INTRODUCTION

Uterine fibroids, also known as leiomyomas, are the most common pelvic mass found in women. Fibroids are benign tumors that arise from the uterine muscular tissue (myometrium). They occur in 20-50% of women, with increasing incidence as women get older. They are found more commonly, tend to occur at younger age, and present with greater number and size in women of African-American descent compared to Caucasian, Asian and Hispanic women.

Fibroids can be found on the outer surface of the uterus (subserosal), embedded within the myometrial wall (intramural), within the inner cavity of the uterus (submucosal), or a combination of the 3 locations. As will be discussed below, the location of the fibroid is an important determinant of the clinical significance for a particular woman. Their presence can vary in size and number from woman to woman. Oftentimes they are asymptomatic. If symptomatic, the most common problems are excessive or irregular vaginal bleeding, pelvic pain, and pressure on surrounding organs such as the bladder and intestines. The likelihood and severity of the symptoms often, but not always, correlate with an increasing number and size of the tumors. Fibroids re also associated with an increased risk of infertility and miscarriage.

Large fibroids can often be detected on a pelvic exam. Most small or asymptomatic fibroids are typically discovered by pelvic sonography (ultrasound) but this method of imaging is often inadequate to accurately identify the precise location of the fibroids within the uterus. Hysterosalpingography (HSG) can better characterize the uterine cavity, demonstrating a distortion or enlargement caused by fibroids, however HSG does not demonstrate the myometrial component of the mass. HSG's are also used to evaluate the patency of the fallopian tubes. If the fallopian tubes are blocked in the corneal section of the uterine wall (where the tube traverses) in a woman with multiple fibroids, it is likely that the fibroids may be playing a role in the tubal obstruction. The disadvantage of the HSG is the significant false positive and false negative findings, which can occur in up to 50% of studies performed. Sonohysterography (SIS), also referred to as a saline sonogram, is better suited to accurately delineate the location of fibroids. While performing a SIS there is concomitant visualization of the cavity (due to the instillation of saline) and the myometrium, providing a precise determination of both the intracavitary and intramural components of a fibroid. Sonohysterograms, however, will not evaluate tubal patency. Hysteroscopy is considered the "gold standard" to document the presence of a submucous fibroid, but alone it fails to evaluate the remainder of the uterus and the fallopian tubes. Given the strengths and weaknesses of each imaging modality, it is oftentimes necessary to undergo multiple imaging procedures to accurately define the extent of disease and whether or not treatment is necessary.

Given the commonality of fibroids, they will be diagnosed in many women with infertility. Fibroids can be found in 5-10% of infertile and it is estimated that only 1-3% of infertile women have fibroids as the only finding after an extensive evaluation. In most other circumstances, women are found to have other factors that contribute to infertility such as tubal disease, ovulatory dysfunction, advanced maternal age and male

factor. Given the trend to delay childbearing, it is expected that fibroids will be more commonly found among patients presenting for both infertility services and general obstetrical care. Despite the frequent occurrence, the impact of fibroids on a woman's ability to conceive and maintain a pregnancy remains controversial.

Multiple mechanism(s) have been postulated to explain how fibroids may interfere with the establishment or continuation of a pregnancy. One hypothesis includes an interference with normal sperm transport due to changes in the contours of the uterine cavity, contractility of the uterine musculature or obstruction of the fallopian tubes. Another possibility is that fibroids can interfere with the ability of the embryo to implant due to a thinning of the endometrial lining, increased inflammation in the cavity or alterations of the normal and required blood flow to the site of implantation.

An association between fibroids and infertility is often cited. Reports have found a higher incidence of assisted conception treatments (i.e. IVF, IUI, ovulation induction) and the longer period of time to conceive in women who were found to have fibroids in pregnancy compared to those women who had a normal uterus. Numerous authors have reported increased pregnancy rates of 25-70% after surgical removal of fibroids (myomectomy). Interestingly, pregnancy rates after myomectomy in women who had no other associated infertility factor were higher (47-70%) than the pregnancy rates among those women who had other diagnoses that may impair the likelihood of a pregnancy (20-50%). Fibroids have also been associated with a higher likelihood of pregnancy loss. Studies have found higher first trimester pregnancy loss rates in women with fibroids and also a lower miscarriage rate in women after myomectomy.

SUBMUCOSAL FIBROIDS

Submucosal fibroids are those that are found within the uterine cavity. A submucosal fibroid can be entirely within the cavity or it can have both a submucosal and intramural component (partly embedded within the muscular wall of the uterus). Finally, some intramural fibroids may not actually protrude in to the cavity but they may distort the size, location or shape of the cavity. In a review of the literature, 3 papers address the impact of fibroids that distort the cavity.

In an Italian study, they compared the pregnancy and miscarriage rates in infertile women with submucous fibroids who did or did not undergo a myomectomy. After surgery these women were instructed to have timed intercourse and did not receive any fertility enhancing treatments. The pregnancy rate without surgery was 27%, but was increased to 43% after surgery. The miscarriage rate decreased to from 50% before to 38% after surgery. An Australian center compared the clinical pregnancy rates (the presence of a fetal heart beat) in women with submucous, intramural, subserosal, or no fibroids at all in their IVF program. Only 1% of women with the submucous fibroids achieved a pregnancy compared to 16% with intramural fibroids, 34% with subserosal fibroids and 30% without fibroids. Finally, an older paper from Israel reported a substantially lower pregnancy rate and higher miscarriage rate in their IVF program in women with

submucous fibroids. Women with fibroids that caused a distortion of the cavity had a 10% pregnancy rate and 40% miscarriage rate compared to women without fibroids, who had a 25% pregnancy rate and 25% miscarriage rate.

In summary, fibroids that distort the cavity seem to have a profound negative impact on a woman's chance to both conceive and to carry a pregnancy to viability. Given this information, all gynecologists would advise surgery to remove these fibroids when a woman desires pregnancy (if not sooner due to symptoms) and certainly if any assisted reproductive technologies (IVF, IUI, donor egg) are necessary.

INTRAMURAL FIBROIDS

Many studies have tried to evaluate the impact of the intramural fibroids on spontaneous pregnancy rates and after assisted reproductive technologies (ART). Unfortunately the data and results are not nearly as clear-cut or definitive as the case for submucous fibroids.

The largest study conducted compared the IVF pregnancy rates in 112 women with small intramural fibroids ($\leq$ 5 cm) to 322 women who did not have fibroids. There were no differences in these 2 groups of women in regards to infertility diagnosis, years of infertility, amount of medication used or number of eggs retrieved however the women with fibroids were, on average, significantly older (36.4 years) than women without fibroids (34.6 years). The ongoing pregnancy rates were twice as high in the women without fibroids (28%) compared to women with fibroids (15%). The significant difference was maintained even after taking age (greater than or less than 40 years old) and number of embryos transferred into consideration.

In another large study 94 women with intramural fibroids were compared to an equal number of women without fibroids. The women were matched according to age, and the number and quality of embryos transferred. Again, in this trial, all fibroids were 5 cm or less in overall size and did not cause a distortion of the cavity. Both the pregnancy and delivery rates were approximately 30% lower in the women with fibroids. This group also analyzed the miscarriage rate between the 2 groups of women but did not find a significant difference.

Another paper evaluated the pregnancy loss rate and delivery rate in 50 women before and after a myomectomy. Unlike the previously mentioned papers, 40 of these women had "large fibroids", defined as greater than 5 cm in size or that the overall size of the uterus was greater than a 12 week pregnant uterus. Before the surgery 60% of these women had experienced a pregnancy loss (early and late) and 40% had had a successful pregnancy. After the myomectomy, the loss rate was reduced to 24% and the delivery rate had increased to 76%. Although one would assume that the women with the largest fibroids would derive the greatest benefit from the surgery, it is interesting to note that the improvement in the pregnancy and miscarriage rates did not appear to correlate with the size of the fibroids. There were 2 other important findings in this study: women who were less than 36 years old were more likely to conceive (74%) compared to women 36

years and older (30%) and women who did not have a history of infertility were more likely to conceive (76%) than those women who did have a history of infertility (43%).

Despite the results of these 3 papers, there are numerous other studies that completely contradict their findings. A 2007 paper compared 94 egg donor recipients with intramural fibroids that ranged in size from 4-8 cm to 275 recipients without fibroids. The excellent egg quality essentially eliminates any other confounding factor that may skew the overall results of the study. No difference was found in the clinical pregnancy rates between the 2 groups of women. Although the miscarriage rate in the women without fibroids (9%) was half that of women with fibroids (18%), the results were not statistically different. Thus the conclusion of this study is that intramural fibroids did not have a significant impact on the pregnancy or miscarriage rates.

In another IVF study that compared the IVF pregnancy rates in 245 women with and without small intramural fibroids (defined as less than 7 cm), again no difference was found in the pregnancy, delivery, miscarriage and preterm delivery rates. When these investigators evaluated the subgroup of patients with fibroids that were greater than 4 cm in size, they did find a trend toward lower pregnancy rates and higher miscarriage rates.

In summary, management of the intramural fibroid that does not distort the cavity remains inconclusive. Overall there appears to be a slightly greater pregnancy rate and lower miscarriage rate amongst women without fibroids or after myomectomy. There is some data that supports that large fibroids confer a poorer prognosis. Furthermore, other studies note that reproductive potential might be improved after removal of symptomatic fibroids that cause excess bleeding problems. The age of the woman and the presence of other causes of infertility must be taken into consideration when deciding on the benefit of a myomectomy.

SUBSEROSAL FIBROIDS

Subserosal fibroids, without any intramural component, probably have little impact on the reproductive potential of women. Most of the published studies that address subserosal fibroids typically report their findings combined with the outcome of intramural fibroids; hence it is very difficult to discern a precise difference in the clinical implications between the 2 locations. In a study mentioned above (the “Subserosal Fibroid” section), the IVF pregnancy rates were similar in the women with subserosal fibroids compared to those without any fibroids at all. Unless the fibroid is very large, causes symptoms, or is found along with multiple other fibroids, most gynecologists would not advise surgery for subserosal fibroids.

TREATMENT

Medications that decrease estrogen production, such as GnRH agonists (for example, Lupron), lead to a marked shrinkage in the size of uterine fibroids and diminution of symptoms. The effect however is temporary, only lasting while the treatment is being

administered. Upon discontinuation of the medication a prompt re-growth of the fibroids occurs, rendering it an ineffective method of treatment in the infertile population.

Myomectomy, or the surgical removal of fibroids, is the accepted treatment for women with symptomatic fibroids who wish to maintain their ability to conceive. It is well documented that the uterus heals well and can support a pregnancy after a myomectomy. Nevertheless, given the lack of agreement of the reproductive benefits of the removal of intramural fibroids, a thorough evaluation of the goals and risks of surgery is obligatory. One must keep in mind the age of the woman, her previous history of infertility or pregnancy loss, and the symptoms attributable to the fibroids. The known general and myomectomy-specific complications of surgery, such as problems with anesthesia, infection, hemorrhage, post-operative adhesion formation that can lead to tubal disease, and scarring of the uterine cavity, must be considered. If a complete transmural (through-and-through) incision is made during a myomectomy, a Cesarean delivery will be necessary due to the increased risk of uterine rupture in labor. Finally, fibroids can recur in up to 40% of women. This occurs more commonly in women who are afflicted with fibroids at a younger age and in women who develop multiple fibroids.

Today, there are a myriad of surgical approaches that include hysteroscopy, laparoscopy, and abdominal myomectomy. The decision to choose one method over the other depends on the size and location of the fibroid, and the skill and experience of the surgeon.

Fibroids that are entirely submucous, or with a very small intramural component, are best removed vaginally with a hysteroscope. This approach precludes the need for an abdominal incision, and avoids the concerns of both pelvic scar tissue formation and the requirement for Cesarean delivery. Rarely, the submucous fibroid(s) is so large or are so numerous that total resection cannot be safely accomplished in 1 day and must be staged as 2 procedures. To minimize the likelihood of scarring of the uterine lining (endometrium) after a hysteroscopic myomectomy, antibiotics will be given to avoid infection and postoperative estrogen may be prescribed to hasten endometrial regrowth. Occasionally, an intrauterine balloon will be placed in the cavity for 5-7 days to prevent the resected and denuded walls from adhering to each other.

For intramural fibroids, the decision to perform a myomectomy by either laparoscopy or laparotomy (with a bikini-line incision on the abdominal wall) depends on the expertise of the surgeon, as well as the number and size of the fibroids. If multiple incisions on the uterus are required to remove the fibroids or if the fibroid is large, the abdominal approach is preferable.

Myomectomies are well known to be rather “bloody” procedures, especially if multiple fibroids are to be removed. Pre-operative treatment with iron is important to build up one’s blood count. Utilization of the Cell Saver, a device that allows suction and storage of the blood lost during a surgical procedure, can also decrease the need for blood transfusions from an anonymous donor. If an excess amount of blood is lost during the surgery, it can be “transfused” back in to the patient before she leaves the operating room.

Uterine artery embolization (UAE) is new modality of treatment that exists for symptomatic fibroids, generally as a means to avoid hysterectomy. Under X-ray guidance, particles are injected into the uterine arteries to cause a complete obstruction of the blood flow. The lack of oxygen leads to an irreversible necrosis, or death, of the fibroids and results in a decrease in the symptoms and uterine size. The trials that have been conducted utilizing this procedure were not designed to evaluate the effect of UAE on fertility or to compare the efficacy of embolization and myomectomy on the future reproductive potential of these women. In a 2010 review of the literature (Homer & Saridogan, F&S 2010) 227 completed pregnancies after UAE were evaluated for obstetrical complications. Although a large number of the pregnancies were uneventful, there was a 2-3 fold greater incidence of miscarriage, a 2 fold greater likelihood of cesarean delivery, and a 6 fold greater likelihood of postpartum maternal hemorrhage in the women who had undergone a UAE. Furthermore, there is evidence by FSH testing, that ovarian reserve is compromised in all women after UAE. Transient and permanent ovarian failure after UAE, particularly in the older population of women, has also been reported. At this time, the American College of Obstetrics and Gynecology considers the desire for a future pregnancy to be a relative contraindication to UAE.

A new experimental technique, called MRI-guided focused ultrasonic treatment, has been introduced. This procedure destroys fibroids in a nonsurgical manner using the power of sound waves that are directed by MRI localization. Pregnancies after this treatment has been reported, nevertheless until there is greater evaluation and follow-up of this new modality it must be considered experimental and should not be offered to women who wish to maintain their ability to get pregnant, unless they are enrolled in a study protocol.

IN CONCLUSION

Uterine fibroids are an extremely common gynecologic problem. Evidence strongly suggests that submucous fibroids have a deleterious effect on a woman's ability to conceive and carry a successful pregnancy. The role of the intramural fibroids, especially if small, remains controversial. If it is deemed beneficial to remove fibroids to enhance a woman's reproductive potential, myomectomy remains the standard of care. The decision to perform a myomectomy by hysteroscopy, laparoscopy or abdominal laparotomy is determined by the size and location of the fibroids and the experience and expertise of the surgeon. UAE is a newly accepted method to treat symptomatic fibroids, however at this time it should be avoided in women who desire future fertility.