the no drug group. The data obtained when patients were on leuprolide acetate was examined separately from the placebo and the no drug group. The data obtained from the placebo group was compared to the no drug group to detect any differences in the clinical data due to a "placebo effect" on the subjective information given by the patients. No significant differences in the results were noted ($p > 0.05$), so the placebo group results were combined with the no drug group results for further statistical analysis.

VI. PRELIMINARY DATA ANALYSIS

The uterine and leiomyoma volumes were computed using the equation: Volume (cc) = $^4/_3\pi \times AP/_2 \times CC/_2 \times TR/_2$. The non-leiomyoma uterine volume was obtained as the difference between the uterine volume and the total leiomyoma volume in each uterus. Nine uterine size estimations by bimanual exam were expressed as the number of centimeters above the pubic symphysis. These measurements were converted to gestational weeks size, by referring to data compiled by Baeyertz that related symphysio-fundal height in 127 women to the gestational age in weeks of their fetuses (2). The uterine size in gestational weeks was converted to volume measurements with the use of an equation derived by Flickinger et al (17):

$$\text{Volume} = 0.113w^3 + 2.084w^2 + 12.396w + 23.397$$

The uterine volumes obtained by MRI and bimanual exams were then examined for any correlation. The MRI uterine volumes were plotted on a graph against the bimanual uterine volumes, and the correlation coefficient was calculated. The clinical findings of menorrhagia, metrorrhagia, abdominal/pelvic pain, back pain, dysmenorrhea, dyspareunia, infertility, and spontaneous abortion were correlated with concurrent MRI findings of leiomyoma locations, types, degeneration, and volumes, uterine volumes and junctional zone disruption. The significance of the information obtained from these correlations was tested with chi-square analysis.

3. RESULTS

Forty-three of the 45 patients had one or more symptoms. The most frequently reported symptom was menorrhagia, followed by abdominal/pelvic pain, metrorrhagia, dysmenorrhea, dyspareunia, infertility, spontaneous abortion, and back pain (Table 1). The number of leiomyomas per patient ranged from 1-10 discrete countable tumors, with a total of 136 different leiomyomas for 43 of the patients. The two other patients had tumors that were multiple, tiny (< 0.5 centimeters diameter) and could not be counted.

TABLE 1. Frequency of patients' symptoms and signs.

Symptoms/Signs	Number of Patients (%)
Menorrhagia	32 (71%)
A/P Pain	23 (51%)
Metrorrhagia	22 (49%)
Dysmenorrhea	21 (47%)
Dyspareunia	10 (22%)
Infertility	10 (22%)
Spontaneous Abortion	4 (9%)
Back Pain	2 (4%)

I. JUNCTIONAL ZONE (JZ) DISRUPTION

The junctional zone on 111 scans clearly defined. The junctional zone was not seen clearly enough on 3 scans to be categorized as intact or disrupted.

Menorrhagia:

Leuprolide acetate

1/38 (3 %) of all scans with JZ disruption had menorrhagia.

1/10 (10%) of all scans with intact JZ had menorrhagia.

$p = 0.8822$

No Drug Treatment

32/42 (76%) of all scans with JZ disruption had menorrhagia.

11/21 (52%) of all scans with intact JZ had menorrhagia.

$p = 0.1038$

Leuprolide acetate compared to no drug treatment

1/38 (3 %) of all scans with JZ disruption on leuprolide acetate had menorrhagia compared to 32/42 (76%) on no drug treatment.

$p = 0.0001$

1/10 (10%) of all scans with intact JZ on leuprolide acetate had menorrhagia compared to 11/21 (52%) on no drug treatment.

$p = 0.0615$

Metrorrhagia:

Leuprolide acetate

13/38 (34%) of all scans with JZ disruption had metrorrhagia.

1/10 (10%) of all scans with intact JZ had metrorrhagia.

$p = 0.268$

No Drug Treatment

15/42 (36%) of all scans with JZ disruption had metrorrhagia.

3/21 (15%) of all scans with intact JZ had metrorrhagia.

$p = 0.1391$

Leuprolide acetate compared to no drug treatment

13/38 (34 %) of all scans with JZ disruption on leuprolide acetate had metrorrhagia compared to 15/42 (36%) on no drug treatment.

$p = 0.9252$

1/10 (10%) of all scans with intact JZ on leuprolide acetate had metrorrhagia compared to 3/21 (15%) on no drug treatment.

$p = 0.6101$

Spontaneous Abortion:

4/32 (13%) of patients with JZ disruption had a history of spontaneous abortion compared to 0/12 (0%) of patients with intact JZ.

$p = 0.4866$

Infertility:

11/29 (38%) of patients with disrupted JZ had a history of infertility compared to 1/10 (10%) of patients with intact JZ.

$p = 0.2102$

II. LEIOMYOMA LOCATION

The dominant leiomyoma within each uterus from each MRI study

was evaluated for the location, which was then correlated with A/P and back pain, pressure and infertility.

Pressure:

Leuprolide Acetate

3/33 (9%) of all scans with the dominant leiomyoma in the uterine body had pressure.

0/2 (0%) of all scans with the dominant leiomyoma in the uterine cervix had pressure.

2/8 (25%) of all scans with the dominant leiomyoma in the uterine fundus had pressure.

0 scans had the dominant leiomyoma in the broad ligament.

0/3 (0%) of all scans with the dominant leiomyoma in multiple uterine sites had pressure.

0 scans had no leiomyomas visualized.

$p = 0.4999$

No Drug Treatment

12/34 (47%) of all scans with the dominant leiomyoma in the uterine body had pressure.

1/1 (100%) of all scans with the dominant leiomyoma in the uterine cervix had pressure.

3/13 (23%) of all scans with the dominant leiomyoma in the uterine fundus had pressure.

1/1 (100%) of all scans with the dominant leiomyoma in the broad ligament had pressure.

1/7 (14%) of all scans with leiomyomas in multiple uterine sites had pressure.

0/2 (0%) of all scans with no leiomyomas visualized had pressure.

$p = 0.2453$

Leuprolide acetate compared with no drug treatment

3/33 (9 %) of scans with the dominant leiomyoma in the uterine body on leuprolide acetate had pressure compared with 12/34 (47%) of scans on no drug treatment.

$p = 0.0356$

0/2 (0 %) of scans with the dominant leiomyoma in the uterine cervix on leuprolide acetate had pressure compared with 1/1 (100%) of scans on no drug treatment.

$p = 0.655$

2/8 (25%) of scans with the dominant leiomyoma in the uterine fundus on leuprolide acetate had pressure compared with 3/13 (23%) of scans on no drug treatment.

$p = 0.6694$

0 scans had the dominant leiomyoma in the broad ligament on leuprolide acetate.

0/3 (0%) of scans with the dominant leiomyoma in multiple uterine sites on leuprolide acetate had pressure compared with 1/7 (14%) of scans on no drug treatment.

0 scans had no leiomyomas visualized on leuprolide acetate.

$p = 0.6455$

Abdominal/Pelvic Pain:

Leuprolide Acetate

7/33 (21%) of scans with the dominant leiomyoma in the uterine body had abdominal/pelvic pain.

0/2 (0%) of scans with the dominant leiomyoma in the uterine cervix had abdominal/pelvic pain.

2/8 (25%) of scans with the dominant leiomyoma in the uterine fundus had abdominal/pelvic pain.

0 scans had leiomyomas in the broad ligament.

1/3 (33%) of scans with the dominant leiomyoma in multiple sites had abdominal/pelvic pain.

0 scans had no leiomyomas visualized.

$p = 0.838$

No Drug Treatment

14/34 (47%) of scans with the dominant leiomyoma in the uterine body had abdominal/pelvic pain.

0/1 (0%) of scans with the dominant leiomyoma in the uterine cervix had abdominal/pelvic pain.

7/13 (54%) of scans with the dominant leiomyoma in the uterine fundus had abdominal/pelvic pain.

0/1 (0%) of scans with the dominant leiomyoma in the broad ligament had abdominal/pelvic pain.

4/7 (57%) of scans with the dominant leiomyoma in multiple sites had abdominal/pelvic pain.

0/2 (0%) of scans with no leiomyomas visualized had abdominal/pelvic pain.

$p = 0.239$

Leuprolide acetate compared to no drug treatment

7/33 (21%) of scans with the dominant leiomyoma in the uterine body on leuprolide acetate had abdominal/pelvic pain compared with 14/34 (47%) of scans on no drug treatment.

$p = 0.438$

0/2 (0 %) of scans with the dominant leiomyoma in the uterine cervix on leuprolide acetate had abdominal/pelvic pain compared with 0/1 (0%) of scans on no drug treatment.

$p =$ *not calculable*

2/8 (25%) of scans with the dominant leiomyoma in the uterine fundus on leuprolide acetate had abdominal/pelvic pain compared with 7/13 (54%) of scans on no drug treatment.

$p = 0.3991$

0 scans had the dominant leiomyoma in the broad ligament on leuprolide acetate.

1/3 (33%) of scans with the dominant leiomyoma in multiple uterine sites on leuprolide acetate had abdominal/pelvic pain compared with 4/7 (57%) of scans on no drug treatment.

0 scans had no leiomyomas visualized on leuprolide acetate.

$p = 0.6455$

Back Pain

Leuprolide Acetate

2/2 (100%) of scans with back pain had the dominant leiomyoma in the uterine body.

No Drug Treatment

0 scans were associated with back pain.

Infertility

6/32 (19%) of all patients with a dominant leiomyoma in the uterine body had a prior history of infertility.

1/2 (50%) of all patients with a dominant leiomyoma in the uterine cervix had a prior history of infertility.

3/9 (33%) of all patients with a dominant leiomyoma in the uterine fundus had a prior history of infertility.

0/1 (0%) of all patients with a dominant leiomyoma in the broad ligament had a prior history of infertility.

0/1 (0%) of all patients with a dominant leiomyoma in multiple uterine sites had a prior history of infertility.

0 patients with leiomyomas that were not visualized had a history of infertility.

$p = 0.6752$

III. LEIOMYOMA TYPE

The different types of leiomyomas (submucosal, intramural, and subserosal) in each MRI study were evaluated, and correlated with menorrhagia, dysmenorrhea, infertility, and spontaneous abortion.

Infertility:

13/32 (41%) of patients with submucosal leiomyomas had a prior history of infertility.

7/22 (32%) of patients with intramural leiomyomas had a prior history of infertility.

2/11 (18%) of patients with subserosal leiomyomas had a prior history of infertility.

0/10 (0%) of patients with multiple leiomyomas had a prior history of infertility.

3/9 (33%) of patients with no leiomyomas visualized had a prior history of infertility.

$p = 0.1441$

Spontaneous Abortion:

4/32 (25%) of patients with submucosal leiomyomas had a prior history of spontaneous abortion.

2/24 (8%) of patients with intramural leiomyomas had a prior history of spontaneous abortion.

1/13 (7%) of patients with subserosal leiomyomas had a prior history of spontaneous abortion.

0/10 (0%) of patients with multiple leiomyomas had a prior history of infertility.

0/9 (0%) of patients with no leiomyomas visualized had a prior history of spontaneous abortion.

$p = 0.6213$

Dysmenorrhea:

Leuprolide Acetate

1/46 (2%) of all scans with at least 1 submucosal leiomyoma had dysmenorrhea.

2/23 (12%) of all scans with at least 1 intramural leiomyoma had dysmenorrhea.

1/15 (7%) of all scans with at least 1 subserosal leiomyoma had dysmenorrhea.

0/3 (0%) of all scans with multiple leiomyomas had dysmenorrhea.

0/5 (0%) of all scans with no leiomyomas visualized had dysmenorrhea.

$p = 0.7126$

No Drug Treatment

14/49 (29%) of all scans with at least 1 submucosal leiomyoma had dysmenorrhea.

15/25 (60%) of all scans with at least 1 intramural leiomyoma had dysmenorrhea.

5/19 (36%) of all scans with at least 1 subserosal leiomyoma had dysmenorrhea.

0/7 (0%) of all scans with multiple leiomyomas had dysmenorrhea.

3/3 (100%) of all scans with no leiomyomas visualized had dysmenorrhea.

$p = 0.0016$

Leuprolide acetate compared to no drug treatment

1/46 (2%) of all scans with at least 1 submucosal leiomyoma on leuprolide acetate had dysmenorrhea compared to 14/49 (29%) of scans with no drug treatment.

$p = 0.0012$

2/23 (12%) of all scans with at least 1 intramural leiomyoma on leuprolide acetate had dysmenorrhea compared to 15/25 (60%) of scans with no drug treatment.

$p = 0.0006$

1/15 (7%) of all scans with at least 1 subserosal leiomyoma on leuprolide acetate had dysmenorrhea compared to 5/19 (36%) of scans with no drug treatment.

$p = 0.2987$

0 scans with multiple leiomyomas had dysmenorrhea.

0/5 (0%) of all scans with no leiomyomas visualized on leuprolide acetate had dysmenorrhea compared to 3/3 (100%) scans on no drug treatment.

$p = 0.0381$

Menorrhagia:

Leuprolide Acetate

1/38 (3%) of all scans with at least 1 submucosal leiomyoma had menorrhagia.

0/2 (0%) of all scans with at least 1 intramural leiomyoma had menorrhagia.

0/4 (0%) of all scans with at least 1 subserosal leiomyoma had menorrhagia.

0/2 (0%) of all scans with multiple leiomyomas had menorrhagia.

1/2 (50%) of all scans with both intramural and subserosal leiomyomas had menorrhagia.

$p = 0.0255$

No Drug Treatment

32/42 (76%) of all scans with at least 1 submucosal leiomyoma had menorrhagia.

5/7 (71%) of all scans with at least 1 intramural leiomyoma had menorrhagia.

3/6 (50%) of all scans with at least 1 subserosal leiomyoma had menorrhagia.

0/5 (0%) of all scans with multiple leiomyomas had menorrhagia.

3/3 (100%) of all scans with both intramural and subserosal leiomyomas had menorrhagia.

$p = 0.0063$

Leuprolide acetate compared to no drug treatment

1/38 (3%) of all scans with at least 1 submucosal leiomyoma on leuprolide acetate had menorrhagia compared to 32/42 (76%) of scans with no drug treatment.

$p = 0.0001$

0/2 (0%) of all scans with at least 1 intramural leiomyoma on leuprolide acetate had menorrhagia compared to 5/7 (71%) of scans with no drug treatment.

$p = 0.3241$

0/4 (0%) of all scans with at least 1 subserosal leiomyoma on leuprolide acetate had menorrhagia compared to 3/6 (50%) of scans with no drug treatment.

$p = 0.3241$

0/2 (0%) of all scans with multiple leiomyomas on leuprolide acetate had menorrhagia compared to 0/5 (0%) scans on no drug treatment.

$p =$ *not calculable*

1/2 (50%) of all scans with both intramural and subserosal leiomyomas on leuprolide acetate had menorrhagia compared to 3/3 (100%) of scans with no drug treatment.

$p = 0.8195$

IV. LEIOMYOMA DEGENERATION

A total of 296 leiomyomas were evaluated for any association between degenerative changes, tumor volume and pain.

Leiomyoma Volume:

Leuprolide Acetate

1/85 (1%) of all the leiomyomas with volumes between 0-49.9 cc had carneous degeneration.

3/17 (18%) of all the leiomyomas with volumes between 50-99.9 cc had carneous degeneration.

4/24 (17%) of all the leiomyomas with volumes between 100-499.9 cc had carneous degeneration.

0/2 (0%) of all the leiomyomas with volumes between 500-999.9 cc had carneous degeneration.

There were no leiomyomas with volumes between 1000-2200 cc.

$p = 0.0071$

No Drug Treatment

5/108 (5%) of all the leiomyomas with volumes between 0-49.9 cc had carneous degeneration.

3/16 (19%) of all the leiomyomas with volumes between 50-99.9 cc had carneous degeneration.

4/20 (20%) of all the leiomyomas with volumes between 100-499.9 cc had carneous degeneration.

4/14 (20%) of all the leiomyomas with volumes between 500-999.9 cc had carneous degeneration.

0/1 (0%) of all the leiomyomas with volumes between 1000-2200 had carneous degeneration.

$p = 0.0143$

Leuprolide Acetate

51/85 (60%) of all the leiomyomas with volumes between 0-49.9 cc had no degeneration.

0/17 (0%) of all the leiomyomas with volumes between 50-99.9 cc had no degeneration.

0/24 (0%) of all the leiomyomas with volumes between 100-499.9 cc had no degeneration.

0/2 (0%) of all the leiomyomas with volumes between 500-999.9 cc had no degeneration.

There were no leiomyomas with volumes between 1000-2200 cc.

$p = 0.0001$

No Drug Treatment

55/108 (51%) of all the leiomyomas with volumes between 0-49.9 cc had no degeneration.

3/16 (19%) of all the leiomyomas with volumes between 50-99.9 cc

had no degeneration.

1/20 (5%) of all the leiomyomas with volumes between 100-499.9 cc had no degeneration.

0/14 (0%) of all the leiomyomas with volumes between 500-999.9 cc had no degeneration.

0/1 (0%) of all the leiomyomas with volumes between 1000-2200 had no degeneration.

$p = 0.0001$

Leuprolide Acetate

33/85 (39%) of all the leiomyomas with volumes between 0-49.9 cc had non-specific degenerative changes.

14/17 (82%) of all the leiomyomas with volumes between 50-99.9 cc had non-specific degenerative changes.

20/24 (83%) of all the leiomyomas with volumes between 100-499.9 cc had non-specific degenerative changes.

2/2 (100%) of all the leiomyomas with volumes between 500-999.9 cc had non-specific degenerative changes.

There were no leiomyomas with volumes between 1000-2200 cc.

$p = 0.0001$

No Drug Treatment

49/108 (45%) of all the leiomyomas with volumes between 0-49.9 cc had non-specific degenerative changes.

10/16 (63%) of all the leiomyomas with volumes between 50-99.9 cc had non-specific degenerative changes.

15/20 (75%) of all the leiomyomas with volumes between 100-499.9 cc had non-specific degenerative changes.

10/14 (71%) of all the leiomyomas with volumes between 500-

999.9 cc had non-specific degenerative changes.

1/1 (100%) of all the leiomyomas with volumes between 1000-2200 cc had non-specific degenerative changes.

$p = 0.0442$

Leuprolide acetate compared to no drug treatment

1/85 (1%) of leiomyomas with volumes between 0-49.9 cc on leuprolide acetate had carneous degeneration compared to 5/108 (5%) on no drug treatment.

$p = 0.3398$

3/17 (18%) of leiomyomas with volumes between 50-99.9 cc on leuprolide acetate had carneous degeneration compared to 3/16 (19%) on no drug treatment.

$p = 0.7118$

4/24 (17%) of leiomyomas with volumes between 100-499.9 cc on leuprolide acetate had carneous degeneration compared to 4/20 (20%) on no drug treatment.

$p = 0.9148$

0/2 (0%) of leiomyomas with volumes between 500-999.9 cc on leuprolide acetate had carneous degeneration compared to 4/14 (29%) on no drug treatment.

$p = 1.0000$

51/85 (60%) of leiomyomas with volumes between 0-49.9 cc on leuprolide acetate had no degeneration compared to 55/108 (51%) on no drug treatment.

$p = 0.2661$

0/17 (0%) of leiomyomas with volumes between 50-99.9 cc on leuprolide acetate had no degeneration compared to 3/16 (19%) on no drug treatment.

p = 0.2053

0/24 (0%) of leiomyomas with volumes between 100-499.9 cc on leuprolide acetate had no degeneration compared to 1/20 (5%) on no drug treatment.

p = 0.9264

0/2 (0%) of leiomyomas with volumes between 500-999.9 cc on leuprolide acetate had no degeneration compared to 0/14 (0%) on no drug treatment.

p = not calculable

33/85 (39%) of leiomyomas with volumes between 0-49.9 cc on leuprolide acetate had non-specific degenerative changes compared to 49/108 (45%) on no drug treatment.

p = 0.4452

14/17 (82%) of leiomyomas with volumes between 50-99.9 cc on leuprolide acetate had non-specific degenerative changes compared to 10/16 (63%) on no drug treatment.

p = 0.3741

20/24 (83%) of leiomyomas with volumes between 100-499.9 cc on leuprolide acetate had non-specific degenerative changes compared to 15/20 (75%) on no drug treatment.

p = 0.7588

2/2 (100%) of leiomyomas with volumes between 500-999.9 cc on leuprolide acetate had non-specific degenerative changes compared to 10/14 (71%) on no drug treatment.

$p = 1.0000$

Abdominal/Pelvic Pain:

Leuprolide Acetate

1/8 (13%) of all the carneous leiomyomas were associated with abdominal/pelvic pain.

13/51 (26%) of all the leiomyomas with no degeneration were associated with abdominal/pelvic pain.

15/72 (21%) of all the leiomyomas with non-specific degenerative changes were associated with abdominal/pelvic pain.

$p = 0.6588$

No Drug Treatment

9/16 (56%) of all the carneous leiomyomas were associated with abdominal/pelvic pain.

13/59 (22%) of all the leiomyomas with no degeneration were associated with abdominal/pelvic pain.

25/90 (28%) of all the leiomyomas with non-specific degenerative changes were associated with abdominal/pelvic pain.

$p = 0.0262$

Leuprolide acetate compared to no drug treatment

1/8 (13%) of all the carneous leiomyomas on leuprolide acetate were associated with abdominal/pelvic pain compared to 9/16 (56%) on no drug treatment.

$p = 0.1073$

13/51 (26%) of all the leiomyomas with no degenerative changes on leuprolide acetate were associated with abdominal/pelvic pain compared to 13/59 (22%) on no drug treatment.

$p = 0.8411$

15/72 (21%) of all the leiomyomas with non-specific degenerative changes on leuprolide acetate were associated with abdominal/pelvic pain compared to 25/90 (28%) on no drug treatment.

$p = 0.4036$

Back Pain:

Only 2 leiomyomas in the entire study were associated with back pain; both were on leuprolide acetate treatment, and had no degenerative changes (2/59).

Dysmenorrhea:

Leuprolide Acetate

0/8 (0%) of all the carneous leiomyomas were associated with dysmenorrhea.

2/60 (3%) of all the leiomyomas with no degeneration were associated with dysmenorrhea.

3/72 (4%) of all the leiomyomas with non-specific degenerative

changes were associated with dysmenorrhea.

$$p = 0.8269$$

No Drug Treatment

9/16 (56%) of all the carneous leiomyomas were associated with dysmenorrhea.

25/71 (35%) of all the leiomyomas with no degeneration were associated with dysmenorrhea.

30/90 (33%) of all the leiomyomas with non-specific degenerative changes were associated with dysmenorrhea.

$$p = 0.0753$$

Leuprolide acetate compared to no drug treatment

0/8 (0%) of all the carneous leiomyomas on leuprolide acetate were associated with dysmenorrhea compared to 9/16 (56%) on no drug treatment.

$$p = 0.0253$$

2/60 (3%) of all the leiomyomas with no degenerative changes on leuprolide acetate were associated with dysmenorrhea compared to 25/71 (35%) on no drug treatment.

$$p = 0.001$$

3/72 (4%) of all the leiomyomas with non-specific degenerative changes on leuprolide acetate were associated with dysmenorrhea compared to 30/90 (33%) on no drug treatment.

$$p = 0.1333$$

Dyspareunia:

Leuprolide Acetate

0/8 (0%) of all the carneous leiomyomas were associated with

dyspareunia.

6/60 (10%) of all the leiomyomas with no degeneration were associated with dyspareunia.

2/72 (3%) of all the leiomyomas with non-specific degenerative changes were associated with dyspareunia.

$p = 0.1586$

No Drug Treatment

4/16 (25%) of all the carneous leiomyomas were associated with dyspareunia.

12/71 (17%) of all the leiomyomas with no degeneration were associated with dyspareunia.

9/90 (10%) of all the leiomyomas with non-specific degenerative changes were associated with dyspareunia.

$p = 0.1946$

Leuprolide acetate compared to no drug treatment

0/8 (0%) of all the carneous leiomyomas on leuprolide acetate were associated with dyspareunia compared to 4/16 (25%) on no drug treatment.

$p = 0.3329$

6/60 (10%) of all the leiomyomas with no degenerative changes on leuprolide acetate were associated with dyspareunia compared to 12/71 (17%) on no drug treatment.

$p = 0.3473$

2/72 (3%) of all the leiomyomas with non-specific degenerative changes on leuprolide acetate were associated with dyspareunia compared to 9/90 (10%) on no drug treatment.

$p = 0.1333$

V. TOTAL UTERINE VOLUME

The total uterine volumes from each MRI study measurements were evaluated, and correlated with A/P pain and pressure.

Abdominal/Pelvic Pain:

Leuprolide Acetate

5/36 (14%) of scans with total uterine volume between 0-599.9 cc were associated with abdominal/pelvic pain.

4/12 (33%) of scans with total uterine volume between 600-1199.9 cc were associated with abdominal/pelvic pain.

$p = 0.2857$

No Drug Treatment

14/27 (52%) of scans with total uterine volume between 0-599.9 cc were associated with abdominal/pelvic pain.

8/27 (30%) of scans with total uterine volume between 600-1199.9 cc were associated with abdominal/pelvic pain.

3/8 (38%) of scans with total uterine volume between 1200-1799.9 cc were associated with abdominal/pelvic pain.

1/3 (33%) of scans with total uterine volume between 1800-2399.9 cc were associated with abdominal/pelvic pain.

0/1 (0%) of scans with total uterine volume between 2400-2999.9 cc were associated with abdominal/pelvic pain.

$p = 0.4716$

Leuprolide Acetate compared to no drug treatment

5/36 (14%) of scans with total uterine volume between 0-599.9 cc on leuprolide acetate were associated with abdominal/pelvic pain compared to 14/27 (52%) on no drug treatment.

$p = 0.0035$

4/12 (33%) of scans with total uterine volume between 600-1199.9 cc on leuprolide acetate were associated with abdominal/pelvic pain compared to 8/27 (30%) on no drug treatment.

$p = 0.8851$

Pressure:

Leuprolide Acetate

2/36 (6%) of scans with total uterine volume between 0-599.9 cc were associated with pressure.

2/12 (16%) of scans with total uterine volume between 600-1199.9 cc were associated with pressure.

$p = 0.5464$

No Drug Treatment

12/27 (44%) of scans with total uterine volume between 0-599.9 cc were associated with pressure.

8/27 (30%) of scans with total uterine volume between 600-1199.9 cc were associated with pressure.

1/8 (13%) of scans with total uterine volume between 1200-1799.9 cc were associated with pressure.

0/3 (0%) of scans with total uterine volume between 1800-2399.9 cc were associated with pressure.

0/1 (0%) of scans with total uterine volume between 2400-2999.9

cc were associated with pressure.

$$p = 0.2591$$

Leuprolide Acetate compared to no drug treatment

2/36 (6%) of scans with total uterine volume between 0-599.9 cc on leuprolide acetate were associated with pressure compared to 12/27 (44%) on no drug treatment.

$$p = 0.0008$$

2/12 (16%) of scans with total uterine volume between 600-1199.9 cc on leuprolide acetate were associated with pressure compared to 8/27 (30%) on no drug treatment.

$$p = 0.6467$$

VI. UTERINE NON-LEIOMYOMA VOLUME

To eliminate errors in analysis that would be introduced because of the effect of leuprolide acetate on uterine and leiomyoma volumes, the uterine volume measurements from the first MRI study of each patient, performed without leuprolide acetate, were used. These were then correlated with spontaneous abortion and infertility.

Spontaneous Abortion:

2/22 (9%) of patients with uterine non-leiomyoma volume < 500 cc had a history of spontaneous abortion.

1/12 (8%) of patients with uterine non-leiomyoma volume between 500-999.9 cc had a history of spontaneous abortion.

0/2 (0%) of patients with uterine non-leiomyoma volume between 1000-1499.9 cc had a history of spontaneous abortion.

$p = 0.9056$

Infertility:

4/22 (15%) of patients with uterine non-leiomyoma volume < 500 cc had a history of infertility.

2/12 (17%) of patients with uterine non-leiomyoma volume between 500-999.9 cc had a history of infertility.

1/2 (50%) of patients with uterine non-leiomyoma volume between 1000-1499.9 cc had a history of infertility.

$p = 0.529$

VII. TOTAL UTERINE VOLUME BY BIMANUAL EXAM COMPARED WITH MRI CALCULATED VOLUME

The uterine volume was calculated from each bimanual exam estimation, and for each MRI study measurement, as described previously in the methods section. This data was then tabulated (Table 2), and graphed (fig. 7) to determine any correlation.

TABLE 2. Uterine Volumes by MRI measurements and gestational size estimates.

GWKS EQ	MRI UT VOL/CC	CALC UT VOL/CC
17	849.1	1391.6
9.5	895.3	426.1
9	611.4	386.1
14	479	915.5
19.5	981.3	1895.4
14.5	868.2	985.8
12.5	872.5	724.7
16.5	1115.3	1302.9
16	920.2	1218.1
12	592	667.5
18	1219.6	1580.8
17	818.6	1391.6
10.5	615.4	514.1
17.5	414.5	1484.2
12	444.6	667.5
8	235.9	313.8
15.5	792.2	1137.0
9	254.3	386.1
18.5	1086.9	1681.5
8	327.7	313.8
18.5	994.3	1681.5
7	403.2	251.0
16.5[a]	237.4	1302.9
18	864.6	1580.8
9	507.7	386.1
13.5[a]	506.6	848.6
6	401.9	197.2
15[a]	353.3	1059.6
13	297.2	785.0
13	244.9	785.0
5.5	200.8	173.4
13.5[a]	804.5	848.6
10	635.9	468.8
9.5	784.4	426.1
6	720.2	197.2
26	2732.2	3740.6

12.5	294.3	724.7
12	362.3	667.5
15.5	481.7	1137.0
11.5	334.9	613.4
7	319.4	251.0
20.5[a]	789.8	2126.8
9	364.7	386.1
7	282.6	251.0
8	312.2	313.8
8	159.3	313.8
19.5[a]	802.6	1895.4
16	944.8	1218.1
14.5	584.1	985.8
13.5	993.3	848.6
19	1480.8	1786.3
10	611.2	468.8
15	900.4	1059.6
12	481.3	667.5
11.5[a]	149.7	613.4
18	1625.7	1580.8
12	1014.4	667.5
17	714.4	1391.6
15.5	559.1	1137.0
8	237.8	313.8
10	531.9	468.8
11	316	562.3
16.5	1090.2	1302.9
15	377.3	1059.6
19.5	1173.3	1895.4
13.5[a]	205.5	848.6
10	474.8	468.8
18	2172.3	1580.8
15.5	612.3	1137.0
12.5	666.8	724.7
20.5[a]	1066.5	2126.8
15	1104.2	1059.6
9.5	313.4	426.1
8	264.8	313.8
24	1477.1	3083.4

20	837.4	2008.9
8.5	1077	1681.5
20	1444.2	2008.9
20	1350.5	2008.9
15	1393	1059.6
9	402.3	386.1
5.5	385.3	173.4
19.5	1350.1	1895.4
9.5	390	426.1
8	289.2	313.8
17	588.8	1391.6
18	1046.7	1580.8
9	440	386.1

[a] Symphysio-fundal height was converted to gestational size in weeks (2).

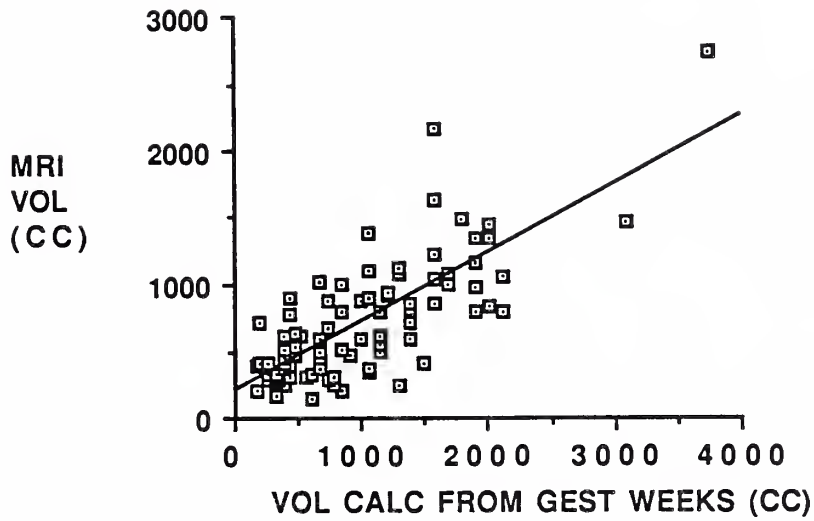

Figure 7. Graph demonstrating the correlation of the calculated MRI uterine volumes (cc) with the uterine volumes calculated from bimanual gestational age estimations.

$y = 197.4 + 0.52x$; $r = 0.77$, $r^2 = 0.59$.

4. DISCUSSION

Uterine leiomyomas have always been associated with the gynecological complications of menorrhagia, metrorrhagia, dysmenorrhea, dyspareunia, pressure, abdominal/pelvic pain, infertility and spontaneous abortion. Menorrhagia has been variously attributed to leiomyoma characteristics, such as submucosal tumor locations with endometrial ulceration (9, 29. 42), mechanical interference with the uterine blood supply (15, 16), and decreased uterine hemostasis due to the presence of intramural tumors (42). More recently, Hricak et al. reported hypermenorrhea in all of the 11 patients who had disruption of the MRI detected junctional zone in her study (27). However, our results show no statistically significant correlation between junctional zone disruption (which was considered equivalent to the incidence of submucosal leiomyomas in our study) and menorrhagia or metrorrhagia. When patients with intact junctional zones were examined, the presence of intramural leiomyomas was associated with menorrhagia in patients on no drug treatment. This supports the theory that impaired uterine hemostasis, which occurs as a result of decreased contraction due to the presence of intramural leiomyomas, causes the increased bleeding (42). The relative insignificance of the presence of submucosal leiomyomas is somewhat contradictory to the results of Farber-Brown et al., which implied more of a correlation with menorrhagia. However, their studies also confirmed that intramural and even subserosal tumors can cause compression of the blood vessels predisposing the patient to menorrhagia (15, 16). The most significant difference occurred between the LA treated and no drug

treatment groups, where LA was clearly effective in decreasing the incidence of menorrhagia. This is most likely due to its supressive effects on the pituitary-ovarian axis , through its GnRH agonist-antagonist actions. Since the patients are rendered amenorrheic, their menorrhagia is effectively eliminated.

Abdominal/pelvic pain and pressure are also frequent symptoms associated with uterine leiomyomas. These are believed to be due to the enlarged leiomyomatous uterus impinging on the abdominal/pelvic organs and nerves (29, 42) and stretching of pelvic adhesions. We evaluated total uterine volume and the symptoms of pain and pressure in each patient, but did not find any statistically significant relationship between them. This is probably due to the fact that the sensation of pain or pressure is very subjective, and depends more on the patients' tolerance levels and the rate of growth of the tumor. Carneous leiomyomas were associated with A/P pain in patients with no drug treatment. This differs from the results of Persaud et al., who found no correlation between A/P pain and the degenerative changes of leiomyomas on pathologic examination (45). The association of carneous leiomyomas causing acute pain during pregnancy has always been generally accepted (42). However, none of these patients were pregnant. Treatment with LA decreased the incidence of pain in patients with uterine volumes less than 600 cc, but did not have a significant effect on the occurence of pain in patients with any type of degenerated leiomyomas. This may be due to the fact that uterine volumes in patients on LA represent a decrease from larger pretreatment volumes. This decrease in uterine size is likely to eliminate, or at least diminish, more serious complaints that existed previously - a subjective bias that patients on no drug therapy would not exhibit. LA also decreased the

incidence of pressure in patients with a dominant leiomyoma in the uterine body. The urinary bladder is in close proximity to the body of the uterus, and patients are more likely to be sensitive to uterine volume changes in this location.

Dysmenorrhea has been associated with cramping due to intramural leiomyomas (42). This was observed in our patient group that did not receive any LA. Patients, in both groups, with intramural tumors were more likely to have dysmenorrhea than patients with subserosal and submucosal tumors. This increased cramping is probably due to the mass of the intramural leiomyomas opposing contraction of the myometrium during menses. Dysmenorrhea was again decreased in LA treated patients, since they were amenorrheic. Dyspareunia is believed to be more common in patients with cervical leiomyomas. Only two patients in our study had cervical tumors, and neither patient complained of dyspareunia. This number of patients is too small to generate a definite conclusion. The effect of LA in decreasing the incidence of dyspareunia when uterine volumes were less than 600 cc can also be explained (as above for A/P pain) as a subjective feeling of improvement experienced by the patients due to the decrease in uterine volume.

It is generally believed that the location or type of leiomyoma can increase the incidence of infertility and spontaneous abortion (9). We did not find any statistically significant relationship when we evaluated junctional zone disruption, the location, and the type of leiomyoma in 12 patients with infertility and four patients with spontaneous abortion. We also could not find any correlation between uterine non-leiomyoma volumes and infertility or spontaneous abortion. Since only about 2-10% of infertility problems can be attributed solely to the presence of

leiomyomas (9, 29), it is not too surprising that we were not able to detect any definite relationship in the small patient sample that we evaluated. It is, however, interesting that we had so few patients (4/45) with a history of spontaneous abortion, since the incidence in women with leiomyomas has been reported as high as 41% (9). It would seem logical that as a result of decreased intrauterine volume and alteration of the normal endometrium caused by the tumors (9), the patients might be more prone to spontaneous abortions. However, several women with large leiomyomas have had children without difficulty, so there are probably other factors to be considered when fertility is being assessed in these women.

We found that the type of degeneration that occurred in leiomyomas was dependent on leiomyoma size. Smaller tumors tended to have either no degenerative changes or a non-specific degenerative pattern which may have been hyaline change, but we could not confirm this with pathologic correlation. The larger tumors all had either non-specific or carneous degeneration. Hricak et al. made a similar observation relating the size of the tumors to the presence of degeneration (27). This confirms the association of degenerative changes with the growth of leiomyomas, which causes a decrease in relative blood supply (42). Friedman et al. found a relationship between LA treatment and an increased incidence of hyaline degeneration (20), but we did not find any such association with any of the tumor degenerative changes that we noted.

We also compared the uterine volumes calculated from estimates of gestational week size (17) to those calculated from MRI measurements. Since no nomogram of MRI volumes of non-gravid enlarged uteri has been constructed yet, we decided to assess how well the estimations from

pelvic examinations correlated with our MRI volumes. The two uterine volumes correlated well, (fig. 7), with a correlation coefficient of 0.77, and a coefficient of determination of 0.59. The estimations of gestational week size can therefore be reliably predicted from MRI measurements about 59% of the time. The 41% variability observed can be explained by the fact that the pelvic examinations were performed by several different people. Bimanual examinations have always been known to be relatively inaccurate and unreliable, depending on the experience level of the examiner. We obtained MRI volumes of 872.5 cc and 294.3 cc, both corresponding to gestational sizes by examination of 12.5 weeks or 724.7 cc (Table 2). This further serves to illustrate the marked variation that occurs with bimanual estimations of uterine size. The errors introduced by the equation used to calculate the MRI uterine volume increase with the more irregularly shaped uteri. It is important to be able to accurately evaluate uterine volume, since it is often used by clinicians to make therapeutic decisions. In patients who are already being evaluated with MRI, this additional service could be made available if a standardized nomogram were constructed.

This is the first comprehensive study to examine the MRI characteristics of uterine leiomyoma disease, and attempt to correlate them with the clinical symptoms of the patients. The only significant MRI-clinical correlations occurred between dysmenorrhea and intramural tumors, degeneration and tumor size, and LA treated patients and patients with no drug treatment. However, it is possible that if future studies were to correlate each clinical symptom with more than one characteristic of the leiomyomas, more statistically significant associations might be found, and we would be closer to understanding the symptomatology of

uterine leiomyomas.

5. FIGURES

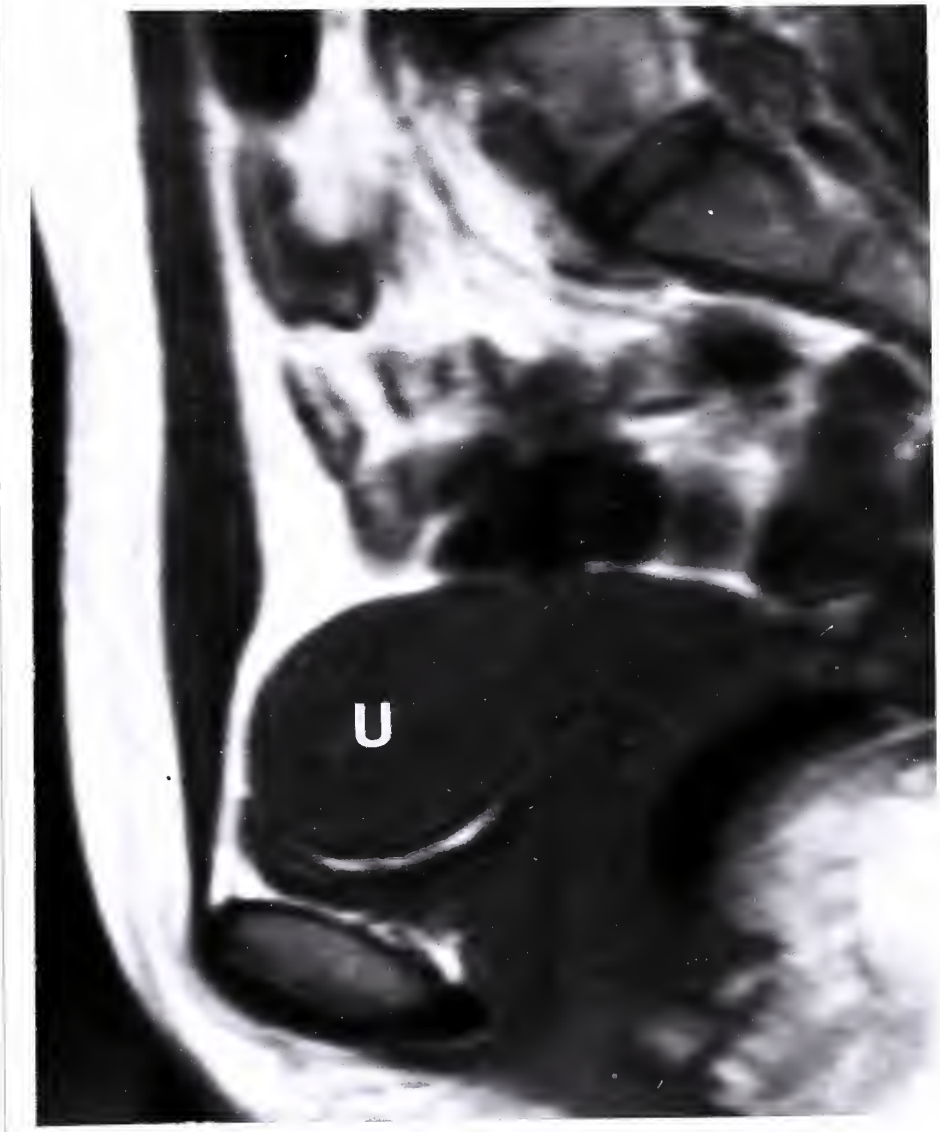

Figure 1a. Sagittal T1 weighted (TR=400, TE=25) images of a normal uterus demonstrating demarcation of the uterus (U) from the surrounding fat. No internal uterine anatomy is seen.

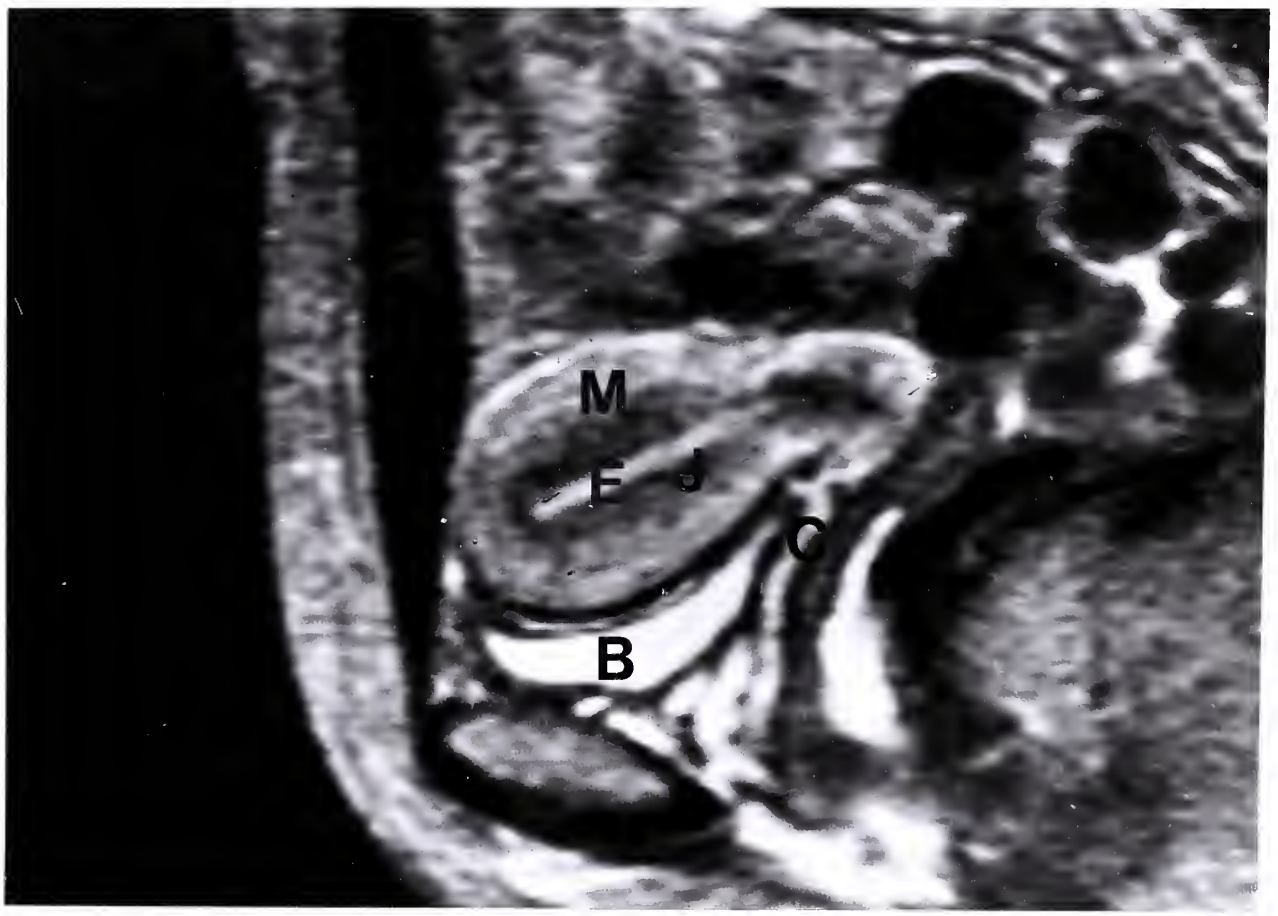

Figure 1b. Sagittal T2 weighted (TR=2000, TE=80) images of the normal uterus in 1a. Note the internal uterine anatomy. Endometrial stripe (E), Junctional zone (J), Myometrium (M), Endocervical canal (C), Bladder (B).

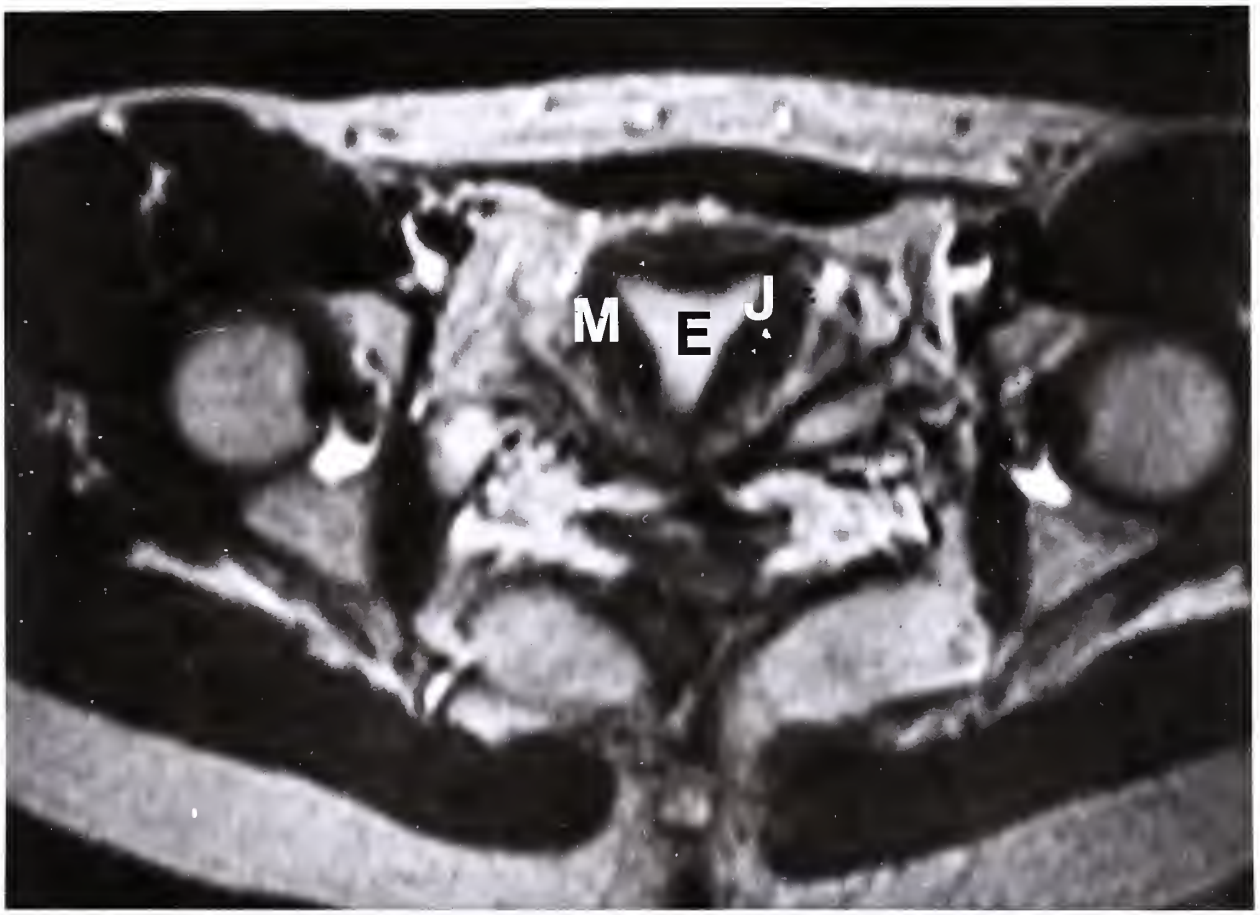

Figure 1c, Transverse T2 weighted (TR=2000, TE=80) images of the normal uterus in 1a. Note the internal uterine anatomy. Endometrial stripe (E), Junctional zone (J), Myometrium (M).

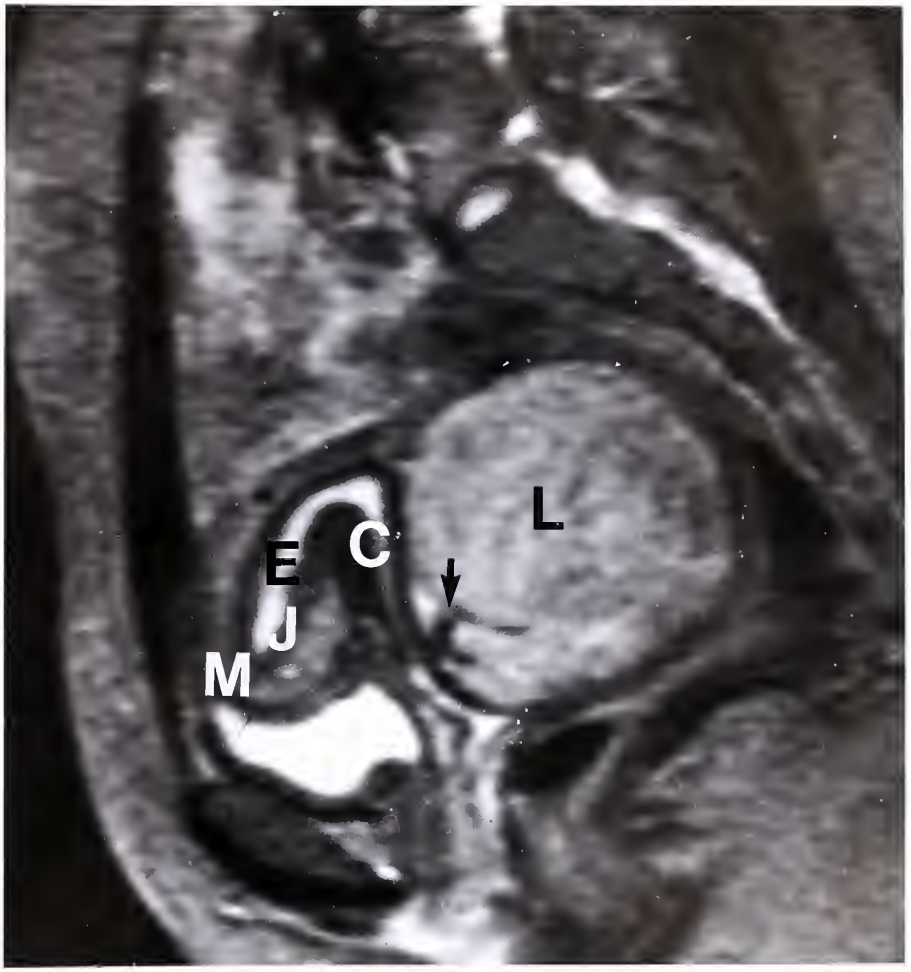

Figure 2. Sagittal T2 weighted (TR=1700. TE=80) image of a subserosal cervical leiomyoma with an increased inhomogeneous internal signal. Endometrial stripe (E), Junctional zone (J), Myometrium (M), Endocervical canal (C), Leiomyoma (L), Feeding vessel (arrow).

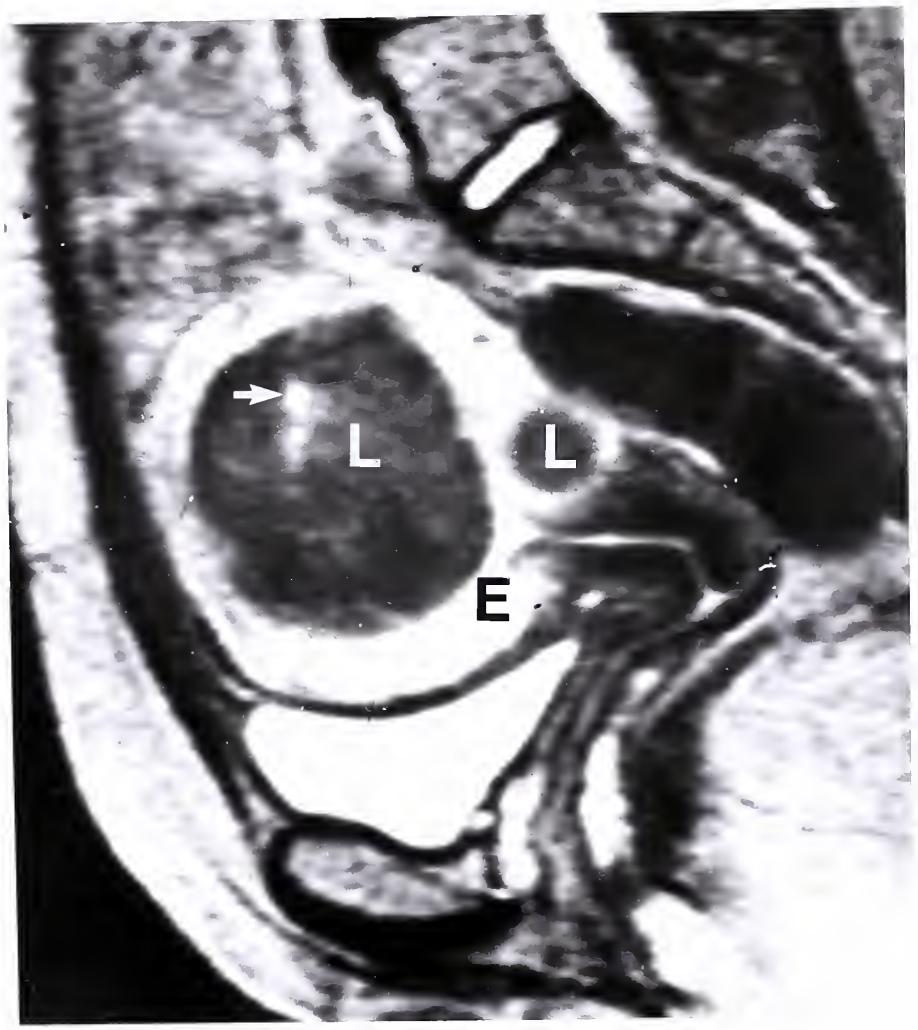

Figure 3. Sagittal T2 (TR=1700, TE=80) weighted image demonstrating splaying of the endometrial stripe (E) by two submucosal leiomyomas (L). Note the increased signal of degenerative change in the larger leiomyoma (arrow).

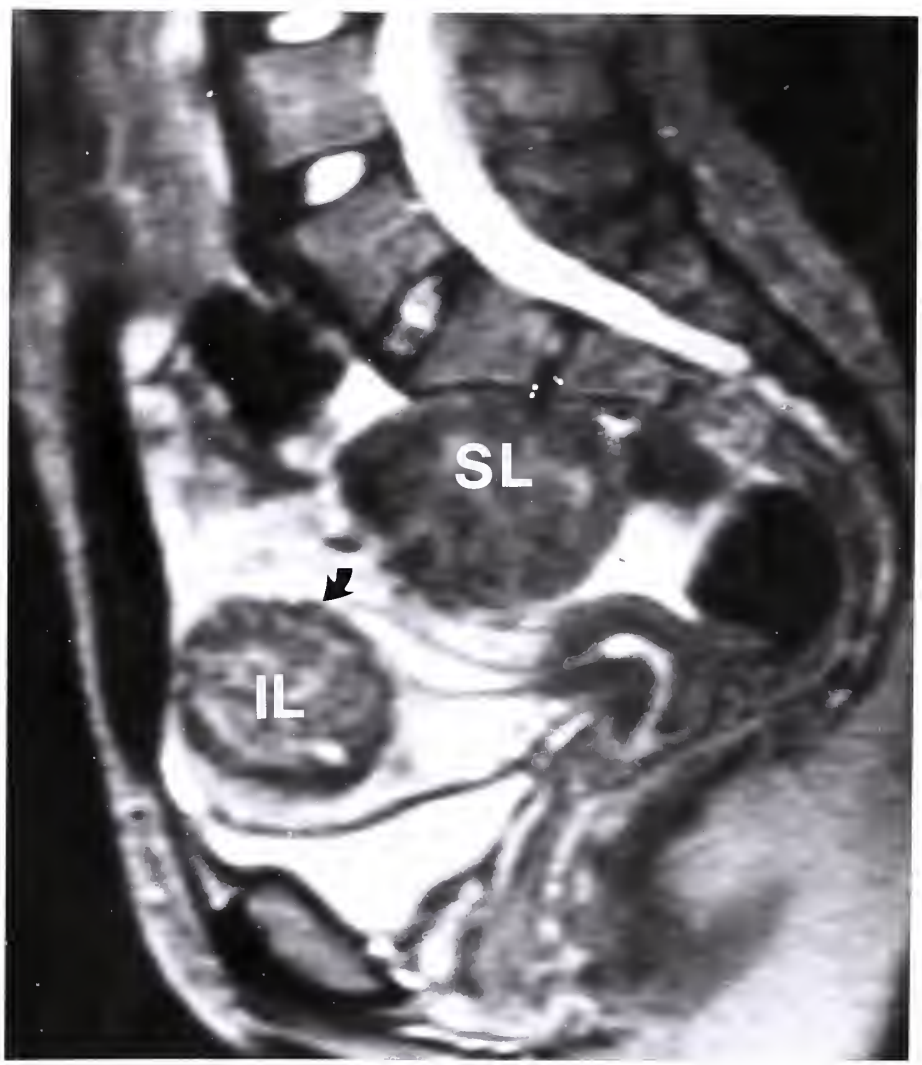

Figure 4. Sagittal T2 weighted (TR= 1800, TE= 80) image demonstrating an intramural leiomyoma (IL) with a submucosal component disrupting the junctional zone (arrow), and a large subserosal leiomyoma (SL). Note the inhomogeneous increased signal in both leiomyomas. Endometrial stripe (E), Junctional zone (J), Myometrium (M).

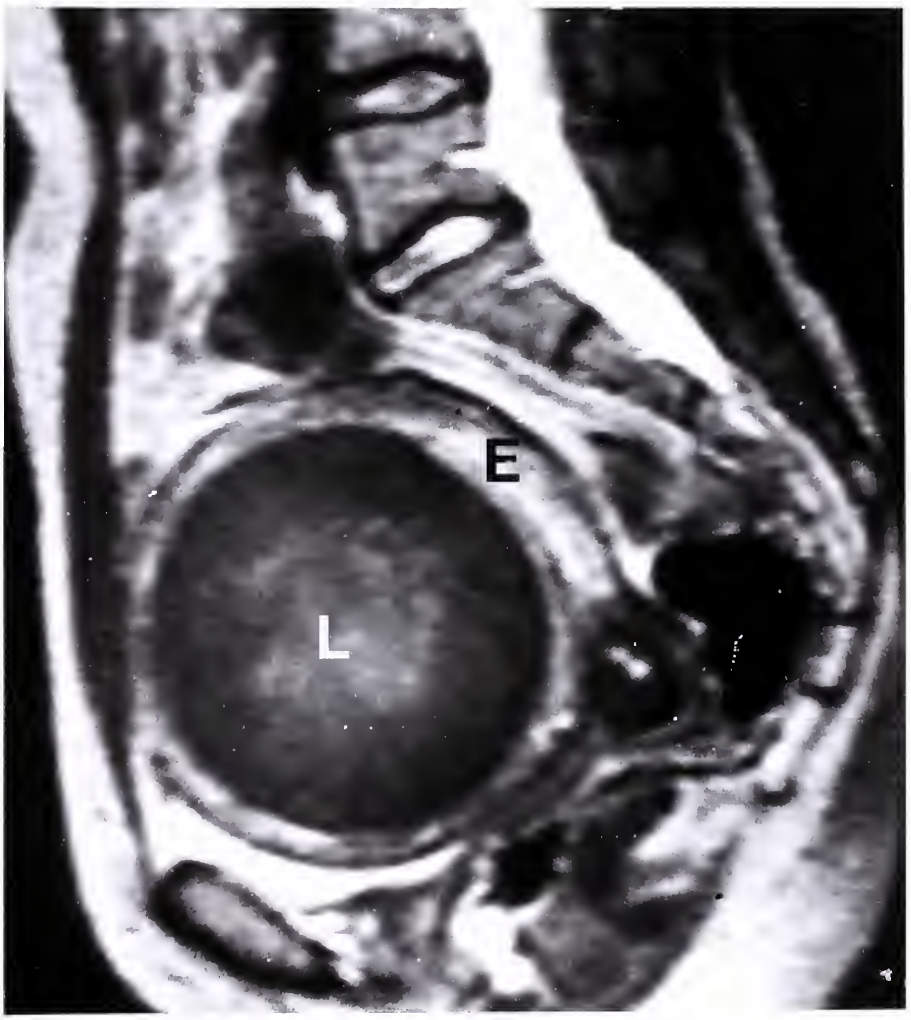

Figure 5. Sagittal T2 weighted (TR=1800, TE=80) image of intramural leiomyoma (L) with inhomogeneous increased signal. Note the displaced uterus and endometrial stripe (E).

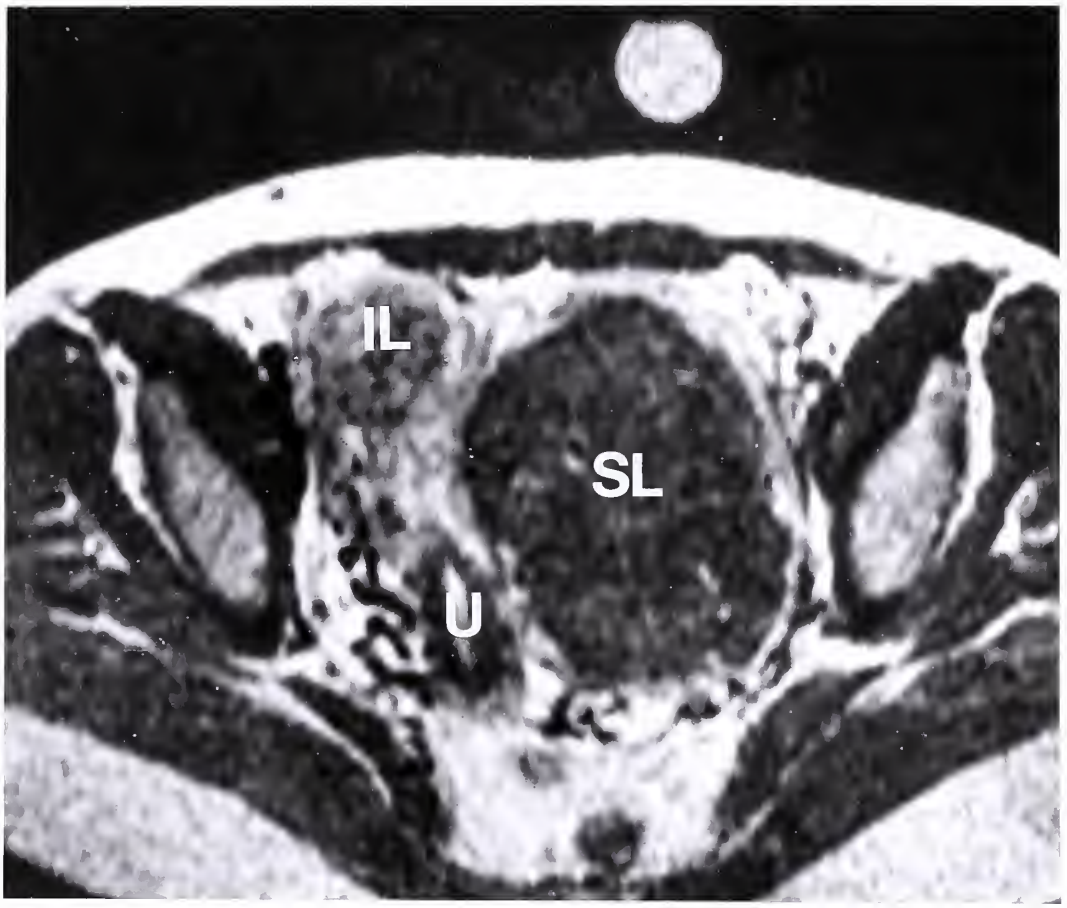

Figure 6. Transverse T2 (TR= 1700, TE= 80) weighted image of a large subserosal leiomyoma (SL) extending into the broad ligament. Note the uterus is displaced to the right (U). Also note the intramural leiomyoma (IL) with increased signal.

6. BIBLIOGRAPHY

1. Andreotti, R. F., Zusmer, N. R., Sheldon, J. J., and Ames, M. Ultrasound and Magnetic Resonance Imaging of Pelvic Masses. Surg. Gynecol. and Obstet. 1988; 166: 327-332.

2. Baeyertz, J, D. Assessment of Gestational Maturity Using a New Fundal Height Measuring Tape. New Zeal. Med. J. 1983; 96: 1059-1060.

3. Baltarowich, O. H., Kurtz, A. B., Pennell, R. G., Needleman, L., Vilaro, M. M., and Goldberg, B. B. Pitfalls in the Sonographic Diagnosis of Uterine Fibroids. AJR 1988; 151: 725-728.

4. Bloch, F., Hansen, W. W., and Packard, M. E. Nuclear Induction. Phys. Rev. 1946; 69: 127.

5. Borgstein, R. L., Shaw, J. J., and Pearson, R. H. Uterine Leiomyomata: Sonographic Mimicry. Br. J. Radiol. 1989; 62 (743): 1019-1021.

6. Bryan, P. J., Butler, H. E., LiPuma, J. P., Haaga, J. A., El Yousef, S. J., Resnick, M. I., Cohen, A. M., Malviya, V. K., Nelson, A. D., Clampitt, M., Alfidi, R. J., Cohen, J., and Morrison, S. C. NMR Scanning of the Pelvis: Initial Experience with a 0.3 T System. AJR December 1983; 141: 1111-1118.

7. Budinger, T. F. Nuclear Magnetic Resonance (NMR) In Vivo Studies: Known Thresholds for Health Effects. J. Comp. Assist. Tomo. December 1981; 5 (6): 800-811.

8. Butler, H., Bryan, P. J., LiPuma, J. P., Cohen, A. M., El Yousef, S., Andriole, J. G., and Lieberman, J. Magnetic Resonance Imaging of the Abnormal Female Pelvis. AJR December 1984; 143: 1259-1266.

9. Buttram, V. C. Jr. and Reiter, R. C. Uterine Leiomyomata: Etiology, Symptomatology, and Management. Fertil. and Steril. October 1981; 36 (4): 433-445.

10. Cohen, M. D., McGuire W., Cory, D. A., and Smith, J. A. MR Appearance of Blood and Blood Products: An in Vitro Study. AJR June 1986; 146: 1293-1297.

11. Comite, F. GnRH Analogs and Safety. Obstet. Gynecol. Surv. 1989; 44: 319-325.

12. Demas, B. E., Hricak, H., and Jaffe, R. B. Uterine MR Imaging: Effects of Hormonal Stimulation. Radiol. 1986; 159: 123-126.

13. Dudiak, C. M., Turner, D. A., Patel, S. K., Archie, J. T., Silver, B., and Norusis, M. Uterine Leiomyomas in the Infertile Patient: Preoperative Localization with MR Imaging versus US and Hysterosalpingography. Radiol. 1988; 167: 627-630.

14. Dwyer, A. J. and Frank, J. A. Basic Concepts of Magnetic Resonance Imaging (MRI). In: Magnetic Resonance of the Reproductive System. 1-21. McCarthy, S., Haseltine, F. (Eds) Slack Inc., Thorofare, 1987.

15. Farber-Brown, G., Beilby, J. O. W., and Tarbit, M. H. The Vascular Patterns in Myomatous Uteri. J. Obstet. Gynaecol. Br. Comm. 1970; 77: 967-975.

16. Farber-Brown, G., Beilby, J. O. W., and Tarbit, M. H. The Venous Changes in the Endometrium of Myomatous Uteri. Obstet. Gynecol. 1971; 38 (5): 743-751.

17. Flickinger, L., D'Ablaing III, G., Mishell Jr, D. R. Size and Weight Determinations of Nongravid Enlarged Uteri. Obstet. Gynecol. 1986; 68 (6): 855-858.

18. Fraser, I. S. Hysteroscopy and Laparoscopy in Women with Menorrhagia. Am. J. Obstet. and Gynecol. May 1990; 162: 1264-1269.

19. Friedman, A. J. Clinical Experience in the Treatment of Fibroids with Leuprolide and Other GnRH Agonists. Obstet. Gynecol. Surv. 1989; 44: 311-313.

20. Friedman, A. J., Rein, M. S., Harrison-Atlas, D., Garfield, J. M., and Doubilet, P. M. A Randomized Placebo-Controlled Double-Blind Study Evaluating Leuprolide Acetate Depot Treatment Before Myomectomy. Fertil. Steril. 1989; 52 (5): 728-733.

21. Friedman, A. J., Hoffman, D. I., Browneller, R. W., and Miller, J. D. Treatment of Leiomyomatous Uteri with Leuprolide Acetate Depot: A Double-Blind, Placebo-Controlled Multicenter Study. In Press.

22. Gross, B. H., Silver, T. M., and Jaffe, M. H. Sonographic Features of Uterine Leiomyomas: Analysis Of 41 Proven Cases. J. Ultrasound Med. 1983; 2: 401-406.

23. Hamlin, D. J., Pettersson, H., Fitzsimmons, J., and Morgan, L. S. MR Imaging of Uterine Leiomyomas and Their Complications. J. Comput. Assist. Tomo. 1985. 9 (5): 902-907.

24. Hricak, H. MRI of the Female Pelvis: A Review. AJR June 1986; 146: 1115-1122.

25. Hricak, H., Alpers, C., Crooks, L. E., and Sheldon, P. E. Magnetic Resonance Imaging of the Female Pelvis: Initial Experience. AJR December 1983; 141: 1119-1128.

26. Hricak, H., Lacey, C., Schriock, E., Fisher, M. R., Amparo, E., Dooms, G., and Jaffe, R. Gynecologic Masses: Value of Magnetic Resonance Imaging. Am. J. Obstet. Gynecol. 1985; 153 (1): 31-37.

27. Hricak, H., Tscholakoff, D., Heinrichs, L., Fisher, M. R., Dooms, G. C., Reinhold, C., and Jaffe, R. B. Uterine Leiomyomas: Correlation of MR, Histopathologic Findings, and Symptoms. Radiol. 1986; 158: 385-391.

28. Janus, C. L., Wiczyk, H. P., and Laufer, N. Magnetic Resonance Imaging of the Menstrual Cycle. Mag. Res. Imag. 1988; 6: 669-674.

29. Lacey, C. G. Benign Disorders of the Uterine Corpus. In: Current Obstetric and Gynecologic Diagnosis and Treatment. 6th Ed. 657-669. Pernoll, M. L., Benson, R. C. (Eds). Appleton and Lange, Norwalk, 1987.

30. Lauterbur, P. C. Image Formation for Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. Nature 1973; 242: 190.

31. Lee, J. K. T., Gersell, D. J., Balfe, D. M., Worthington, J. L., Picus, D., and Gapp, G. The Uterus: In Vitro MR-Anatomic Correlation of Normal and Abnormal Specimens. Radiol. 1985; 157: 175-179.

32. Lev-Toaff, A. S., Coleman, B. G., Arger, P. H., Mintz, M. C., Arenson, R. L., and Toaff, M. E. Leiomyomas in Pregnancy: Sonographic Study. Radiol. 1987; 164: 375-380.

33. Lufkin, R. B. The MRI Manual. Year Book Med. Pub. Inc. 1990.

34. Makow, L. S. Magnetic Resonance Imaging: A Brief Review of Image Contrast. Radiol. Clin. North Amer. 1989; 27 (2): 195-218.

35. Mansfield, P., and Maudsley, A. A. Planar and Line Scan Spin Imaging by NMR. Br. J. Radiol. 1977; 50 (591): 188-194.

36. McCarthy, S. MRI of the Uterus: In: Magnetic Resonance of the Reproductive System. 143-159. McCarthy, S., Haseltine, F. (Eds). Slack Inc., Thorofare, 1987.

37. McCarthy, S. MRI in the Evaluation of Infertile Women. MR Quarterly 1990; 6 (4): 239-249.

38. McCarthy, S. Gynecologic Applications of MRI. Crit. Rev. Diag. Imag. 1990; 31 (2): 263-281.

39. McCarthy, S., Scott, G., Majumdar, S., Shapiro, B., Thompson, S., Lange, R., and Gore, J. Uterine Junctional Zone: MR Study of Water Content and Relaxation Properties. Radiol. 1989; 171: 241-243.

40. McCarthy, S., Tauber, C., and Gore, J. Female Pelvic Anatomy: MR Assessment of Variations during the Menstrual Cycle and with Use of Oral Contraceptives. Radiol. 1986; 160: 119-123.

41. Mendelson, E. B., Bohm-Velez, M., Joseph, N., and Neiman, H. L. Gynecological Imaging: Comparison of Transabdominal and Transvaginal Sonography. Radiol. 1988; 166: 321-324.

42. Merrill, J. A. and Creasman, W. T. Disorders of the Uterine Corpus. In: Danforth's Obstetrics and Gynecology. 6th Ed. 1023-1039. Scott, J. R., DiSaia, P. J., Hammond, C. B., and Spellacy, W. N. (Eds). J. P. Lippincott Co, Philadelphia, 1990.

43. Novak E. R., and Woodruff, J. D. Novak's Gynecologic and Obstetric Pathology With Clinical and Endocrine Relations. 8th Ed. 260-279. W. B. Saunders, Philadelphia, 1979.

44. Odeblad, E., and Lindstrom, G. Some Preliminary Observations On the Proton Magnetic Resonance in Biologic Samples. Acta Radiologica 1955; 43: 469-476.

45. Persaud, V., and Arjoon, P.D. Uterine Leiomyoma. Incidence of Degenerative Change and a Correlation of Associated Symptoms. Obstet. Gynecol. 1970; 35 (3): 432-436.

46. Persson, B. R. R. and Stahlberg, F. Health and Safety of Clinical NMR Examinations. CRC Press, Inc. Boca Raton, 1989.

47. Purcell, E. M., Torrey, H. C., and Pound, R. V. Resonance Absorbtion by Nuclear Magnetic Moments in a Solid. Phys. Rev. 1946; 69: 37.

48. Rein, M. S., Friedman, A. J., Stuart, J. M., MacLaughlin, D. T. Fibroid and Myometrial Steroid Receptors in Women Treated with GnRH agonist Leuprolide Acetate. Fertil. Steril. 1990; 53 (6): 1018-1023.

49. Reid, A., Smith, F. W., and Hutchison, J. M. S. Nuclear Magnetic Resonance Imaging and its Safety Implications: Follow-Up of 181 Patients. Br. J. of Radiol. 1982; 55: 784-786.

50. Robbins, S. L., Cotran, R. S., and Kumar, V. Pathologic Basis Of Disease. 3rd Ed. 1136-1137. W. B. Saunders Co. Philadelphia, 1984.

51. Schlaff, W. D., Zerhouni, E. A., Huth, J. A. M., Chen, J., Damewood, M. D., and Rock, J. A. A Placebo-Controlled Trial of a Depot Gonadotropin-Releasing Hormone Analogue (Leuprolide) in the Treatment of Uterine Leiomyomata. Obstet. Gynecol. 1989; 74 (6): 856-862.

52. Scoutt, L. M., and McCarthy, S. M. Gynecologic Imaging. Postgrad. Radiol. January 1990; 10: 4-24.

53. Seeger, L. L. Physical Principles of Magnetic Resonance Imaging. Clin. Orthop. Relat. Res. July 1989; 244: 7-16.

54. Speroff, L., Glass, R. H., and Kase, N. G. Investigation of the Infertile Couple: In: Clinical Gynecologic Endocrinology and Infertility. 4th Ed. 513-546. Williams and Wilkins, Baltimore. 1989.

55. Swensen, S. J., Keller, P. L., Berquist, T. H., McLeod, R. A., and Stephens, D. H. Magnetic Resonance Imaging of Hemorrhage. AJR November 1985; 145: 921-927.

56. Tamaya, T., Fujimoto, J., and Okada, H. Comparison of Cellular Levels of Steroid Receptors in Uterine Leiomyomata and Myometrium. Acta Obstet. Gynecol. Scand. 1985; 64: 307-309.

57. Togashi, K., Ozasa, H., Konishi, I., Itoh, H., Nishimura, K., Fujisawa, I., Noma, S., Sagoh, T., Minami, S., Yamashita, K., Nakano, Y., Konishi, J., and Mori, T. Enlarged Uterus: Differentiation between Adenomyosis and Leiomyoma with MR Imaging. Radiol. 1989; 171: 531-534.

58. Townsend, D. E., Sparkes, R. S., Baluda, M. C., and McClelland, G. Unicellular Histogenesis of Uterine Leiomyomas as Determined by Electrophoresis of Glucose-6-Dehydrogenase. Am. J. Obstet. Gynecol. 1970; 107: 1168-1173.

59. Weinreb, J. C., Barkoff, N. D., Megibow, A., and Demopoulos, R. The Value of MR Imaging in Distinguishing Leiomyomas from Other Solid Pelvic Masses When Sonography is Indeterminate. AJR February 1990; 154: 295-299.

60. Wilson, E. A., Yang, F., and Rees, E. D. Estradiol and Progesterone Binding in Uterine Leiomyomata and in Normal Uterine Tissues. Obstet. Gynecol. January 1980; 55 (1): 20-24.

61. Zawin, M., McCarthy, S., Scoutt, L., and Comite, F. High-Field MRI and US Evaluation of the Pelvis in Women with Leiomyomas. Mag. Res. Imag. 1990; 8: 371-376.

62. Zawin, M., McCarthy, S., Scoutt, L., Lange, R., Lavy, G., Vulte, J., and Comite, F. Monitoring Therapy with a Gonadotropin - releasing Hormone Analog: Utility of MR Imaging. Radiol. 1990; 175: 503-506.

HARVEY CUSHING / JOHN HAY WHITNEY
MEDICAL LIBRARY

MANUSCRIPT THESES

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

NAME AND ADDRESS DATE