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I declare that work contained herein is my own and that work of others is appropriately acknowledged.
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Abstract

Uterine fibroids are the most common tumour of the reproductive tract in women of reproductive age. Although they are benign tumours that are often asymptomatic, they may cause debilitating symptoms in many women, such as abnormal uterine bleeding, abdominal pain, increased abdominal girth, urinary frequency, constipation, pregnancy loss, dyspareunia, and in some cases infertility.

Several approaches are available for the treatment of uterine fibroids. These include pharmacologic options, such as hormonal therapies and gonadotropin-releasing hormone agonists; surgical approaches, such as hysterectomy, myomectomy; myolysis, laparoscopic uterine artery occlusion, uterine artery embolisation and magnetic resonance imaging-guided focused ultrasound surgery. The choice of approach may be dictated by factors such as the patient’s desire to become pregnant in the future, the importance of uterine preservation, symptom severity, and tumour characteristics. There is however, no widely agreed therapeutic strategy. There is a widespread view that hysterectomy is overused in the UK; the Chief Medical Officer in his annual report ‘On the state of public health’ in 2005, highlighted that hysterectomy in younger women is associated with complications, hospital stays, procedure-related interference with normal life and is costly. In addition he outlined the need to reduce the number of hysterectomies. This, along with the change in cultural attitudes amongst patients, who are becoming increasingly reluctant to undergo these conventional invasive procedures, has increased the need for new treatment options.

Ideally new treatment options for uterine fibroids would be minimally invasive, have long-term data demonstrating efficacy and safety, have minimal or no incidence of fibroid recurrence, be easy to perform, preserve fertility, and be cost effective. New treatment approaches are under investigation, with the goals of being effective, safe, and less invasive.
MRgFUS is a non-invasive thermo-ablative hybrid technique which uses both MR and ultrasound to destroy tumours. It is an outpatient procedure, which avoids the need for an anaesthetic, has a short recovery period, and is uterine sparing.

The main objective of this work was to set out the rationale for using Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) for the treatment of uterine fibroids. In order to achieve this aim, four main bodies of work are necessary;

1) Identifying patient selection criteria and investigating mitigating techniques to increase the pool of women for whom this treatment can be offered.
2) Investigating a method designed to overcome the problem of safely treating women with abdominal scars for whom this treatment can cause potential morbidity.
3) Investigating the potentiality of using MRgFUS to prolong the tumour shrinkage effect of GnRH analogue injections.
4) Investigating the safety of MRgFUS in treating symptomatic women who wish to preserve fertility.

Results: the first aim of this project was to identify patient selection criteria and to investigate methods to widen the selection criteria. In our retrospective review it was found that 74% of women presenting were deemed technically suitable to proceed with treatment and several mitigating techniques that solved current technical difficulties were identified and allowed for less restrictive MRgFUS selection criteria for treatment of symptomatic uterine fibroids. These less restrictive criteria are expected to expand the pool of patients for whom MRgFUS is a viable treatment option for uterine fibroid symptoms.

The second aim was to identify a method of overcoming the problem of treating women with previous abdominal scars safely. We identified a unique method of highlighting the scar by painting it with a paramagnetic iron oxide material which clearly outlined the scar on MR scanning allowing complete avoidance of the scar using MR guidance. In this small pilot study, all women were treated safely with no skin burns.
The third aim of this project looked at the potentiality of prolonging the shrinkage effect of GnRH analogues by following a course of 3 injections with MRgFUS treatment. In this prospective study of fifty women, there was a 50% reduction in the mean symptoms severity score at 6 months which was maintained for 24 months post treatment. There was an average reduction in target fibroid volume which was maintained for 24 months.

The final aim of the project was to investigate the safety of using MRgFUS as a treatment option for those women who wished to preserve their fertility. In this multicentre international study, One hundred and sixteen women were recruited from five centres. There were sixty four reported pregnancies in Sixty one women, with 30 completed deliveries. There were no reported cases of uterine rupture, premature labour, abnormal placentation or placental abruption.

Conclusion: There is a growing body of data from clinical trials and more than four years of clinical experience to validate the safety and efficacy of MRgFUS for the treatment of uterine fibroids. MRgFUS is a totally non-invasive outpatient procedure that is not associated with the typical surgical risks of bleeding, infection and has minimal recovery time. Additionally, the procedure allows women to address their symptoms whilst preserving the uterus. Consequently, MRgFUS is an alternative treatment option for suitable patients who have refused other interventions due to concerns about lost productivity, risks of surgical complications or future fertility.
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CTG</td>
<td>Cardiotocograph</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FUS</td>
<td>Focused ultrasound Surgery</td>
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<td>GE</td>
<td>General Electric</td>
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<td>GnRHa</td>
<td>Gonadotrophin releasing hormone Analogue</td>
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<tr>
<td>IUD</td>
<td>Intra-uterine Device</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LEDR</td>
<td>Low Energy Density Region</td>
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<td>MOQ</td>
<td>Menorrhagia Outcome Questionnaire</td>
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<td>MRgFUS</td>
<td>Magnetic Resonance guided Focused Ultrasound Surgery</td>
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<td>MR</td>
<td>Magnetic Resonance</td>
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<td>MRI</td>
<td>Magnetic Resonance Image</td>
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<tr>
<td>NPV</td>
<td>Non Perfused Volume</td>
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<tr>
<td>PRF</td>
<td>Proton Resonance Frequency</td>
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<td>Abbreviation</td>
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<tr>
<td>SSS</td>
<td>Symptom Severity Score</td>
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<td>TAH</td>
<td>Total Abdominal Hysterectomy</td>
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<td>T1W</td>
<td>T1 Weighted</td>
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<td>T2W</td>
<td>T2 Weighted</td>
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<td>UAE</td>
<td>Uterine Artery Embolisation</td>
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<td>UF</td>
<td>Uterine Fibroid</td>
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<td>UFS-QOL</td>
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CHAPTER 1.1: UTERINE FIBROIDS
1.1.1 Definition and Introduction

Uterine leiomyomata are the most frequent myometrial disorders and the most common pelvic tumour in women. Although they are commonly referred to as fibroids, the tumour consists of uterine smooth-muscle tissue and is encased in fibrous extracellular matrix (Stewart 2001). In some cases, fibroids appear to originate from smooth-muscle cells of the uterine blood vessels (Cramer and Patel 1990).

Macroscopically, these clonal tumors are firm, round, or oval-shaped. Microscopically, they are composed of smooth-muscle bundles in a whirl-like pattern, well circumscribed but not encapsulated. Of importance in therapy, they are often highly vascular. They can be singular, but generally, there are multiple fibroids in the same uterus varying in dimensions and location.

A common misconception is that of malignant transformation of fibroids. Sarcomas are almost certainly not the result of malignant transformation of myomas. Levy et al in their article on cytogenetic analysis state that myomas and leiomyosarcomas have different chromosomal abnormalities, and that transformation from myoma to leiomyosarcoma has never been confirmed (Levy, Mukherjee et al. 2000).

Eighty percent of women have myomas found at hysterectomy, so it is not surprising that a sarcoma arises in a uterus with myomas coincidentally present. A study by Parker et al identified only 1 out of 371 women admitted with rapidly growing myomas had a sarcoma, confirming this as an exceedingly rare association (Parker, Fu et al. 1994).
1.1.2 Incidence and Risk factors

The prevalence of clinically significant fibroids peaks toward the end of a woman’s reproductive cycle, in her peri-menopausal years, and declines after menopause (Flake, Andersen et al. 2003). Although most women with uterine fibroids do not seek therapy, 20% to 25% of women in the reproductive age do have sufficiently significant symptoms caused by fibroids to cause her to seek and warrant (Buttram and Reiter 1981). Genetic predisposition seems to contribute. Fibroids are particularly common in Afro-Caribbean populations with a three-fold increase in incidence compared to Caucasian populations. Also, the clinical disease of these women is more severe (Kjerulff, Langenberg et al. 1996).

Although uterine leiomyomata affect the reproductive health and well-being of approximately 25% of premenopausal women, risk factors are poorly understood. Elevated adult body mass index is associated with a modest increased risk of uterine leiomyomata among premenopausal women (Luoto, Kaprio et al. 2000), as is a familial tendency to develop fibroids. Parity reduces risk, and the risk reduces with the number of births (Lethaby and Vollenhoven 2002). Dietary associations with fibroids have been investigated and the presence of fibroids is associated with beef and ham consumption, whereas high intake of green vegetables seems to have a protective effect (Chiaffarino, Parazzini et al. 1999).

Elevated diastolic blood pressure may increase fibroid risk through uterine smooth muscle injury, not unlike atherosclerosis. Boynton-Jarret et al prospectively examined the relation between diastolic blood pressure and incidence of clinically detected leiomyomata. The sample included 104,233 premenopausal nurses from 14 US states enrolled in the Nurses’ Health Study II. Participants, aged 25–42 years, had intact uteri and no history of cancer or fibroids at enrolment in 1989. During the 827,348 woman-years of follow-up (1989–1999), 7,466 incident diagnoses of uterine leiomyomata confirmed by ultrasound or hysterectomy, were reported. With adjustment for age, ethnicity, body mass index, and reproductive history, it was concluded that elevated blood pressure has an independent, positive

Several correlative risk factors were derived from the Black Women’s Health Study, a U.S. prospective cohort study of black women who completed biannual mailed health questionnaires. From 1997 through 2001, 21,506 premenopausal women with intact uteri and no prior diagnosis of uterine leiomyomata were followed. It concluded that BMI and weight gain exhibited a complex relation with risk of uterine leiomyomata in the Black Women’s Health Study. The association with BMI was an inverse J-shaped curve and findings were stronger in parous women. Weight gain was positively associated with risk among parous women only (Wise, Palmer et al. 2005).

In US black women, risk of uterine leiomyomata was positively associated with current consumption of alcohol, particularly beer. Cigarette smoking and caffeine consumption were unrelated to risk overall. During 76,711 person years of follow-up, 2,279 new cases of ultrasound- or hysterectomy-confirmed uterine leiomyomata were self-reported. After adjustment for age, body mass index, smoking, alcohol intake, and other reproductive covariates, the risk of ultrasound- or hysterectomy-confirmed leiomyomata was inversely associated with age at menarche, parity, and age at first birth and positively associated with years since last birth. Overweight or obesity appeared to attenuate the inverse association between parity and uterine leiomyomata (Wise, Palmer et al. 2004).

Current use of progestin-only injectables was inversely associated with risk. No consistent patterns were observed for other forms of hormonal contraception. Reproductive history is an important determinant of leiomyomata risk in premenopausal US Black women. Progestin-only injectables may reduce risk (Wise, Palmer et al. 2004).

Fibroids decrease in size during menopause and under other hypo-oestrogenic conditions and also after down-regulation treatment with gonadotrophin-releasing hormone (GnRH) agonists (West, Lumsden et al. 1992). This supports the fact
that fibroids are steroid-dependant tumours. Although oestrogen has been implicated as the important hormone, evidence has been found to show that progesterone also plays a role in the growth of fibroids. It is controversial whether oestrogen or progesterone is the more important influence (Sankaran and Manyonda 2008).

1.1.3 Classification

Fibroids are classified by their location (see figure 1), which affects the symptoms they may cause and how they can be treated. Leiomyomas may be subserosal, submucosal, or intramural; however, most fibroids are combinations. Subserosal fibroids are on the external surface of the uterus, the uterine serosa and can be sessile or pedunculated. This type of fibroid is the easiest to remove by laparoscopy. Submucous myomas are in the inner aspect of the myometrium, immediately below the endometrium. These fibroids often pouch into the endometrial cavity and can be removed by hysteroscopic resection. Intramural leiomyomas predominantly occur within the thick myometrial layer of the uterus. They may distort the uterine cavity or cause an irregular external uterine contour. Many of these do not cause symptoms unless they become quite large. (See figure 2)
Chapter 1 fig. 1. An artistic impression of the uterus showing the various classifications of fibroids.
Chapter 1 fig. 2. A T2 weighted coronal image of a massive fibroid clearly causing compression of retro-peritoneal structures (source: St Mary’s Radiology department).
1.1.4 Symptoms

Fibroids can present with a variety of symptoms depending on their size, location, and the reproductive status of the woman. Uterine fibroids can cause abnormal uterine bleeding, pain and pelvic pressure symptoms (Buttram and Reiter 1981). The impact of uterine leiomyomata on reproduction is more controversial and will be discussed further in this thesis, however it will be addressed here briefly for completeness.

Bleeding

The most common kind of abnormal bleeding associated with leiomyomas is menorrhagia or hypermenorrhoea, prolonged or excessively heavy menstruation i.e. an increase in the amount of blood loss per month (Stewart 2001). The heavy bleeding frequently results in iron deficiency anaemia, and the frequent change of tampons or pads may cause a significant disruption to daily activities, social isolation and loss of productive time (Parker 2007)

The exact mechanism by which fibroids cause abnormal bleeding is unknown, however some theories include:

- Increased endometrial surface area (Stovall 2001)
- Increased vascularity of the uterus
- Interference with normal uterine contractility
- Endometrial ulceration over submucous leiomyomas, which could also cause inter-menstrual bleeding and
- Compression of the venous plexus within the myometrium, leading to endometrial venule ectasia which results in the congestion of myometrium and endometrium leading to profuse menstrual bleeding (Farrer-Brown, Beilby et al. 1971)

It must be remembered however that women presenting with menorrhagia must be investigated fully to exclude other endometrial pathologies, as this symptom is not specific to myomas.
Pelvic pressure

Pelvic pressure is due to mass effects from the fibroid and enlargement of the uterus. The pelvic and abdominal discomfort is analogous often to the discomfort women experience during pregnancy. These symptoms develop insidiously and are often attributed to simply putting on weight, especially if there are no associated changes in menstrual pattern. The location of pressure is related to the location of the fibroids, thus as the tumour grows neighbouring structures can be compressed by the fibroid and this may lead to difficulty with urination when there is an anterior fibroid or problems with defecation and dyspareunia when there is a posterior wall fibroid.

Reproductive dysfunction

It is estimated that approximately 30% of women have a fibroid(s) by the age of 30 years and is the current trend in developed countries, women are looking to start their family in their 30s or later; as such fibroids are frequently found in association with pregnancy (Bukulmez and Doody 2006). The vast majority of women have successful pregnancies, it is therefore reasonable to suggest that the majority of fibroids do not have an adverse effect on pregnancy. While this is likely to be the case, depending on their size, number and location, fibroids may result in a distortion of uterine anatomy, thereby interfering with normal uterine physiology. It is therefore logical to say that in some cases, fibroids could indeed have an adverse effect on reproductive function. It has been suggested that this could include sub-fertility, miscarriage and later pregnancy complications, including pain (red degeneration), premature rupture of membranes, pre-term labour, placental abruption, mal-presentations, unstable lie and increased operative deliveries.

Acute pain

Acute pain is rare, but can occur in situations where there is degeneration of the fibroid due to an insufficient blood supply; so called red degeneration, which occurs during a pregnancy. Uterine myomas as large as 100 lbs have been reported. These large myomas may outgrow their blood supply, leading to ischaemia and necrosis within the tumour. This degeneration is usually associated
with severe acute pain which may necessitate surgical exploration (Bukulmez and Doody 2006). Such large myomas can also be expected to cause respiratory compromise (Stovall 2001). Acute pain may also be due to torsion of a pedunculated fibroid or to cervical dilatation where a submucous fibroid extrudes through the uterus. Pain can also occur when the uterus with the fibroid becomes incarcerated within the pelvis (Phelan 1995). Rarely, myomas in the broad ligament may cause unilateral lower abdominal pain or sciatic nerve pain (Stovall 2001). Another rare cause of acute pain and collapse can be caused by the spontaneous rupture of a superficial fibroid vessel, leading to a surgical emergency. There are however, only approximately twenty such reported cases in the literature (Sehgal and Haskins 1960).

It is important to emphasise, however, that pain is not a common presenting feature of fibroids, and as such other pathologies such as ectopic pregnancy, rupture/torsion of an ovarian cyst must be considered in any women with identifiable myomas who experiences acute abdominal pain.

### 1.1.5 Diagnosis

Suspicion of a diagnosis of fibroid is made when a patient presents with a gradual increase in the size of their abdomen, heavy but regular periods and a negative pregnancy test. Other causes for an increased abdominal girth include; adenomyosis, ovarian cysts/ovarian neoplasms or non-gynaecological causes. It is difficult to differentiate between these simply on abdominal palpation, and an ultrasound (usually transvaginally) can confirm the diagnosis and exclude other conditions (see figure 3). Unfortunately although very sensitive for the detection of bulky enlarged uteri, ultrasound is not very specific for the diagnosis or precise location of fibroids.
Chapter 1 fig.3. An ultrasound image of a fibroid. Although sensitive for detection of masses, ultrasound is not very specific for the diagnosis (source St Mary’s Radiology department archives)

Magnetic Resonance Imaging (MRI) has gained widespread use and popularity for use in pelvic imaging and in gynaecology. It is non-invasive and safe, with no radiation effects, especially important for younger women. The multi-planar sequences allow differentiation of the substructure of the uterus, cervix, vagina and ovaries (see figure 4).
Chapter 1 fig.4. MRI of normal uterus. The uterus is anteverted (1) the endometrial cavity (2), cervix (3) and vagina (4) are all clearly seen (source St Mary's radiology department archives).

It allows the radiologist to differentiate uterine anatomy and reliably localises, with precision, pelvic pathology. The routine use of both T1 and T2–weighted (T1W and T2W) sequences, before and after the injection of i.v gadolinium, allows for optimization of the inherent tissue contrast available with MRI. It is uniquely able to characterise soft tissues with these sequences and can provide precise diagnoses for many forms of abnormalities.

This has special advantages for imaging of fibroids. The first and foremost one is to confirm the diagnosis. There are many different types of fibroids, clinically and pathologically, with a broad range of features and so not surprisingly, there are variations in their location and appearance on MRI (see figure 5).
Chapter 1 fig.5. MRI of pelvis showing enlarged uterus with multiple fibroids, intra-mural (1), sub-serosal (2) and pedunculated(3) types. (source: St Mary's radiology department).

Magnetic Resonance (MR) allows characterisation of the fibroids; with accurate size and volume measurement, the tissue can also be characterised into hyper-intense or hypo-intense when compared to the myometrium, this gives an indication as to how vascular the fibroid is (see figure 6).
Chapter 1 fig.6. A T2 weighted sagittal image showing a large hyper-intense anterior wall intramural fibroid (Source: St Mary's Radiology department).

By using i.v. contrast, the perfusion and therefore presence of necrosis and degeneration can be determined (See figure 7).
Chapter 1 fig.7. A T2 weighted sagittal image of the treated fibroid on the left. An IV contrast enhanced image of the same fibroid on the right showing non-perfusion (outlined in red) hence necrosis of the treated fibroid. (Source: St Mary’s radiology department).

The ability to classify tissue on MRI is based upon a multi-parametric analysis of all the sequences with T1, T2, T1 fat-suppressed, and i.v. contrast-enhanced sequences all playing critical roles. The T2W images first allow location and diagnosis of fibroids as described above. The MR signal on any of the sequences can be iso-intense and higher or lower than skeletal muscle. IV contrast can determine the solid or cystic/necrotic nature of the tissue and if done in rapid bolus fashion can help with perfusion analysis. The gradient echo technique used for gadolinium imaging can also be used to detect fat or calcium. The ‘classic’ fibroid is a well-circumscribed mass with low signal intensity on all pulse sequences. On T2W MRI exams, uterine fibroids are usually easily identifiable. Adenomyosis may give a very similar appearance on MR, however the mass is usually less defined and more diffuse (See image 8).
Chapter 1 fig. 8. Sagittal MR image of a uterus with extensive adenomyosis. A gynaecological condition which is often misdiagnosed as uterine fibroids on ultrasound scan. The superior imaging capacity of MR allows for easy differentiation. (Courtesy of www.ufeinfo.com).
1.1.6 Treatment

Uterine myomas can generally be managed expectantly unless they cause symptoms. Several approaches are available for the management of symptomatic tumours. The approach will be dictated by factors such as the patient’s desire to become pregnant in the future, the importance of uterine preservation, symptom severity, and tumour characteristics.

Pharmacological options

At present, pharmacological therapies are only used for short-term therapy because of the significant risks with long-term therapy, or lack of evidence regarding the benefits and risks of long-term therapy with the newer medical agents. A number of options are available, including hormonal therapies, such as gonadotrophin-releasing hormone analogues (GnRHα) agonists/antagonists, aromatase inhibitors selective oestrogen receptor modulators (SERM), anti-progestins (mifipristone and asnoprisnil) and cabergoline. The combined oral contraceptive and progestins are used to manage bleeding but no evidence supports their efficacy in actually influencing myoma size.

GnRH analogues

First synthesised in the 1970s, GnRHa has been used extensively in clinical medicine, there are over 2000 analogues with both antagonistic and agonistic properties. Used in the treatment of hormone dependent tumours in other clinical areas such as for prostatic cancer, in gynaecological practice they are used for a variety of conditions such as endometriosis, hirsuitism, dysfunctional uterine bleeding, premenstrual syndrome, assisted reproduction and fibroids. They were first used for uterine fibroids in the late 1980s. GnRHa undoubtedly induce fibroid tumour shrinkage, the degree of which has been shown to be inversely proportional to the percentage of cells that are oestrogen positive, thus implicating oestrogen as a major effector of tumour growth and its reduction as the central mechanism of fibroid shrinkage with GnRHa therapy. Continuous administration of a GnRH agonist acts to produce hypo-menorrhoea or amenorrhoea and can
reduce the size of myomas (Chillik and Acosta 2001). Currently limitations are placed on duration of use due to risk of significant bone loss from the profound oestrogen deficiency created (Chavez and Stewart 2001). Co-administration with agents such as oestradiol, norethindrone, raloxifene, and tibolone appears to prevent GnRH agonist related bone loss in pre-menopausal women with uterine fibroids (Palomba, Orio et al. 2002). Calcified fibroids appear to be resistant to therapy with GnRH agonists (Chavez and Stewart 2001).

**Selective oestrogen receptor modulators**

Best known for their use in the treatment of oestrogen receptor positive breast cancer, SERMs are non-steroidal oestrogen receptor ligands that act as oestrogens in some tissues while blocking oestrogen action in others. Any molecule that blocks oestrogen activity has the potential for therapeutic activity against fibroids, since oestrogen is known to influence fibroid growth. SERMs are therefore within this category of molecule. A 60 mg daily dose of Raloxifene has been shown to reduce fibroid volume for up to one year, but only in post-menopausal women (Palomba, Sammartino et al. 2001). Pre-menopausal women given the same treatment did not respond even when higher doses (180 mg/day) of raloxifene were used (Palomba, Orio et al. 2002). The explanation may simply be that raloxifene is able to counteract the low concentrations of background oestradiol seen in post-menopausal women (Marsh and Bulun 2006). Side effects of raloxifene include; hot flushes, increased appetite, weight gain, gastralgia, dry skin and venous thrombo-embolism (Jirecek, Lee et al. 2004).

**Aromatase inhibitors**

Aromatase inhibitors markedly suppress plasma oestrogen levels in postmenopausal women by inhibiting or inactivating aromatase, the enzyme which catalyses the synthesis of oestrogens from androgenic substances such as androstenedione (Smith and Dowsett 2003). Leiomyoma cells and subcutaneous fat cells express aromatase, and are therefore able to synthesise oestrogen. This observation may explain why fibroids do not always regress in post-menopausal women, and also suggests a possible therapeutic role for aromatase inhibitors in the treatment of symptomatic fibroids in premenopausal and menopausal women.
(Shozu, Murakami et al. 2004). To date, the use of aromatase inhibitors for the treatment of fibroid disease is confined to case reports. Kanuitz described the successful use of Anastrozole, a third-generation non-steroidal aromatase inhibitor, in treating uterine bleeding associated with fibroids in an obese post-menopausal woman (Kaunitz 2007). Anastrozole use was associated with a reduction in the size of the woman’s dominant fibroid, thinning of her endometrium and cessation of bleeding. Japanese investigators have reported the successful use of an aromatase inhibitor, Fadrozole, in reducing the dimensions of a fibroid tumour causing urinary retention in a peri-menopausal woman. They reported a 71% reduction in fibroid volume in 8 weeks (Shozu, Murakami et al. 2003).

**Anti-progesterones**

**Mifipristone**
The use of Mifipristone 5 or 10 mg/day for six months was shown in a study of 40 symptomatic pre-menopausal women to reduce mean uterine volume by almost one half. Mean menstrual blood loss indices decreased significantly with both doses from baseline to the end of the study. Some of the side effects associated with mifipristone include hot flushes, headache, nausea, decreased libido and mood swings. In addition although no atypical hyperplasia was noted, simple endometrial hyperplasia occurred in over a quarter of subjects and hepatic enzymes were elevated in 8% (Fiscella, Eisinger et al. 2006).

**Asoprisnil (selective progesterone receptor modulator)**
Asoprisinil was shown in vitro in uterine leiomyoma cells to down regulate the expression of several growth factors (and their receptors) and is thought to have a role in the pathogenesis of uterine fibroids (Wang, Ohara et al. 2006). In vitro comparisons of its effects on uterine leiomyoma cells and normal myometrial cells demonstrated that asoprisnil inhibited proliferation, activated the tumour necrosis factor-related apoptosis-inducing ligand mediated signalling pathways, and induced apoptosis in leiomyoma cells but not normal myometrial cells, suggesting direct targeting of leiomyoma cells (Chen, Ohara et al. 2006) (Sasaki, Ohara et al. 2007). Although still investigational, preliminary studies have
demonstrated dose–dependent suppression of the duration and intensity of uterine bleeding and dose-dependent induction of amenorrhoea. Adverse effects include, bloating, flatulence, breast pain and vasomotor symptoms including hot flushes and night sweats. (Chwalisz, Larsen et al. 2007).

**Cabergoline**

Cabergoline a lysergic acid derivative is a dopamine agonist which is used widely in the treatment of prolactinoma and to inhibit lactation. The theoretical basis for its use in myoma treatment lies in its inhibitory effect on the secretion of GnRH. Only one study, has compared the effects of GnRHα with cabergoline. This study found significant fibroid regression with both treatments. The extent of tumour regression correlated positively with the number of tumour nodules. Cabergoline was well tolerated and had fewer adverse effects compared with GnRHα (Melli, Farzadi et al. 2007).

**Surgical therapy**

**Hysterectomy** can be used to treat all types of fibroids and is considered the ‘gold-standard’ treatment for uterine fibroids. By removing the fibroids along with their site of origin, this eliminates the existing pathology and the potential for new fibroids to develop. Uterine fibroids are the leading indication for hysterectomy and hysterectomy has been associated with a patient satisfaction rate of over 90% (Farquhar, Harvey et al. 2006). However, hysterectomy may not be an appropriate treatment solution for those women still wishing to conceive; therefore, other methods have evolved with the goal of sparing the uterus and reducing morbidity. Although hysterectomy is the definitive treatment for fibroids, it results in a permanent loss of fertility and requires major surgery under general anaesthesia. In one recent study, as many as 43% of women who underwent hysterectomy expressed regret about their loss of fertility (Farquhar, Harvey et al. 2006). Reported complication rates vary from as low as 1.5% to as high as 29.3% (Meyers and Steege 1998). Risks include; surgical morbidity/mortality such as blood loss, bowel injury, bladder and urethral injury, infection, post-operative pain, and death (Farquhar, Harvey et al. 2006). Typical recovery times for hysterectomy are approximately 6-8 weeks.
**Myomectomy**, which like hysterectomy has been available for over 150 years, is the surgical removal of the fibroids alone and thus preserves fertility. Myomectomy can be performed via hysteroscopy, laparoscopy or via laparotomy. Laparotomy or abdominal myomectomy, is useful for treating subserosal or intramural fibroids (Bernard, Darai et al. 2000), while the hysteroscopic route is more appropriate for submucosal fibroids (Wallach and Vlahos 2004). Laparoscopic myomectomy is useful for treating easily accessible tumours, such as superficial or pedunculated subserosal fibroids (Wallach and Vlahos 2004), a prolapsed submucous myoma may also be resected transvaginally. Comparison of outcomes after myomectomy performed by laparotomy or laparoscopy in infertile patients revealed that laparoscopic myomectomy was superior in terms of febrile morbidity, haemoglobin levels, blood transfusion requirements and post-operative hospital stay. However, no differences in post-surgery pregnancy rate, abortion rate, pre-term delivery rate or caesarean section rate were seen (Seracchioli, Rossi et al. 2000). Myomectomy can be difficult in women with large, multiple myomas, or in those who have previously undergone multiple myomectomies; in these cases, hysterectomy may be preferable (Wallach and Vlahos 2004). Surgeons with adequate skill and experience to manage the extensive blood loss and uterine reconstruction necessitated by the extensive dissection may offer myomectomies in these patients.

Although viewed as less traumatic than hysterectomy, myomectomy is a surgical procedure and therefore, surgical morbidity and mortality are disadvantages to this approach. There is also the potential for significant blood loss during the procedure (Parker 2006). Consequently, various techniques for reducing blood loss have been employed; including pre-operative embolisation, misoprostol, intramyometrial injection of bupivacaine plus epinephrine, vasopressin, and tourniquets (Kongnyuy and Wiysonge 2007). A 20% recurrence rate is reported after myomectomy and (Seracchioli, Rossi et al. 2000) and the risk of recurrence appears to increase with multiple fibroids (Doridot, Dubuisson et al. 2001; Hanafi 2005). Additional complications with myomectomy include a high risk of adhesion formation and the potential for uterine rupture during pregnancy (Frishman and Jurema 2005). Average recovery times vary by the procedure.
performed; a six to eight week recovery time is associated with abdominal myomectomy, whereas patients undergoing a laparoscopic surgery may resume normal activities within one to two weeks (Hurst, Matthews et al. 2005) and patients receiving a hysteroscopic procedure may recover within seven to ten days (Polena, Mergui et al. 2007).

**Uterine Artery Embolisation (UAE)**

With UAE, the uterine arteries are accessed under fluoroscopic guidance and injected with a mass of trisacryl gelatine microspheres or polyvinyl alcohol particles for occlusion (see figure 9).

Chapter 1 fig 9. An illustration of UAE. Embolic material is injected via the femoral artery through to the uterine arteries (image courtesy of www.northsideradiology.com).
Because the uterine arteries are responsible for approximately 94% of the blood supply to uterine fibroids, with the remainder received from the ovarian arteries via the infundibulopelvic ligament (Kroencke, Scheurig et al. 2006), this procedure significantly interrupts the blood supply to the fibroids. It is believed that through the induction of transient uterine ischaemia, the small vessels in the myometrium become occluded with clots, which are lysed over time as fibrinolytic substances from the collateral circulation in the uterus perfuse the region. As the fibroids cannot lyse clots, they infarct and undergo ischaemic necrosis (Burbank and Hutchins 2000). Consequently this procedure has the advantage of treating the uterus globally.

Generally, UAE is most useful in treating intramural fibroids, pedunculated fibroids should not be treated with UAE, due to the potential for the stalk to infarct and disconnect from the uterus (Marshburn, Matthews et al. 2006). Finally, compared to hysterectomy, UAE has been associated with a shorter recovery time (< 10 days) and a lower procedural cost (Dembek, Pelletier et al. 2007).

Risks associated with UAE include passage of submucosal myomata, uterine necrosis and sepsis and haematoma. UAE has been associated with the potential for ovarian failure resulting from unintentional embolisation of the ovarian blood supply; in an observational study of 66 pre-menopausal, symptomatic women followed for 12-27 weeks after UAE, ovarian failure was found in 43% of patients who were at least 45 years of age (Chrisman, Saker et al. 2000). In another study, of 108 women trying to become pregnant after UAE, 33 did so (Walker and McDowell 2006). The National Institute for health and Clinical Excellence (NICE) guidelines on heavy menstrual bleeding, state that ‘women should be informed that UAE or myomectomy will potentially allow them to retain their fertility’ (Clinical guideline CG44).

Considerable debate remains regarding the optimal management of fibroids, however increasingly women are expressing reluctance to undergo open pelvic surgery, in particular for a recurrent benign condition. UAE’s effect on fertility is at best unclear, especially for women >40 years of age. If the current trend for
increasing maternal age at childbirth continues, then an effective non-invasive, fertility preserving treatment solution for uterine fibroids is required.

1.1.7 Fibroids and fertility

The relationship between leiomyomas and infertility remains a subject of debate. The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be between 1 and 2.4 % (Buttram and Reiter 1981). There are no studies however, that compare pregnancy rates in women with and without fibroids and the causal relationship seems to have been assumed from case series of women who have conceived after their fibroid was removed (Bajekal and Li 2000).

A variety of theories have attempted to provide an explanation of how fibroids may cause infertility. One theory explains that fibroid sufferers may have anovulatory cycles resulting from the hyper-oestrogenic environment (Buttram and Reiter 1981), another explains that changes caused by fibroids such as elongation and distortion of the endometrial glands, cystic glandular hyperplasia and endometrial venule ectasia may be responsible for implantation failure (Deligdish and Loewenthal 1970). Another theory may be that sperm migration or ovum transport can be affected by the dysfunctional uterine contractility caused by fibroids (Deligdish and Loewenthal 1970).

What is generally agreed on however is that the anatomical location of the fibroid is important in its effect on fertility. Sub-mucosal fibroids are seen as the most problematic due to the distortion caused to the endometrial cavity and the possible disruption to endometrial blood supply. Local inflammation caused by mucus ulceration can change the biochemistry of the intrauterine fluid. The role of intramural fibroids is more controversial. Subserosal and pedunculated fibroids, with greater than 50% of their mass outside the myometrial border are seen as unlikely to cause adverse outcomes (Richards, Richards et al. 1998).
Fibroids and outcomes of Assisted Reproductive Technology (ART)

The effect of uterine fibroids on fertility in association with the use of ART has been the subject of many published articles. Studies of women undergoing in-vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) have demonstrated that submucosal and intramural fibroids in the presence of distortion of the endometrial cavity are associated with reduced implantation and pregnancy rates compared with women with similarly located fibroids in the absence of endometrial cavity distortion. This has been shown with both small (<5 cm diameter) (Farhi, Ashkenazi et al. 1995; Stovall, Parrish et al. 1998) and large (>4cm) intramural fibroids (Oliveira, Abdelmassih et al. 2004). Some studies however have also reported impaired IVF and ICSI outcomes in the presence of sub-serosal fibroids (Oliveira, Abdelmassih et al. 2004) (Stovall, Parrish et al. 1998). In contrast, other authors have shown that ART outcomes are not affected by the presence of subserosal myomas. In this same study the authors reported significantly lower pregnancy and implantation rates in the presence of both intramural and submucosal fibroids, even when associated with an undistorted endometrial cavity (Eldar-Geva, Meagher et al. 1998) The relationship between uterine fibroids and ART has been investigated repeatedly, and whilst study outcomes are often conflicting, overall the evidence supports the concept that submucosal and intramural fibroids which distort the endometrial cavity have a negative impact on outcomes of ART. However, the effects on fertility of both subserosal and intramural fibroids in the presence of a normal endometrial cavity remain unclear.

Fertility following myomectomy

Whilst hysterectomy remains the gold-standard treatment for fibroids, in terms of eliminating fibroid-associated symptoms immediately and guaranteeing no recurrence of symptoms, it is an unacceptable treatment option for women who...
wish to conserve their fertility. Myomectomy, which involves removal of the fibroid with conservation of normal myometrial tissue and hence fertility, remains the alternative surgical treatment option for women who wish to conceive in the future, although the actual effects of the procedure on fertility remain uncertain. Studies on clinical outcomes following myomectomy have yielded inconsistent data, and tend to be of poor design, many being retrospective and uncontrolled. In a retrospective study, Surrey et al did not find a significant difference in outcomes in terms of implantation, ongoing pregnancy or early pregnancy loss rates when comparing both pre-cycle abdominal myomectomy and hysteroscopic resection of small submucosal fibroids with control (Surrey, Minjarez et al. 2005). In contrast, a number of retrospective observational studies have highlighted that fertility outcomes do improve after myomectomy (Dubuisson, Fauconnier et al. 2000) (Rossetti, Sizzi et al. 2001). However, there are no published randomised controlled studies with sufficient power to support the theory that myomectomy improves fertility outcome. Similarly, there is no evidence at present to suggest that there is any difference in clinical pregnancy and live-birth rates between the various techniques available to remove fibroids (Griffiths, D'Angelo et al. 2006).

**Fibroids and miscarriage**

Fibroids have the potential to cause a number of problems in pregnancy, including miscarriage and pregnancy wastage. A number of studies have shown that spontaneous miscarriage rates in the first and second trimesters of pregnancy are higher in women with fibroids. Some believe that the rates of miscarriage are likely to be higher if implantation occurs over a sub-mucosal myoma. It has been shown that fibroids in close proximity to the placenta are more likely to be associated with bleeding in early pregnancy and spontaneous miscarriage (Muram, Gillieson et al. 1980) (Rosati, Bellati et al. 1989). Benson et al demonstrated almost double the rate of spontaneous pregnancy loss in women with fibroids compared with age-matched women with normal uteri (Benson, Chow et al. 2001). In addition, the loss rate observed was found to be higher in women with multiple fibroids compared with women with a single myoma, whilst no association between loss rate and fibroid size or location was noted. Miscarriage rates in women with fibroids vary widely in the literature, with loss
rates of 40% in the first trimester and 17% in the second trimester being reported in the presence of intramural and submucosal fibroids (Li, Mortimer et al. 1999).

**Summary**

In counselling patients with fibroids pre-conceptually, it is important to recognize that most patients with asymptomatic fibroids can conceive spontaneously. In patients presenting with infertility, sub-mucosal fibroids have been associated with markedly lower ongoing pregnancy rates in small studies, but no randomized, controlled trials evaluating the benefit of hysteroscopic myomectomy have been reported. Women with intramural fibroids should be counselled that there is conflicting evidence on the effect that these fibroids have on infertility, with the cumulative effect of such lesions unlikely to be large. Subserosal fibroids appear to have no effect on fecundity.
CHAPTER 1.2: PHYSICS OF MAGNETIC RESONANCE GUIDED FOCUSED ULTRASOUND SURGERY
1.2.1 Background

The concept of ‘the perfect’ tumour surgery is to excise or remove the neoplastic tissue without damaging adjacent normal structures. This concept requires a non-invasive non-incisional surgical approach, which limits the tissue destruction to the targeted tumour. Non-invasive surgery would lead to even shorter recovery time and result in even less complications than currently available minimally invasive techniques. Implementing such non-invasive surgical procedures will transform current medical specialities, change existing clinical practices and could therefore be an important tool in reducing the cost of patient care. In the surgical speciality, emphasis on manual skills and practical training will be replaced by a mostly technical knowledge base. Patients will return home and to work much faster without any significant reduction in quality of life caused by the procedure.

Magnetic Resonance guided Focused Ultrasound (MRgFUS) is such a technology. Unlike invasive surgery, it requires no incision, and the acoustic energy penetrates through intact skin and through the tissues surrounding the tumour, without causing any significant bio-effects. Energy deposition takes place mainly at the focal spot where heat-induced thermal coagulation of the targeted tissue is accomplished. As in ionising radiation-based therapy, the localisation of the target volume requires image guidance. Using intra-procedural MRI, this technique provides the best possible tumour margin definition and with real-time MRI thermometry, the closed loop feedback control of energy deposition is also accomplished. This real-time targeting and control makes MRgFUS superior to radiation surgery. In addition because of the lack of any tissue toxicity, Focused Ultrasound Surgery (FUS), unlike radio-surgery, can be repeated multiple times if necessary.

The idea of using focused acoustic energy for thermal coagulation deep within the tissue as a non-invasive surgical method is not new. It was first proposed over 60 years ago for the destruction of central nervous system tissue (Lynn, Zwemer et al. 1942). In the 1950s, a complex sonication system that used x-rays to determine the target location with respect to skull bones was developed by William and Francis Fry at the University of Illinois (Fry, Barnard et al. 1955; Fry, Barnard et
The system was clinically tested for the treatment of Parkinson’s disease with success, but was not used outside the research setting (Fry and Fry 1960). The primary difficulty with the treatment was the localisation of target tissues and the complexity of the procedure. The use of ultrasound for image guidance soon superseded the use of x-rays (Fry 1970), and remains in current practice.

Currently two trans-rectal ultrasound surgery devices for prostate cancer are in clinical use in Europe and several other countries. Furthermore, external ultrasound-guided devices are in clinical use in China, where tens of thousands of patients have been treated so far. Although targeting using diagnostic ultrasound works well in some cases, treatment is still relying on open-loop, uncontrolled energy delivery. This means that the power settings for the exposures are based on experimental and theoretical models as well as clinical experience with no live monitoring of the target location or temperature levels achieved.

This makes the treatment sensitive to patient-to-patient variations. Just the propagation of the wave through the overlying tissue layers can significantly distort the power deposition pattern at the focus (Liu, McDannold et al. 2005). To eliminate these variations, the energy delivery and its biological effects should be monitored online, and exposure variations should be adjusted to give comparable thermal exposure to all patients whilst avoiding over-exposure of tissues outside of the target volume.

The advent of MR and its temperature sensitivity allowed for real-time thermal monitoring (Jolesz, Bleier et al. 1988) and thus the development of ultrasound surgery systems combined with MRI. This allowed not only the monitoring of online temperature information received, but perhaps more importantly, more accurate definition of the targeted tumour volume than surgical inspection with the eye or other imaging modalities such as ultrasound or computed tomography.

Currently there is only one commercial device available on the market, the ExAblate 2000 manufactured by Insightec Ltd, Haifa. The device has been approved in the United States by the Food and Drug Administration for the
treatment of uterine fibroids. It has been recognised by the National Institute of Clinical Excellence, and has been awarded the conformitee europeenne (CE mark) for fertility.
1.2.2 Fundamental principles of therapeutic Ultrasound

Ultrasound is a pressure wave with a frequency above the audible range of a human ear (18-20KHz); it is generated by a mechanical motion that induces the molecules in a medium to oscillate around their rest positions. Due to the bonding between the molecules, the disturbance is transmitted to neighbouring molecules. The motion causes compressions and rarefactions of the medium and thus a pressure wave travels with the mechanical disturbance (figs 10 and 11).

Chapter 1 Figure 10: A mechanical ultrasound wave progresses through tissues (top), causing alternating cycles of increased and reduced pressure (compression and rarefaction respectively- bottom). Image courtesy of www.olipiados.it/components.com.
Chapter 1 Figure 11: The particle movement responsible for the propagation of longitudinal and shear waves. Image courtesy of www.me.berkeley.edu/-adarsh/masters.pdf

As a result, an ultrasound wave requires a medium for propagation. In most cases, the molecules vibrate along the direction of the propagation (longitudinal wave), but in some instances, the molecular motion is across the direction of the wave propagation (shear wave). Shear waves propagate in solids such as bone but are quickly attenuated in soft tissues. Therefore, most current medical ultrasound methods utilise longitudinal waves (Wells 1977).

1.2.3 Ultrasound transducers

Ultrasound is generated by applying radio-frequency voltage across a material that is piezoelectric, that is it expands and contracts in proportion to the applied voltage. This phenomenon is the inverse of the piezoelectric effect, which was discovered by Jacques and Pierre Curie in natural quartz crystals in 1880. Since then, many piezoelectric materials have been discovered and developed. From these materials, a group of artificial piezoelectric materials known as polarised
polycrystalline ferroelectrics are used for medical ultrasound applications. The piezoelectric property is lost above a material–specific temperature—the Curie point. Also, piezoelectric material rods or grains can be placed into a polymer matrix to have more control over the acoustic and electrical properties of the material. These so-called piezo-composite materials are used especially in phased array transducers.

For many applications of ultrasound therapy, transducers capable of producing high-power, single-frequency, continuous waves are needed. In figure 12, a simplified version of a high-powered transducer is shown.

![Diagram of a high-powered transducer](image)

Chapter 1 Figure 12: Diagram of an ultrasound therapy transducer.

The ultrasound wave is generated by a piezoelectric plate of uniform thickness that has electrodes on its front and back surfaces. The electrodes are connected to the driving radio-frequency line. Maximum power from a transducer can be delivered when it is operated close to its resonant frequency, which is achieved when the thickness of the plate is equal to the wavelength/2. However, a range of frequencies can be used with piezo composite materials. The frequency, which corresponds to the half-wavelength thickness, is called the fundamental resonant frequency of the transducer and it gives the maximum displacement amplitude at
the transducer faces. The transducer can be driven at a frequency which is three, five or so on times its fundamental frequency. The conversion efficiency is, however, reduced when compared with the fundamental frequency operation. At a frequency of 1 MHz, the half-wavelength thickness is approximately 2 mm in PZT-4, thus high-frequency transducers are thin and more difficult to manufacture.

In order to maximize energy output, all of the acoustic energy should be radiated through the face of the transducer. This can be achieved by selecting a backing material so that the acoustic impedance of the transducer is much larger than the acoustic impedance of the backing. In practice, air-backing gives almost complete energy transmission through the front of the transducer.

Ultrasound transducers can be manufactured in practically any desired shape and size. Spherically curved focused transducers of various sizes up to 30 cm diameter hemispherical transducer arrays have been manufactured (Ebbini and Cain 1991; Clement, Sun et al. 2000; Hynynen, Clement et al. 2004). Both non-focused and focused, single and multi-element transducers and arrays have been manufactured for endo-cavity use (Diederich and Hynynen 1989). Interstitial applicators inserted directly into the tissue via catheter have been constructed down to the size of 1 mm in diameter (Hynynen 1992). Catheter based applicators, inserted via the vascular route into the heart, have been developed for ablating cardiac tissue (He, Zimmer et al. 1994). Special care in the selection of transducer materials has to be taken when applicators for use in magnetic resonance imaging (MRI) - guided interventions are developed.

1.2.4 Focused ultrasonic fields

The ultrasound field generated by a transducer depends on the size, shape and, vibration frequency of the source. If the diameter of an ultrasound source is much larger than the wavelength in the medium, then the ultrasonic wave can be focused by lenses or reflectors, or by making the transducer self-focusing.
Focusing can be achieved by using arrays of small transducers that are driven with signals having suitable phase delays to obtain a common focal point (electrical focusing). The wavelength imposes a limitation on the size of the focal region and the sharpness of the focus is determined by the ratio of the aperture of the radiator to the wavelength, and the distance of the focus from the transducer (see figure 13).

Chapter 1 Figure 13: Ultrasound beams may be focused by curving the piezoelectric plate or by interposing a lens or reflector between a flat plate and the target. A phased array of transducers is focused electronically. Image courtesy of citeseerx.ist.psu.edu.

The theory of spherically curved transducers vibrating with uniform normal surface velocity was developed by O’Neil in 1949. It is possible to focus energy in the near field of an equivalent diameter planar transducer, due to the finite size of the wavelength. The ultrasound field between the acoustical focus and the
transducer resembles the near field of a planar transducer. Beyond the focus, the field follows the geometrical divergence angle of the transducer. The shape of the focus is a long narrow ellipsoid with dimensions dependent on the transducer diameter, radius of curvature, and frequency. The geometrical focusing of a transducer is often described by an F-number, which is the ratio between the radius of curvature and the diameter of the transducer (F-number = R/d). By increasing the radius of curvature (R), the maximum intensity can be pushed deeper into the tissue but at the cost of the focal region becoming longer and the peak intensity lower. This is due to the reduced focusing effect of the transducer and the attenuation within the tissue. It is possible to induce an intensity maximum at any practical depth in a human body with a suitable choice of transducer parameters, as long as the beam entry is not restricted by gas or bone (Hynynen, Watmough et al. 1981).

1.2.5 Electrical Focusing

Ultrasonic beams can be focused by using one or two dimensional arrays of transducers, with each element driven by radio-frequency signals of a specified phase and amplitude, so that the waves emitted by all of the elements are in phase at the desired focal point. The element size will determine the volume within which the focus can be moved because the focus has to be within the volume where all of the beams generated by the elements are overlapping. Focusing to a location outside this volume will result in secondary focal spots. An ultrasound beam can be focused anywhere in front of the array when the element centre-to-centre spacing is wavelength/2 or smaller see figure 13 above.

So far, all of the phased array systems developed for ultrasound treatments have had a limited focal range because the large size of the arrays needed results in thousands of elements. However, it has been demonstrated that adequate power outputs can be achieved with wavelength/2 test arrays (70) and thus there is no technology barrier to constructing such arrays.
Although electric focusing and beam steering has been used extensively in diagnostic ultrasound (Pernot, Aubry et al. 2003), its adoption in therapy systems has been much slower. The first attempt to utilise electrical focusing in ultrasound therapy was by Do-Huu and Hartemann (Do-Huu et al 1981). They constructed a concentric ring transducer that allowed the focus to be moved along the axis but not in any other direction. A full range of axial focal spot movement can be achieved with ring centre spacing of one wavelength (Ebbini and Cain 1991). Large spacing can be used if the array is spherically curved and the focal range is limited (Diederich and Hynynen 1991). A similar approach can be used for achieving a limited range, three-dimensional motion with phased arrays with large element sizes (Ebbini and Cain 1991).

There has been a lot of progress in using phased arrays for ultrasound surgery and especially for MRI-guided ultrasound surgery (Daum and Hynynen 1999). Today, phased arrays are the method of choice for clinical devices, with the concentric ring design providing control over the depth of focus with added sectors to provide limited beam steering to make the focus larger (Fjield, Fan et al. 1996). Phased arrays have also made it possible to compensate for wave distortion induced by overlying tissues such as skull (Clement, Sun et al. 2000). Similarly, phased arrays offer significant advantages for applicators that deliver the ultrasound energy via body cavities (Hutchinson, Dahleh et al. 1998).

1.2.6 Biological effects of ultrasound

Ultrasound interacts with tissue through the particle motion and pressure variation associated with wave propagation. First, all ultrasound waves are continuously losing energy through absorption resulting in an increase in temperature within the tissue. If the temperature elevation is large enough and is maintained for an adequate period, the exposure causes tissue damage. This thermal effect that can be used for tissue coagulation or ablation is similar to that obtained using other heating methods with equal thermal exposure. Secondly, at high-pressure amplitudes, the pressure wave can cause formation of small gas bubbles that concentrate acoustic energy. Similar focusing of energy can be induced by the oscillation of small bubbles already present. This type of interaction between a
sound wave and a gas body is called cavitation and it can cause a multitude of bio-effects from cell membrane permeability changes to complete destruction of tissue. Finally, the mechanical stress and strain associated with wave propagation may sometimes cause direct changes in a biological system. The mechanical interactions between ultrasound and tissue include radiation force and pressure, radiation torque, and streaming (shearing stress).

1.2.7 Thermal effects

The thermal effects produced by ultrasound have been utilised in hyperthermia as a cancer therapy as well as in many ultrasound surgery applications. In order to induce thermal tissue damage, the exposure at a given temperature has to exceed a threshold time below which the tissue recovers. The thermal damage threshold depends amongst other things on tissue type and physiological factors (pH and O2). A given intensity or power of the ultrasonic field does not necessarily induce a known temperature elevation. The temperature elevation in a tissue depends on the absorption and attenuation coefficients of the tissue, the size and shape of the ultrasound field (thermal conduction effects), and also strongly on the local blood perfusion rate.

At short exposures, in the order of seconds, the blood perfusion effects are small and the heat transference is dominated by thermal conduction (Billard, Hynynen et al. 1990) (Kolios, Sherar et al. 1996). At longer exposures, perfusion dominates the heat transfer and thus has a major impact on the actual temperature elevation achieved. All of these tissue parameters (except thermal conduction) vary from tissue to tissue and location to location. Therefore the temperature elevation during an ultrasound exposure has to be measured to ensure that adequate thermal exposure has been achieved. (Sapareto and Dewey 1984; Dewhirst, Viglianti et al. 2003).

Although the actual temperature threshold varies from tissue to tissue, the threshold is linearly proportional to the log of exposure duration such that a 1°C temperature increase reduces the required exposure duration to half. This
relationship is characterised by a thermal dose equation that describes the thermal exposure as the time in minutes at 43°C that achieves an equivalent bio-effect (Dewhirst, Viglianti et al. 2003). To summarise from thermal exposure literature, a thermal dose of 240 minutes at 43°C is sufficient to cause necrosis in all tissues (Sapareto and Dewey 1984; Dewhirst, Viglianti et al. 2003). Similarly, all tissues can survive an exposure of a few minutes at 43°C. There are however many potentially useful thermal effects at exposures that do not cause tissue necrosis, for example, sensitization of tumours to radiation or chemotherapy (Dewhirst, Viglianti et al. 2003) and the increase of tissue perfusion such that higher quantity of drugs could be delivered in the tissue. Thermal exposures can enhance the blood vessel permeability, release therapeutic agents from liposomal carriers (Magin and Niesman 1984) (Needham and Dewhirst 2001), and activate drugs or gene therapy (Moonen 2007). MRI guided focused ultrasound can offer highly controllable thermal exposures and thus may provide a method to explore the clinical use of these non-lethal thermal exposures.
1.2.8 *Fundamental principles of Magnetic Resonance Temperature Imaging*

Clinical Magnetic Resonance Imaging (MRI) uses the magnetic properties of hydrogen and its interaction with both a large external magnetic field and radio-waves to produce highly detailed images of the human body.

In its early days, MRI was known as NMR. This stands for Nuclear Magnetic Resonance. Although the name has changed (primarily due to the negative connotation of the word “nuclear”), the basic principles are the same.

MRI produces images by using a magnetic field to induce changes in proton spin within tissues. Normally, the magnetic axes of multiple protons within tissues are randomly aligned. When surrounded by a strong magnetic field, as in an MRI machine, the magnetic axes align along the field. Application of a radiofrequency pulse causes the axes of all protons to momentarily align against the field in a high-energy state; some protons then relax back to their baseline state within the magnetic field. The magnitude and rate of energy release that occurs with return to baseline alignment (T1 relaxation) and with the wobbling (precession) of protons during the process (T2 relaxation) are recorded as spatially localized signal intensities by a coil (antenna). These intensities are used to produce images. The relative signal intensity (brightness) of tissues on an MR image is determined by multiple factors, including the radiofrequency pulse and gradient waveforms used to obtain the image, intrinsic T1 and T2 tissue characteristics, and tissue proton density.

Pulse sequences are computer programs that control the radiofrequency pulse and gradient waveforms, which determine how an image is weighted and how various tissues appear. Images can be T1-weighted, T2-weighted, or proton density-weighted. For example, fat appears bright (high signal intensity) on T1-weighted images and relatively dark (low signal intensity) on T2-weighted images; water and fluids appear as intermediate signal intensity on T1-weighted images and bright on T2-weighted images. T1-weighted images optimally show normal soft-
tissue anatomy (fat planes are well seen as high signal intensity) and fat (e.g. to confirm a fat-containing mass). T2-weighted images optimally show fluid and pathology (e.g. tumours, inflammation and trauma). In practice, T1- and T2-weighted images provide complementary information, so both are important for characterizing pathology.

Contrast may be used to highlight vascular structures (magnetic resonance angiography) and to help characterize inflammation and tumours. The most commonly used agents are gadolinium derivatives, which have magnetic properties that affect proton relaxation times. Gadolinium agents can cause nausea, pain, sensation of cold at the injection site, taste distortion, vasodilatation, and reduced threshold for seizures. Serious contrast reactions are rare and much less common than those with iodinated contrast agents (Jacobson, JA 2008).

1.2.9 Temperature sensitivity of magnetic resonance imaging

Since both the chemical environment and relaxation properties of the nuclei that are the source of the signal in Magnetic Resonance (MR) are sensitive to Brownian motion and the associated molecular tumbling rates, MR imaging (MRI) techniques are intrinsically sensitive to temperature. Of the many MR parameters that can provide temperature sensitive contrast, the temperature dependence and sensitivity of several parameters in particular, have proven useful for monitoring temperature changes in soft tissue during delivery of hyperthermia or thermal therapies: the apparent diffusion of constant of water ($D$), the spin-lattice relaxation time ($T_1$), and the water proton resonance frequency (PRF). The temperature sensitivities associated with each of these parameters are large enough to allow temperature-dependent changes to be observed quantitatively using either direct or indirect measurements using standard MRI devices over a range of temperature relevant for thermal therapy. The development of these techniques to non-invasively measure temperature changes in tissue has brought renewed interest in using these techniques to enhance the guidance of thermal therapy treatments.
Of the available radiological imaging modalities capable of providing real-time temperature feedback, MRI has the desirable properties of excellent soft-tissue contrast and the ability to provide fast, quantitative temperature imaging in a variety of tissue (Cline, Schenck et al. 1992; Hynynen, Darkazanli et al. 1993).

By far the most exploited and widely validated quantitative MR temperature imaging techniques are based on the temperature sensitivity of the water proton chemical shift or phase shift (McDannold 2005) and the T1 weighted (T1W) signal. Diffusion weighted imaging is based on thermal Brownian motion but is impractical in vivo because of long scan time and subsequent motion artefact (Le Bihan, Delannoy et al. 1989).

Phase shift exploits the phase of the MR signal rather than the magnitude. As temperature rises, phase changes, thus producing an excellent thermal map (Harth, Kahn et al. 1997). However phase shift is also highly sensitive to motion and to magnetic field inhomogeneities causing artefact, this is a particular problem in the abdomen due to significant inherent physiological motion (Harth, Kahn et al. 1997) (Botnar, Steiner et al. 2001). T1W dependent temperature mapping is based on a linear inverse relationship between T1 signal and temperature. As temperature rises, T1 signal is lost, with signal becoming increasingly blacker on T1 images (Matsumoto, Oshio et al. 1992). A software tool is used to produce colourised thermal maps of heated areas during heat application for real-time temperature quantification Sun Micro Systems Sparc 20 (Jiang and Zhang 2005) This is particularly useful for showing the very early thermal changes before irreversible necrosis has occurred. The grey-scale loss in T1 signal is converted to a colour spectrum, which ranges from blue (coolest area), through turquoise, green and yellow to red (the hottest area) (de Jode, Lamb et al. 1999). The images are updated every 1.5s at approximately 55°C, irreversible tissue necrosis occurs corresponding to a persistent green colour on the colour scale.

The advantage of real-time imaging and thermal mapping is that it allows the operator greater control and accuracy over the treatment, the duration of heat and power applied can be varied as required to produce reliable, consistent results.
each time, with maximum safety assured. Without real time imaging the extent of tissue necrosis can only be approximated (de Jode, Lamb et al. 1999).
CHAPTER 1.3: FROM 1st GENERATION TO 3rd
GENERATION THERMOABLATION FOR UTERINE
FIBROIDS.
1.3.1 Background

The principles of thermal ablation are that the application of heat leads to a localised tissue destruction. Since the resulting cell necrosis is a coagulative rather than an ischaemic process, the painful infarction syndrome which is recognised after UAE is avoided (Freed and Spies 2010).

First generation thermal ablation was delivered via the laparoscopic approach (Goldfarb 1992). Although this procedure achieved good symptom relief, concerns were raised regarding the high rate of dense pelvic adhesions following the introduction of the live laser fibres into the fibroid at laparoscopy (Donnez, Squifflet et al. 2000). Damage to the uterine serosa was frequently noted due to lack of thermal monitoring. The operator had to rely on a change in the external appearance of the fibroid as the only means of assessment that sufficient heat had been applied. Reports of uterine rupture prior to the onset of labour did little to improve confidence in this technique and indeed it was later suggested that laparoscopic myolysis be reserved for women who had completed their families (Arcangeli and Pasquarette 1997) (Vilos, Daly et al. 1998).

Second generation thermal ablation techniques relied on the superiority of magnetic resonance as an imaging modality and its unique ability to create thermal mapping using phase shift imaging. This gives the operator real time colour map feedback on the temperature levels achieved, together with reassurance that heating is occurring only in the target tissue, thus ensuring both the safety and efficacy of the treatment (Law, Gedroyc et al. 1999).

The technique of MR guided laser ablation was made possible by the design of an open magnet (see figure 14) which allows the operator direct access to the patient. The open scanner is composed of 2 magnet rings ‘the double doughnut’ through the centre of which is placed the patient on the MR table. The scanner allows access to the patient in the vertical plane between the two magnet rings, the operator can stand beside the patient and insert four double bore needles
percutaneously through the abdominal wall and into the uterine fibroids (See figure 15). The protective inner sheath is then pulled back and the live laser fibres are thread through and inserted into the fibroids. The procedure is carried out under real time MRI guidance ensuring that the bladder and bowel can be avoided. The thermal ablation begins distant from the serosal surface and therefore serosal damage is limited to the puncture wounds.

Chapter 1 Figure 14: Photograph of the open scanner, showing the ‘double doughnut’ rings, which allow operator access to the patient.
Chapter 1 Figure 15: Photograph of the operator inserting percutaneous laser fibres.

Hindley, et al 2002, described a total of 66 patients with symptomatic uterine fibroids wishing to avoid surgery, who were treated were MR guided laser ablation (Hindley, Law et al. 2002). MR thermal mapping ensured that maximal doses of energy were applied. Fibroid volume was measured at 3 and 12 months post laser ablation, menstrual blood loss was quantified before and after treatment and a menorrhagia outcomes questionnaire (MOQ) was used to assess patient symptoms and satisfaction. There was a reduction in mean fibroid volume of 31% at 3 months and 41% at 1 year. Quality of life symptom- severity scores were similar to those seen in women undergoing hysterectomy. In summary, 80% of patients said they would recommend the procedure to a friend. In direct contrast to laparoscopic laser ablation, there were no cases of pelvic adhesions. Approximately 150 women have now been treated with MR guided percutaneous laser ablation with consistently good outcomes.
1.3.2 Magnetic Resonance guided Focused Ultrasound Surgery.

As mentioned previously, this method of thermoablation, is a completely non-invasive method of achieving tissue destruction by acoustic energy that converts to heat during absorption. While other methods of thermoablation are only minimally invasive because of the use of percutaneous needles and needle-like probes, MRgFUS is completely non-invasive with no percutaneous probes required. The US waves penetrate soft tissue and can be focused to small focal volumes with dimensions of a few millimetres. The acoustic energy absorption at the focal spot leads to tissue temperature elevations with such sharp thermal gradients that the boundaries of the treated volume are sharply demarcated without damage to the over-lying or surrounding adjacent tissues. No other probe-delivered heating methods can achieve similar, well-controlled, deep thermal ablation.

MRgFUS effectively combines two technologies (MRI and US) into a non-invasive image-guided therapy delivery system that fulfills the requirements of the ‘ideal surgery’ in that it is a method which ensures only the targeted tumour tissue is destroyed without associated injury of the adjacent normal tissue, by using a precisely focused, high-power acoustic beam (see figure 16). Before the sound waves are concentrated at the focus point, they propagate through the tissue without damaging it. At the focus, the intensified acoustic energy beam raises the tissue temperature to an range where tissue is coagulated by protein denaturation and capillary bed destruction.
Chapter 1 Figure 16: Illustration showing high frequency ultrasound beam generated by the transducer, passing through the abdominal wall and being targeted at a fibroid. Only tissue at the focus is damaged. (image courtesy of Insightec).

MRI, with its excellent sensitivity for imaging soft-tissue tumours, is preferable over other imaging modalities for localizing 3D tumour margins and targeting tumour volumes. In addition, because of the excellent temperature sensitivity of MR, the focal point can be visualised and localised well before any irreversible tissue damage is induced at about 20°C above normal body temperature. Moreover, MRI’s ability to capture the temperature change enables the physician to delineate temperature maps and tumour volume and apply this quantitative information in real time (Jolesz and Hynynen 2002) (Jolesz, Hynynen et al. 2005).

Successful design, testing, and development of a clinical MRgFUS system was a significant engineering challenge. Following the early implementation of the technique (Hynynen, Freund et al. 1996) and after the development of a prototype workstation at the Brigham and Women’s Hospital by McDannold et al, Insightec (Haifa, Israel) developed the first commercial MRgFUS therapy delivery system known as the ExAblate®2000. It is this system which has been used throughout the work of this thesis.
1.3.3 System Components

The Exablate 2000 system consists of the following integrated components:

- Operating console
- Patient table
- Equipment cabinet
- Cooling system

Operating console.

The Exablate 2000 console allows the operator to control and monitor both the system and the treatment. It positioned alongside the GE SIGNA workstation in the control room. (see figure 17)

Chapter 1 Figure 17: the operating console of the ExAblate 2000 MRgFUS system.
Patient table

Treatments are conducted with the patient lying on the patient table inside the MR scanner (see figure 18). The patient table contains the focused ultrasound transducer along with the mechanical positioning unit that moves the transducer (see below). Prior to treatment, the patient table is docked to the MR scanner. A quick-coupler cable connects the patient table to the equipment cabinet.

Chapter 1 Figure 18: Showing the modified patient table containing the ultrasound transducer. The transducer is able to move in 3 planes. (Images courtesy of InSightec).
*Equipment cabinet*

The equipment cabinet contains the electrical components of the Exablate 2000 system and the main power switch (see figure 19).

Chapter 1 Figure 19: The equipment cabinet of the ExAblate 2000 system. (Image courtesy of Insightec).
Cooling system

The cooling system incorporates a semi-closed water circulation loop, designed to keep the water in the transducer bath at an optimally low temperature during operation.

The circulating water is never in direct contact with the human body (see figure 20).

Chapter 1 Figure 20: The cooling unit of the ExAblate 2000 system. (Image courtesy of Insightec).
1.3.4 The Treatment process

All MRgFUS procedures, except those in chapter 3, performed for the purpose of this thesis were performed or supervised by S. Zaher.

Treatment is conducted while the patient lies on a patient table inside the Magnetic Resonance scanner. The patient is conscious, able to communicate with the physician during the treatment, and is provided with sedation medication prior to the first sonication. The entire procedure is planned and carried out from the operator console.

There are four major steps in the ExAblate treatment:

**Target localization**

MR images are taken in three orientations to locate the target tissue and surrounding organs (see figure 21). These images are used to position the patient and determine the optimal path to the tumour for the focused ultrasound beam.

Chapter 1 Figure 21: Target tumour is localised in three orientations.
Treatment planning and editing

The physician uses the MR images to identify the target anatomy and evaluates the structures surrounding the fibroid to decide on a treatment region. Bowel, pubic bone and far field bone are marked as low energy density regions (LEDR). This prevents the beam path from coming close to any of these regions and thereby avoiding potential complications such as bowel perforation or neuropraxia.

Contours of the treatment area are drawn on the MR images and verified in three orientations. The Ex-Ablate system calculates the volume of the tissue to be treated and the number of treatment spots required. The beam path is visualized to verify that nothing interferes in any plane.

Treatment

Treatment consists of multiple sonications to ensure tumour ablation. During each sonication, phase sensitive MR images are acquired, and real-time quantitative temperature maps are produced to confirm tissue heating. These temperature maps provide feedback to the physician who can then adjust treatment parameters to optimize thermal ablation. After each sonication, the transducer and MR scan plane are automatically directed to the succeeding point, and the process is repeated until the entire target volume has been treated.
Chapter 1 Figure 22: Sample screen showing the treatment target tissue being identified and markers placed around the borders (red crosses) these markers help to identify if movement occurs.
Chapter 1 Figure 23: Sample screen showing skin line drawn on axial images, temperature levels can be measured at the skin to ensure safe levels. Bowel is marked as a low energy density region (LEDR) pink marker.
Chapter 1 Figure 24: Sample screen showing the calculated volume of tissue to be treated and the number of treatment spots required.
Chapter 1 Figure 25: Sample screen showing treatment consisting of multiple sonications to ensure tumour ablation. Real time thermal maps give the operator feedback on treatment efficacy.
Treatment outcome

At the end of treatment contrast enhanced MR images are acquired to measure the degree of contrast agent uptake. Regions without contrast agent uptake (non-perfused) have been destroyed by the thermal effects of the focused ultrasound. The physician can determine whether sufficient tissue has been treated, or if a repeat treatment is necessary (see figure 26).

Chapter 1 Figure 26. Top image shows coronal view of the accumulated thermal dose. The lower contrast enhanced image shows the non-perfusion achieved which correlated exactly to the treated regions.
CHAPTER 1.4: PRELIMINARY CLINICAL DATA ON MRgFUS
1.4.1 Safety and Feasibility

The initial clinical trial assessing the safety and feasibility of MRgFUS in the treatment of clinically significant uterine fibroid (UF) was conducted in five centres in the United States, Britain, Germany and Israel (Stewart, Gedroyc et al. 2003). A total of 55 patients were treated in this study. The study was designed to assess treatment-related pain and complications prospectively and utilized post-treatment MR imaging to assess treatment effects. At three of the five centres, patients underwent planned hysterectomy following the MRgFUS procedure, enabling a correlation between pathologic and clinical outcomes.

Participants were at least 18 years of age and had no plans for future pregnancy. Subjects with a uterine size >20 weeks of gestation or a dominant UF >10 cm diameter were excluded from the study. Treatment time was planned for less than two hours.

Of the 55 patients enrolled the study, 15 (76%) completed the full treatment session. Three patients received no treatment due to the presence of bowel in the beam path that could not be remedied. Ten other patients received less energy than prescribed in the treatment plan. In most cases this was due to an inability to detect the low-energy test pulse, which resulted in a failure to administer a therapeutic sonication. This was typically caused by the presence of surgical scars or variations in the deposition of fat and muscle within the abdominal wall.

Discomfort was minimal, and no major complications were reported. Thermal injury in the adjacent normal myometrium was observed in only one patient, and is believed to have resulted from a change in the position of the target tissue due to filling of the patient’s bladder during the treatment session. Only 10% of patients with 72-hour follow-up data reported use of pain medication. At the 72-hour visit, the physician observed abdominal skin burns in two patients, which the patients themselves had not reported.
MR imaging with gadolinium immediately following MRgFUS treatment revealed that there was a modest but statistically significant increase in the non-perfused volume compared with the treatment volume (20.0 ±3.2 ml vs. 34.6 ±6.2 ml, P< .004). Patients undergoing hysterectomy underwent additional contrast-enhanced MR imaging at 72 hours post-treatment, and the difference was greater at this time point (6.5 ±0.8 ml vs. 22.6 ±4.3 ml, P< .002). The extension of the effective treatment volume was confirmed by pathologic examination of uterine tissue in patients undergoing hysterectomy.

1.4.2 Phase II

The efficacy of MRgFUS was assessed in a Phase II clinical trial of 35 patients with symptomatic UF who were scheduled for hysterectomy (Hindley, Gedroyc et al. 2004). The study design included prospective analyses of clinical symptoms, patient satisfaction and uterine size 1 month and 6 months after undergoing MRgFUS. Study participants had a uterine size of <20 weeks’ gestation and dominant fibroid size <10 cm in diameter. Treatment was targeted to one or two fibroids in each patient. All procedures were performed on an outpatient basis, and patients were discharged after approximately two hours of post-treatment observation.

A total of 41 fibroids were treated in the 35 study participants. Mean pre-treatment volume of these fibroids was 216 ± 223 ml, and the mean treated volume was 18 ±13.3%. Mean post-treatment NPV was 53 ± 94 ml, corresponding to a mean of 31 ± 23% of the pre-treatment volume. Of the 35 patients, adequate ablation of target tissue was not achieved in four due to technical problems. Three of these four patients opted for hysterectomy. Two patients who received adequate ablation based on the treatment protocol also opted for hysterectomy due to continued UF symptoms.

Twenty-one patients underwent MR imaging studies at 1-month post-MRGUS. At this time point, the mean fibroid volume reduction was 12 ± 16%. A marked increase in UF size was observed in one patient. MR imaging studies were
conducted in 29 patients 6 months after MRgFUS, at which time the mean fibroid volume reduction was 15 ± 27 compared with the mean volume of all 35 patients on the day of treatment. Fibroid volume was markedly increased in one patient at this time point as well Marked or partial improvement in UF symptoms was reported by 37.1% and 31.4% of patients, respectively, in the six months following the MRgFUS procedure.

In the 6 months after MRgFUS, six patients (17%) opted for hysterectomy due to continued UF symptoms. Two of these six had not received adequate ablation, and two others had uterine adenomyosis rather than fibroids. In one additional patient, there was a volume reduction in the two treated fibroids, but six untreated fibroids increased in size.

No major short- or long-term side effects were reported. Minor reported side effects were a small skin burn on the abdomen that resolved within two weeks and transient sciatic pain that resolved after one week. Minor and transient lower abdominal pain, which resolved shortly after MRgFUS, was reported by several patients.
CHAPTER 1.5: MEASURES OF TREATMENT OUTCOME
FOLLOWING MINIMAL INVASIVE TREATMENTS
There are many ways to assess the efficacy of fibroid therapy. Clearly the simplest is complete resolution of symptoms after definitive surgical removal of the entire uterus and all fibroids, as in a hysterectomy. However, with the development of lesser invasive treatment alternatives to hysterectomy, that do not completely eliminate the fibroid, the need for patient–reported outcomes to assess symptom reduction has arisen.

The patient’s subjective response along with physical and imaging findings can be evaluated in total. The classic way to assess outcome has been to assess the size and volume of the uterus. Early studies often did this with unblinded examiners by pelvic exam, which clearly made understanding the real treatment effects difficult. However, with the use of GnRH agonists in the 1980s and 1990s, the use of US volumetric measurements was introduced. This is a powerful technique since a relatively small change in a measure diameter can result in a significant difference in the volume. However, for this reason, it is also prone to error, because small differences in measurement can appear to produce significant differences in volumetric analysis. Additionally, volume reduction is not always necessary or helpful in terms of reducing symptoms. Some women with uterine fibroids have only symptoms of heavy menstrual bleeding, and a volume reduction does not predict clinical success. It has therefore, become increasingly important to find a tool which provides an evaluation of the clinical success of uterine-sparing therapies chosen by patients.

The published data on Health Related Quality of Life (HRQL) associated with uterine fibroids consistently report a lower quality of life for women with fibroids (average score 62) than for women without (average score 86). The Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL) is a uterine fibroid specific questionnaire developed by Spies et al (Spies, Coyne et al. 2002) to evaluate the symptoms of uterine fibroids and their impact on HRQL.

The UFS-QOL has been used in studies of various fibroid treatments, including; UAE (Smith, Upton et al. 2004; Scheurig, Gauruder-Burmester et al. 2006; Siskin, Shlansky-Goldberg et al. 2006), radiofrequency thermal ablation (Bergamini,
Ghezzi et al. 2005; Ghezzi, Cromi et al. 2007) MRgFUS (Stewart, Rabinovici et al. 2006) and treatment with medication, consisting of eight symptom questions and twenty nine health related quality of life questions, the questionnaire was derived from focus groups of women with leiomyomata. A total of 110 patients with confirmed leiomyomata and 29 normal subjects participated in the validation. Among the instruments used for the validation were the short form-36, Menorrhagia Questionnaire, R-W sexual function scale, and a physician and patient assessment of severity.

The final questionnaire accurately discriminated not only from controls, but also from patients with varying degrees of symptom severity (see figure 27). Maximum symptom severity score is 100 with a higher score indicating greater severity of symptoms. A drop of 10 points in the scoring indicates significant improvement of symptoms as reported by Spies et al (Spies, Coyne et al. 2002). This questionnaire has been utilised throughout this work as a tool to measure treatment outcome, wherever symptom improvement was a primary outcome.

Chaper 1 Figure 27: This graph compares the average symptom severity score in 3 groups of women; those without fibroids, those with and those treated in the pivotal group. It can be seen that this group of women are highly symptomatic when compared to those with no fibroids.
CHAPTER 2: MATERIALS AND METHODS
2.1 Patient assessment

All Patients were recruited from the tertiary fibroid clinic. Patients were either referred by their general practitioner or by a gynaecologist for assessment and treatment of uterine fibroids. Each patient was seen by a clinical research fellow (SZ) who obtained the patient’s medical history specifically focusing on gynaecologically significant symptoms and assessed uterine fibroid symptoms according to the UFS-QOL questionnaire a validated health and symptom related questionnaire specific to uterine fibroids (see chapter 1.5 for more details). A clinical examination was performed, in particular of the abdomen to assess uterine size and inspection for any scars.

A full blood count was taken to measure hemoglobin levels. Patients’ eligibility was assessed according to the inclusion-exclusion criteria listed in the Ex-Ablate commercial treatment guidelines (see table below). In general, Patients were excluded, if they had contraindications for MR imaging such as non-MRI compatible implanted metallic devices. Patients deemed unable to comprehend instructions or communicate sensations during treatment were also excluded, as safe treatment relies on the ability of the patient to communicate sensations such as leg, buttock, and skin or back pain to the operator.

If the patient was clinically eligible and interested in MRgFUS, she was then referred for a screening MRI scan.
### Patient Exclusion Criteria

1. Haemoglobin <10

2. Patient has haemolytic anaemia

3. Patient has unstable cardiac status including:
   - Unstable angina pectoris on medication
   - Documented myocardial infarction within 6 months of protocol entry
   - Congestive heart failure requiring medication (other than diuretic)
   - Currently taking anti-arrhythmic drugs
   - Severe hypertension (diastolic BP>100 on medication)
   - Presence of cardiac pacemaker

4. Patient has severe cerebrovascular disease (multiple CVA or CVA within 6 months)

5. Patient is on anticoagulation therapy or has an underlying bleeding disorder

6. Evidence of uterine pathology other than leiomyoma

7. Patient has an active pelvic infection

8. Patient has an undiagnosed pelvic mass outside the uterus.

9. Patient weight >110 kg

10. Patient with extensive longitudinal abdominal scarring in an area of the abdomen directly anterior to the treatment area.

11. Patient with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices.

12. Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 hours.)
2.2 Screening MRI Scan

Screening is performed in the prone position, and consists of three orientations including both T2 weighted images and T1 weighted images before and after gadolinium injection. A radiologist experienced in MRgFUS analyses the screening MR images to determine patient suitability for the procedure.

Patients are deemed technically suitable for MRgFUS if their fibroids mass seemed accessible by the system and treatable in a reasonable time. The majority of the fibroids mass should be no more than 12 cm depth away from the skin line, as this is the upper limit of the system. Patients with bowel that could not be shifted from the potential beam path were also excluded from consideration, as air bubbles or hard particles present in the bowel may reflect or absorb the ultrasonic energy. Patients with more than six uterine fibroids of more than 4cm size each were excluded, as usually in these cases some of the fibroids will be close to the sacrum or hidden behind bowels thus will be inaccessible. Patients with longitudinal scars in the beam path, including those that could not be seen on the MR images, also were excluded, as scar tissue may absorb the ultrasound energy and cause pain or even a skin burn. Other factors for exclusion are calcified fibroids, which ultrasound energy cannot penetrate into; patients with non-enhancing fibroids that are already dead; pedunculated fibroids, that might disconnect after the treatment into the abdominal cavity; and patients with pathologies other than uterine fibroids, such as adenomyosis.

Patients who have total fibroids volume of more than 500cc, or a hyper-intense fibroid on T2 weighted imaging were pre-treated with a GnRH analogue for three months in an effort to reduce the size and vascularity of the fibroid.
2.3 MRgFUS Procedure

All MRgFUS procedures were performed using the ExAblate 2000 (InSightec, Haifa, Israel), which is fully integrated with a 1.5 Tesla MR scanner (GE Medical Systems, Milwaukee, WI).

Patient Preparation

Informed consent was obtained from all patients prior to proceeding to treatment. The procedure is performed as a day surgery or outpatient treatment; the patient is asked to remain fasted for a minimum of 4 hours, and is then prepared before entering the magnet. Preparation involves insertion of an intravenous line and Foley catheter. Examination of the abdominal wall for the presence of scars and a check to ensure complete shaving of the pubic area is essential to prevent the occurrence of skin burns. The patient receives a light sedative and analgesia as requested throughout the procedure. The regimen used comprises of a maximum dose of 10mg of diazemuls, with a starting dose of 20mg; a maximum of 100 mg of pethidine with a starting dose of 20 mg, and 1g of paracetamol given as an intravenous infusion started. This regimen allows the patient to be relatively pain-free, comfortable, awake and responsive throughout. At all times the patient’s pulse and oxygen saturations is monitored using a pulse oximeter.

The MRgFUS treatment step by step

*Turning on ExAblate 2000 Console*

- Turn on by pressing the green power on button on the console
- When the system is ready type in the username and password
- Press OK and ensure that the username and password have been accepted.
- At this point the system will;
- Power up the treatment table (indicated by the light on the quick coupling cable)
- Start up the cooling system and allow it to reach the set temperature value
- It will run checks on the transducer’s motion
Setting up the Treatment Table

- Ensure that the LED on the quick coupling cable is green, if not, return to the ExAblate console and ensure that the system has started up. If you are still having problems discuss with a senior FUS trainer.

Visual inspection of equipment and attaching anterior coil

- Detach the Anterior coil part from the table
- Remove the protective membrane cover off the transducer bath.
- Visually check the integrity of the of the table looking for any loose fittings or cracks
- The transducer bath should be free of air bubbles and leaks.
- Ensure that the Mylar surface is not damaged and free of any dust or any other small particulates as these can create air bubbles when setting up the treatment bath.
- Connect the anterior segment of the imaging coil to the treatment table with the two clips and ensure that is secure.

Positioning Patient Comfort pads

- Directly on the treatment table there is a pad that is shaped to fit the inferior part of the table, and another for the superior part, ensure that both pads are correctly positioned.
- The patient comfort pad is then placed directly over the table so the opening is directly over the transducer bath.
- To ensure that the treatment bath will be deep enough to contain enough of the water. Put a large triangular pad just inferior to the treatment coil and smaller pad at the superior end of the opening.
Creating Treatment Bath

- Mixing Gel and Water to produce Coupling Substance
  - Squeeze out about a third of the Ultrasound gel sachet onto the Mylar then add a splash of water (10-15mls) then mix. This should produce a thin film on the mylar.

- Place plastic membrane on mylar sheath

- Open the plastic membrane and carefully open it ensuring that no extra creases are added to its surface.

- Visually locate the centre of the sheet and then place this in the centre of the transducer bath

- Push the membrane so it is in contact with the mylar surface

- Pour enough water onto the membrane to at least cover the anterior segment of the imaging coil, the water provides a weight to help anchor the membrane to the mylar surface.

- Secure Sheet to Patient Comfort Pad and Anchor
  - Secure the edges of plastic membrane to the patient comfort pad approximately 5cm from the opening, this provides an anchor for the outside of the membrane while providing plenty of extra plastic so that the membrane may move while the patient is being positioned without compromising the integrity of the acoustic coupling.

- Use the Plastic Card to remove any bubbles and excess gel water mixture
  - Use the edge of the plastic card provided in the treatment kit to gently push bubbles out
  - Using movements from the centre to the outer edge of the bath.
  - Pressure used should be enough to remove excess gel and any air bubbles to produce a close contact between the plastic and the mylar without displacing all of the gel.
  - Visually check the plastic/mylar interface to ensure that there are no bubbles and the gel/water mixture is of an even consistency. Fine lines in the interface indicate that there is no gel/water mixture in this particular
area this could lead to air bubbles occurring during the treatment which could lead to equipment damage, therefore this interface must be redone.

**Positioning coupling gel pad in treatment bath**

- Carefully remove the gel pad from the container ensuring that either surface of the pad is not damaged.
- Slide the gel pad into the bath ensuring that there is no air between the plastic and the pad.
- Gently press the pad down to ensure it is right against the plastic/mylar interface.
- Ensure that the surface of the water in the bath is above the gel pad.

**Positioning DQA Phantom on treatment pad**

- The DQA phantom is solid water based crossed linked gel. It can be used for multiple quality assurance tests, however it is fragile so careful handling is required to maintain its integrity.
- Remove the DQA Phantom from plastic container by opening the cover and tipping the container upside down onto an open hand.
- Inspect it for major flaws, if there are any dispose and replace.
- Slide onto treatment pad, so that it is in the middle of the gel pad over the transducer
- Don’t use excess pressure as the phantom may leave an imprint on treatment pad

**Positioning Support and Posterior Coil**

- Place the clear plastic support over the phantom so that the posterior coil can be draped over it.
- Position the wings of the patient comfort pad under the ends of the coil.
- Inspect the flexible MR coil for cracks in the insulating plastic and ensure the gold connectors within the plug are visible.
- Be careful when plugging in an anterior coil, if the coil is seated incorrectly or excessive force is used the gold connectors within the plug will be damaged, resulting in loss or no signal from the posterior coil and in-turn a reduction of image quality.
- Raise the table and plug the anterior coil into the scanners connector port.
- Landmark to the white line on anterior coil, this indicates the centre of the water bath. If the landmark is not centred to this point the transducer template will not appear on the calibration images.
- When the table is moving into iso-centre ensure all cables are free of obstructions.

**Performing Quality Assurance**

- On the HDx Workstation in the scanning window select “new MR Exam”
- Click in Patient ID text box and type “FUS DQA” and press enter
- A dialogue box will pop up, select “first level” then select “Accept”
- Press enter until you get to Patient’s Weight type in 50kg and present enter.
- In the protocol section select Pelvis
- Select protocol P18. FUS DQA
- Select Save Series
- Select Scan
- The MRI scanner will perform one coronal image at posterior 30, which is the centre of the QA Phantom.
- This is performed for two reasons;
  - It provides an image in the centre of the phantom to allow the region of treatment (ROT) to be planned
  - At least one image needs to be performed on the MRI System to provide the ExAblate system with the patient’s entry and position.

**Selection of Treatment Option and Beginning Treatment**

- The status bar on the ExAblate start window should show that the Device and the MR Scanner ready.
Select Uterine Fibroid as the treatment option,
Select the Treatment Button to begin the treatment session.
The system will then load the specific application required for treating fibroids.
In the Physicians name text box, type “QA” and click OK
The System will then open up the Calibrate Screen

Calibrate Stage

This is the first stage of the ExAblate 2000 treatment procedure
The Calibrate stage provides the system with the necessary information to determine the transducer’s home position and orientation.

Scanning Calibration Images

Click MR Scan
A pop-up message will appear on the operating console screen, check and confirm the patient’s name and position is correct.
The MR Scanner will then perform scans in the sagittal and axial planes.

Check the Acoustic Path

While the scans appear on the HDx Console Display window examine each image along the entire acoustic path ensuring that there are no air gaps visible. If there are any air gaps visible between any of the layers appropriate repositioning should be preformed.

Localising the Transducer

Once these scans are completed they will appear in the image strips.
The transducer template is displayed as a yellow overlay; it will be in the positioned in the transducer’s last home position.
Click on the sagittal image with the transducer template so it appears in the selected image window.
- Adjust the display window and level so that the outline of the transducer on the image can be seen accurately
- On the sagittal image click on the transducer template and drag the transducer template so that it overlaps the transducer image.
- Ensure there is no pitch on the transducer image, if there is click on a corner of the transducer template and adjust accordingly.
- Click on the axial image with the transducer template so it appears in the selected image window and adjust the display window and level as done previously.
- Adjust the transducer template on the axial image if necessary. If there is a roll on the transducer image, click on one of the corners of the transducer template and adjust accordingly.

**Calibration**

- When the transducer templates are in place click the Calibrate button to set the transducers home position.
- A message will appear asking whether you wish to accept this as home position.

**Load stage**

- Click Load on the main toolbar to advance to the next stage
- Load Stage allows the selection of the MR images required for treatment planning, once selected these images are transferred from the MR to the ExAblate System.
- Any QA or treatment requires images in all three planes to be acquired, the initial localiser provides the coronal image, and the two transducer calibration series provide the sagittal and axial images.
- Check that the Exam No. corresponds to the current exam. (The “Show only last exam” should ensure this is the case)
- Click on the coronal image in the series list and click Select all
- Check that series appears in the “planning images” section of the screen
- Repeat the last two steps for the sagittal and axial images respectively.
- If you wish to change the images selected click clear and select a different set
- Once all three planes are loaded then click on draw on the main toolbar to advance to the next stage.

**TREATMENT**

**Positioning the Patient**
- Consider the patient’s weight and distance from the inner dimensions of the magnet, to avoid obstruction of the table.

**Acquiring Planning Images**
- After the localiser is performed run through the images and check,
  1. That the region to be treated is directly above the transducer.
  2. Confirm whether bladder or rectal filling is required the Sagittal T2 images may help you decide
- T2 weighted images are obtained in the coronal, axial and sagittal planes
- Examine the images and ensure that;
  1. They clearly identify the region of treatment (ROT) or fibroid(s) to be treated.
  2. They include the entire path from the skin to the target area (Sagittal & Axial).
  3. There are no air gaps visible along the entire acoustic path from the transducer to the lesion.
  4. The patient has not moved during the imaging
Load Stage

**Downloading previous images** (This is particularly useful for patients having second treatments)

- If the patient has had previous treatments it is possible to load the previous post-contrast images to aid in defining the new region of treatment.
- Ensure you know the exam and series numbers of the images you wish to download
- Click show all exams
- Select the exam number from the list all of the series in that exam will appear in the series list.
- Select the series number click Select All
- The images will then appear in the planning to prior image list.
- Repeat last two steps until all of the images you wish to include are loaded.

Continuing Treatment in Case of Movement

- If patient movement is detected during the treatment and new planning images are required, perform registration between the new images with the original planning images in order to preserve the dose volume accumulated up until the current point.
- Click planning to prior
- The system will warn you that some of the data will be lost.
- All planning images will appear in the prior images frame.
- Once the new images have been acquired click refresh to update the MR exam
- Select the new planning images as done previously.
Draw stage

In this stage, the operator defines the Region of Treatment (ROT), selects the treatment protocol, draws the skin line, draws Limited Energy Density Regions (LEDR) and places fiducial markers (red crosses).

Creating or selecting the ROT

- To create a new ROT click the button labelled ROT and select new ROT.
- ROT’s are drawn on the coronal image. In order to identify the coronal image to draw on, the sagittal image can be used to find the maximum diameter of the target lesion.
- Once you have selected the image, in the selected image window click on the target lesion to start the ROT outline.
- Move the cursor in one direction, clicking on successive points to create the ROT outline.
- Click as many points as required to create a rough circumferential lesion. The accepted practice is to leave a 5mm margin from the edge of the targeted lesion.
- The ROT can be moved if adjustment is required by clicking and dragging it. The ROT can be deleted by clicking on it and pressing the delete button.

Treatment protocol

This selects the protocol under which the treatment will proceed. This then sets pre-determined spot sizes and the energy and power to be used to treat. These parameters can be adjusted later by the operator during the treatment stage, dependent on thermal feedback received.

Click on the button and select UF nominal from the drop down menu.

Defining the skin line

- Select and click on an image approximately at the centre of ROT (outlined in yellow), where the skin line is clearly visible. Match this coronal image to its equivalent axial image
- Click the Define skin line button.
- Click at the start of the skin line and click at multiple points, making sure you are clearly marking along where the skin line is.
- Double click to finish.
- To edit a drawn skin line, click on a segment and drag it to the desired location.

**Defining the Limited Energy Density Regions (LEDR)**

- There are 3 LEDRs. These are the bowel, pubic bone and far field bone. The definition of both bowel and pubic bone LEDRs is performed on the Sagittal view. The definition of the far field bone LEDR is performed on the Axial view.

**Pubic Bone**

- Click on a Sagittal view where the pubic bone LEDR is clearly visible. The image will appear in the selected image window.
- Click on the define LEDR button and from the pull down menu select the type of LEDR which is pubic bone.
- Draw the LEDR contour around the pubic bone in the selected image, double click to finish. The contour should be in the rough shape of a parabola completely shielding the pubic bone.
- The contour around the LEDR needs to be drawn only on every other image.
- Ensure that in the images where the catheter tip and balloon appear, that these are also drawn round. Both the catheter tip and the balloon are LEDRs.
- By using the interpolate feature button, the graphic elements will be interpolated on all slices.
- Click through each slice to ensure that the interpolation feature has worked and that the contour line can be seen and is accurately covering the LEDR.
Bowel

- Bowel is a LEDR and the contours are drawn on the sagittal images.
- Click on the define LEDR button and from the dropdown menu select intestine.
- In the same way draw a contour round the bowel, the drawn line should be all the way down the front of any visible bowel, with a small flick at the back. The contour line should look like a back to front tick.
- In the same way every other slice must be drawn on.
- Click on the interpolate feature, to interpolate the contour line on every image
- This step must be checked with a radiologist before proceeding.

Far Field Bone

- Far field bone is considered a LEDR. This is because as bone heats up during treatment, temporary nerve damage (neuropraxia) can occur.
- Contours are drawn on the axial image.
- Click on the define LEDR button and from the dropdown menu select far field bone.
- In the same way draw a line round the contours of the cortical bone in the beam path making sure to include every slice where nerves are present.
- For far field bone, contours are drawn on every slice. Therefore interpolation is not required.
- After drawing the bone cortex contours, make sure that they are fully defined in the entire acoustic pass zone.

Drawing fiducial markers

- The purpose of these markers is to facilitate detection of patient movement.
- Click on the fiducial button and point and click to add a fiducial marker on an anatomical feature as a reference marker.
- Fiducials must be placed around the uterus and bladder if filled, bony landmarks are useful reference points also.
- Monitoring patient movement is important in order to ensure accurate sonication targeting.
- Monitor the fiducial markers during the course of the treatment. This is particularly important if the catheter is clamped, as urine collection in the bladder will lead to alteration in the planned images.

**Plan Stage**

In the plan stage the system calculates and displays the treatment plan intended to cover the tumour surface in the ROT, and automatically determines the beam incidence angle of each one of the sonication spots to be as perpendicular to the tumour surface as possible.

During this stage the operator edits and confirms the treatment plan.

- Optimise the treatment plan such that there are no sensitive organs in the pass zone, and all spots are green
- Examine the treatment plan in all orientations; verify that the sonication spots cover the target tissue.
- If necessary individual sonication may be edited by selecting the individual spot and either angulating or changing the parameters until the spot becomes valid.
- Multiple spots may be selected by pressing the multiple arrow button.
- Remember that changing the sonication location, tilt or acoustic parameters will influence its predicted dose and hence its size and location. Carefully examine each sonication after such a change is performed.
- Before advancing to the verify stage, go into the room, to instruct the nurse and patient that you are about to start sonication. Go through use of the patient button with the patient and ensure they know when to stop
sonication. Any sensations of leg, back, buttock or skin pain must be relayed to the nurse or the present physician.

Verify Stage

Geometric verification- this ensures that the actual ablated spot is in fact the same as the planned target spot. Only sub-therapeutic doses are used to avoid injury at this stage.

The verify stage must be successfully completed before continuing onto the treatment stage.

The information window

The Reflection Data tab shows the result of the reflection measurement performed prior to each sonication. Any pulse appearing in the graph, above the dashed horizontal line, represents a significant reflection from a surface. The surface causing the reflection is located a distance from the transducer as shown in the reflection plot. When this occurs, stop the treatment and improve the acoustic coupling (checking for air bubbles is essential).

The Spectrum Data tab shows the spectrum graph, which helps to detect the presence of cavitations. A spectrum with high shoulders above the dashed horizontal line may indicate the presence of cavitations. When this occurs, stop the treatment and continue with a lower sonication energy.

The Geometric verification procedure

- Select the ROT to perform the verification spot.
- Click the add sonication button and add a reference sonication spot in the selected image window.
- Verify that the sonication test spot is located within the ROT
- Verify that the spot pass zone is not passing through any LEDRs, the system will warn you if the spot is invalid e.g. it is too close to the skin line, far field bone, pubic bone or bowel.
- The system automatically defines sonication parameters for geometric verification.

- Ensure the patient is comfortable and let them know you are about to begin.

- Click the sonicate button to apply the ultrasound energy.

- The sonication starts with the MR scanning images and then starts transmitting ultrasound energy.

- During the sonication, you should be monitoring, patient discomfort, reflection signal, spectrum signal during the transmission of energy, any patient movement by observing fiducials and the evolving temperature rise during sonication.

**Geometric Adjustment**

- On the thermal map, verify that the spot is within 1mm of the planned location. If it is repeat the procedure in the Sagittal view. At this point you may increase the energy to 130% to build up the patient’s tolerance of the procedure.

- If the hot spot is over the 1mm margin, click the adjust button and click in the centre of the hot spot to adjust to the correct position. The adjust function automatically corrects the transducers position according to the offset between the sonication location and the planned spot location. A pop-up will appear asking you accept the adjustment. Click apply, and then discard the measured thermal dose and continue.
- If a hot spot is not acquired it may be that insufficient energy was applied, increase the energy by 10% increments and repeat the procedure, until a hotspot is seen.

- After the spot is aligned in both Sagittal and coronal orientations, you can advance to the treatment stage.

**Treat stage**

During the treatment stage the full therapeutic sonication energy is used and all planned ROTs are treated. Throughout the process the operator can change the treatment plan and the sonication parameters, according to the continuous feedback being received. This is the concept of the closed loop therapy system.

The treat stage elements are similar to the verify stage, but with use of full therapeutic dose energy.

**The Treatment Procedure**

- Verify that the patient is comfortable.

- Examine the next spot to be sonicated, this is picked automatically for you by the system. The Interleave application which is on automatically, allows the system to select spots on the basis of reducing cooling time. Therefore the system selects the furthest spot from the current sonication as the next target.

- When highlighted in blue, this means that this is the current spot to be treated and it is valid. When highlighted in yellow, exercise caution when trying to optimise the location and/or orientation. Check the parameters and assess if the clinical situation allows this sonication. Information on why the spot is not blue is displayed in the information box at the top-right side of the screen.
Based upon the examination of the actual dose and patient feedback, manual changes to the treatment plan are possible at any stage during a treatment. Sonication parameters such as the energy, duration and frequency may be altered. Spots may be added or removed. Spots may be angled to avoid spot pass zone passing through LEDRs.

Remember if there is a need to stop the sonication process press the STOP SONICATION button. This button remains depressed and requires to be manually pulled back to start position.

Before each sonication, ensure that fiducials are placed around the entire target organ the uterus and NOT the fibroid/ ROT. Verify that there are no sensitive organs in the pass zone. Verify that the cooling system light is illuminated continuously and not blinking.

Once all parameters have been checked click the Sonicate button to apply the ultrasound energy. During the sonication, you must monitor
  o Patient discomfort
  o Reflection signal
  o Spectrum signal
  o Patient movement by checking the fiducial markers on the MR magnitude images.
  o The evolving temperature rise during sonication.

After the sonication, evaluate the thermal map, check the temperature at the skin line by dragging the cursor to various points along the skin line. Temperature at the skin line must be below 45 degrees.

Click continue, to the next sonication or to repeat the last sonication the repeat sonication button can be clicked. Do not forget to click back onto the next sonication button. To continue the treatment, accept the measured does of the last sonication.
- Repeat the procedure until all the planned sonications have been performed.

- If the patient moves or is repositioned, you must return to the load stage, scan new planning images, load these and create a new treatment plan based on these images.

**Conclusion of Treatment Session**

At the conclusion of the treatment session, a post treatment contrast enhanced assessment is performed to identify the non-perfused or ablated volume. This identifies treatment success. A series of 3 sagittal scans are performed, 1 axial and coronal, following administration of 10 ml IV gadolinium. A post FUS treatment protocol can be found in the drop down menu.

**2.4 Post-treatment recovery of patient**

Upon completion of the post treatment contrast scans, the patient is assisted off the table and the skin must be checked to exclude superficial ulceration/burns. In the recovery room, the patient’s observations; pulse, blood pressure and oxygen saturations are taken. The urinary catheter and intravenous cannulae are removed. The patient is allowed a meal and is observed for 1-2 hours until total consciousness is regained. The patient is advised to avoid driving for 24 hours and long haul flights for 48 hours.
CHAPTER 3: PATIENT SELECTION CRITERIA FOR MRgFUS AND MITIGATING TECHNIQUES TO INCREASE PATIENT SUITABILITY
Summary

The aim of the study was to assess selection criteria used to determine patient eligibility for proceeding with magnetic resonance-guided focused ultrasound surgery (MRgFUS) for the treatment of symptomatic uterine fibroids. It was aimed to also assess the percentage of patients presenting to a general fibroid clinic suitable for MRgFUS. The hypothesis of this study was that by identifying mitigating techniques we could increase the number of women that the non-invasive technique of MRgFUS could be offered to.

This was a retrospective analysis of 144 patients seeking minimally invasive treatment options for symptomatic uterine fibroids at a single treatment center. Clinical eligibility for MRgFUS was assessed at a gynaecology clinic by S. Zaher, a gynaecology research fellow trained in the procedure and suitability was assessed by magnetic resonance imaging. Several techniques were used to mitigate against factors that are contra-indications for MRgFUS. 100% of patients interested in MRgFUs were deemed clinically eligible for the procedure and 74% were deemed technically suitable to proceed with treatment.

It was found that mitigation techniques allow for less restrictive MRgFUS selection criteria for treatment for symptomatic uterine fibroids. These less restrictive criteria are expected to expand the pool of patients for whom MRgFUS is a viable treatment option for uterine fibroid symptoms.
Introduction

Previous experience with UAE has shown that a key factor in the acceptance of novel treatment options for uterine fibroids is the development and dissemination of consistent and informative patient selection criteria. The patient selection criteria for UAE are now well known and include both relative and absolute contra-indications. Absolute contra-indications for UAE include: a viable pregnancy, pedunculated fibroids, active infection and a suspicion of malignancy. Relative contra-indications include: coagulopathy, renal impairment, the desire to maintain child-bearing potential, and the concurrent use of a Gonadotrophin Releasing Hormone (GnRH) analogue.

Our centre at St Mary’s Hospital, Paddington, was one of the first world-wide to utilize MRgFUS, performing the procedure in up to 500 women with symptomatic uterine fibroids. Based on our institution’s extensive experience using MRgFUS in the treatment of symptomatic uterine fibroids we have developed selection criteria that are designed to maintain the safety and efficacy of the technique, whilst also making it available to as many patients as possible. The aim of this study was to assess the selection criteria used to determine eligibility for MRgFUS and to assess the percentage of patients who are suitable for MRgFUS.

Initial guidelines on patient selection criteria were provided by the manufacturer (Insightec Ltd) and were decided and approved by the Food and Drug Administration (FDA). With further experience these guidelines were found to be more restrictive than those needed for the updated MRgFUS system in use in our centre and many limitations could be overcome, by various mitigating techniques.
Patients and Methods

Patient Population

Patients attending the tertiary fibroid clinic at St. Mary’s Hospital between September 2005 and December 2006, and who specifically expressed interest in minimally invasive treatments for their fibroids, were included in this retrospective analysis. The patients were referred by their general practitioner or by a local gynaecologist. For demographics see table 1 below.

<table>
<thead>
<tr>
<th>Patient Demographics</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Mean (Years)</td>
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<tr>
<td>Range (Years)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Range</td>
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<tr>
<td>Hormonal Status</td>
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<tr>
<td>Pre-menopausal</td>
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<tr>
<td>Peri-menopausal</td>
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<tr>
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<tr>
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<tr>
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<td>12%</td>
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<tr>
<td>African</td>
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</tr>
<tr>
<td>Number of fibroids</td>
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<tr>
<td>Patients with a single fibroid</td>
<td>61%</td>
</tr>
<tr>
<td>Patients with multiple fibroid</td>
<td>39%</td>
</tr>
<tr>
<td>Fibroids intensity on T2w images (relative to myometrium)</td>
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</tr>
<tr>
<td>Patients with hyper-intense fibroids</td>
<td>12%</td>
</tr>
</tbody>
</table>

Chapter 3 Table 1: Potential MRgFUS Patient Demographics
Patients were assessed for clinical eligibility and technical suitability as per chapter 2 methods and materials.

A radiologist experienced in MRgFUS (WG) analyzed the screening MR images to determine patient suitability for the procedure according to set parameters as outlined in Figure 1.

In summary, patients were deemed suitable for MRgFUS if they had up to six uterine fibroids clearly visible on MRI that were no more than 14 cm away from the skin line. Mitigating techniques to overcome issues of an excessive amount of bowel in the potential beam path were attempted. These included bladder filling to physically raise the uterus and push bowel loops upwards and rectal insertion of an inflated Sengstaken tube in an attempt to push the uterus more anteriorly displacing bowel loops. In cases where bowel could not be shifted, patients were excluded from consideration, as air bubbles or hard particles present in the bowel may reflect or absorb the ultrasonic energy. Patients with longitudinal scars in the beam path, and transverse scars that could not be seen on the MR images were excluded, as scar tissue may absorb the ultrasound energy and cause pain or even a skin burn (see figure 2). Overcoming the scar problem is discussed further in this thesis.

Patients with fibroid volumes of more than 500cc, or a hyper-intense fibroid on T2 weighted imaging were pre-treated with a GnRH analogue for three months in an effort to reduce the size and vascularity of the fibroid (this will be discussed further in chapter 4).
Chapter 3 Figure 1: Flowchart showing criteria used to assess patient suitability
Chapter 3 Figure 2: Full thickness scar burn created by treating directly through a previous caesarean section scar. This patient required plastic surgery
**MRgFUS procedure**

All MRgFUS procedures were performed using the ExAblate 2000 (InSightec, Haifa, Israel), which is fully integrated with a 1.5 Tesla MR scanner (GE Medical Systems, Milwaukee, WI) as outlined in chapter 2 Methods and Materials.

**Statistical analysis**

Summary descriptive statistics were used for demographic data, symptom-severity scores (SSS) and volume measurements. A paired Students t-test was used for comparison of SSS and measured volumes before and after treatment. Null hypotheses were rejected at a P level of less than 0.05.
Results

Between September 2005 and December 2006, 144 patients attended the Fibroid Clinic at St. Mary’s Hospital, in search of minimally invasive treatment for their fibroids. Patients were counseled regarding current treatment options, and 100 of them requested to have the non-invasive MRgFUS treatment. The remaining 44 patients opted for either surgical management, UAE or no treatment. The 100 patients requesting MRgFUS form the initial patient group. Demographics and patient characteristics of this group are described in table 1.

All 100 patients requesting MRgFUS were found to be clinically eligible for the treatment after a physical examination, according to the exclusion criteria specified on page --- chapter 2. These patients were sent for screening MRI scans. Of the 100 patients in the initial patient group, 74 patients were assessed as being suitable for MRgFUS and 26 patients were deemed not suitable. Of the 26 patients not suitable for MRgFUS, seven had bowel completely occluding the acoustic window, four had a mixed picture of adenomyosis and fibroids, three had 20 or more fibroids of approximately 1 cm diameter, one had a dermoid cyst, and 11 had scars occluding the treatment window, including four with longitudinal scars. Suitability results are summarized in figure 3.
Of the suitable patients, one patient had bowel across the acoustic window, covering the front of the fibroid. This patient was re-assessed following bladder filling and deemed anatomically suitable for MRgFUS. The filled bladder had elevated the whole uterus, thereby pushing the bowel clear from the acoustic window (see figure 4).
Chapter 3 Figure 4: Figure showing bowel clearance from the acoustic window by bladder filling. Arrows delineate the position of the bowel. Left image is pre-bladder fill, right is post-bladder fill.
Chapter 3 Figure 5: Figure showing bowel clearance from the acoustic window by an inflated sengstaken tube. Arrows delineate the position of the bowel. The top image shows bowel between anterior abdominal wall and the uterus which has been displaced in the lower image by the uterus which has been pushed anteriorly by the Sengstaken tube.
Sixty-five (88%) of the treated patients were given three monthly injections of a GnRH analogue prior to treatment, either to shrink the fibroid (see Figure 7) or to improve the response to MRgFUS for fibroids that were hyper-intense on T2 weighted imaging.

Twenty-eight (38%) patients required two sessions of MRgFUS treatment due to the presence of large or multiple fibroids.

Chapter 3 Figure 6: Comparative images of the same patient pre and post GnRHα pre-treatment, showing shrinkage in overall fibroid
Treatment outcome

The changes in symptom severity score over a period of six months are outlined in the graph below. The average SSS at baseline was 69.4 (SD 14.7, range 22 – 96), this dropped to an average of 47.1 (range 11- 51). At six months there was a further drop in SSS to an average of 38.3 (SD 16.2 range 9- 42). 95% patients experienced significant symptom improvement at 6 months (>10 point drop in score, p<0.0001), see figure 8. The average non-perfusion achieved was 41.9% (range 35- 90%). Average uterine volume at baseline was 768cc (SD 111.4 range 535.5cc - 1200cc) at six months the average uterine volume had decreased by approximately 35% to 504cc range (298 – 734cc) (p<0.0002). Sixty three patients (88%) completed follow up to six months.

Chapter 3 Figure 7: Graph showing symptom improvement over time.

At six months no patients underwent alternative treatments. Two patients required prescriptions of tranexamic acid 3 months post treatment, due to heavy bleeding, however both of these patients had experienced symptom improvement with a shortening in the duration of menses from 10 and 12 days to 4 and 5.
No adverse events were reported post procedure, with most patients tolerating the procedure well (see figure 8).

Chapter 3 Figure 8: Graph illustrating pain experienced by patients pre, during and immediately post treatment.
Discussion

With an increasing numbers of patients looking for treatment options that afford them the least amount of disruption to their daily routine, the appeal of MRgFUS is clear and growing. While MRgFUS provides an effective non-invasive treatment option (106) for uterine fibroids, the ability to make the procedure broadly available to women who may benefit from it requires the establishment of patient selection and suitability criteria that are less restrictive than the guidelines developed using older MRgFUS technology.

In a previous study (Arleo, Khilnani et al. 2007) 63% of patients inquiring about MRgFUS treatment for symptomatic uterine fibroids were clinically eligible, as decided per study exclusion criteria. Of these patients, only 25% were then found anatomically eligible following MRI screening. However, these findings were limited by the use of guidelines and limitations that were more restrictive than those needed for the MRgFUS system used in the current study.

In the retrospective analysis reported here, patients participating in the study had 100% clinical eligibility and 74% anatomical suitability for MRgFUS. The increase in clinical eligibility and anatomical suitability in this study compared with previous reports likely results from differences in inclusion-exclusion criteria (see Table 2).
### Clinical factor

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Prior study</th>
<th>St. Mary’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient symptoms of fibroids</td>
<td>SSS &lt;21 Excluded</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Age &lt;40 or &gt;60 years</td>
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<td>Desires pregnancy</td>
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</tr>
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### Technical factor

<table>
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<td>Too much fibroid volume</td>
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<td>Not relevant</td>
</tr>
<tr>
<td>Bowel</td>
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<td>Partly mitigated</td>
</tr>
<tr>
<td>Significant adenomyosis</td>
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<tr>
<td>Pedunculated fibroids</td>
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<tr>
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<td>Excluded</td>
</tr>
<tr>
<td>Bright T2 fibroid</td>
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<td>Partly mitigated</td>
</tr>
<tr>
<td>Degenerating, necrotic, or infracted fibroids</td>
<td>Excluded</td>
<td>Excluded</td>
</tr>
<tr>
<td>Arterial-venous malformation, calcified fibroids, or conglomerate of fibroids or septated fibroids hard to transmit heat across</td>
<td>Excluded</td>
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</tbody>
</table>

Chapter 3 Table 2: Comparison of assessment criteria used in earlier studies and the St Mary’s centre.
In our hospital, minimal age, menstrual status and minimal symptoms severity score were not factors for exclusion. In addition, patients who desire future pregnancy also are approved for treatment, as there are case reports showing successful live birth post treatment (Gavrilova-Jordan, Rose et al. 2007; Hanstede, Tempany et al. 2007). Additionally, several mitigation techniques used in the current study allowed for the treatment of some patients who initially had bowel obstructing the beam path, large fibroid volumes, scars, or fibroids that were hyper-intense on T2 weighted imaging. For patients with obstructing bowel, simple measures such as rectal and bladder filling effectively clear bowel away from the acoustic window, allowing for increased treatment capacity. Pre-treatment of large fibroids with a GnRH analog helps to reduce fibroid volume, which may improve MRgFUS outcomes. We previously have reported results of a study in which 50 women with fibroids greater than 10cm in diameter were treated with a three-month course of a GnRH analog prior to MRgFUS (Smart, Hindley et al. 2006). This is discussed further in Chapter 5. Results show that 83% of patients treated with this regimen described significant improvement in their uterine fibroid symptoms at 24 months post-MRGFUS. Similarly, from our past experience, of treating hyperintense (hyper-vascular) fibroids, we know that these types of fibroids are generally resistant to treatment (see figure11). By pre-treating hyperintense fibroids with GnRHa we are able to reduce vascularity and hence intensity within the fibroid allowing for more efficacious treatment.
Chapter 3 Figure 9: Left image shows a hyperintense fibroid as compared to normal myometrium. The right image is a planning image prior to MRgFUS treatment showing the same fibroid post 6 months of GnRHa therapy, now hypo-intense when compared to myometrial tissue and smaller.

We also have identified an original method of highlighting transverse scars, which has improved our visualization of scar tissue and enabled us to treat patients who were previously excluded. With this method, scars are painted with a solution of nail varnish and paramagnetic iron oxide particles, providing an obvious artifact along the line of the scar, which can easily be avoided by appropriate positioning and angling of the ultrasound beam. This will be discussed further on in chapter 4.

The strength of this particular study lies in the number of uterine fibroid patients that have been treated with MRgFUS at this institution and long-term experience of the staff in selecting patients for the procedure. This experience has enabled the identification of a variety of techniques that may be used to expand the pool of patients for which MRgFUS may provide a safe and effective treatment for uterine fibroids. The treatment outcomes in this group of women are very comparative with other published data from sites using more restrictive criteria. In 2004 Stewart et al published results on 109 women undergoing MRgFUS. 79.3%
reported significant improvement in symptoms (>10 point improvement of SSS) at six months post treatment (Hindley, Gedroyc et al. 2004).

Guidelines developed from this experience base are expected to provide a greater number of women with a non-invasive approach to managing symptomatic uterine fibroids, without any compromise in efficacy.

The main weakness of the study is that the statistics do not show the suitability of MRgFUS for the general population of women suffering from uterine fibroids symptoms but was dependent on patients who were almost self-selected in that they specifically requested minimal invasive treatments. Referring gynecologists conducted additional assessments prior to referring patients to the Fibroid Clinic, and data related to the screening criteria used by individual physicians were not available for inclusion here.

In conclusion, we have found that the use of the mitigation techniques described above makes it possible to offer MRgFUS to a much larger subset of patients than previously believed. Further studies to evaluate these techniques may help to refine further the selection and suitability criteria for MRgFUS as a treatment for symptomatic uterine fibroids.
CHAPTER 4: MRgFUS IN THE TREATMENT OF WOMEN WITH UTERINE FIBROIDS AND ABDOMINAL SCARS
Summary:

The aim of the study was to identify an effective method of ensuring safe MRgFUS treatment of patients with symptomatic uterine fibroids and abdominal scars.

We describe the treatment and outcomes of 25 patients who presented with symptomatic uterine fibroids and an abdominal scar. A solution containing paramagnetic iron oxide particles was used to highlight the scar during treatment, making it visible on MR images obtained during the planning of treatment.

We hypothesised that by being able to identify abdominal scars on MRI we could accurately target treatment to avoid the scar region, safely treating women who presented with scars.

All women were treated with no immediate complications. No episodes of skin burns, ulceration or skin redness were reported. Quality of life scores were compared at baseline, 3 months and 6 months post treatment. The non-perfused volume achieved in the targeted fibroid tissue was also calculated for each patient, using volumetric analysis, the average ablation created was 65%.

Conclusion: Using Paramagnetic iron oxide solution to highlight transverse abdominal scars, allows them to be easily identified on MRI and therefore avoidance of the scars can be ensured by the operator, allowing safe but also effective treatment of these women, who were previously excluded.
Introduction

The safety profile of MRgFUS has been proven in various studies with only mild adverse events including, urine infection, temporary nerve irritation and skin redness being reported for the majority of patients (Hindley, Gedroyc et al. 2004; Smart, Hindley et al. 2006).

A serious adverse event that was reported in our centre at St Mary’s in one of our early research patients, of a full – thickness skin burn (see Chapter 3 figure 2) that required skin grafting led to the presence of any abdominal scars being a contraindication to treatment with MRgFUS.

Because scar tissue is more fibrotic and less vascular than normal skin tissue, it absorbs more ultrasound energy when compared to normal abdominal tissue. In addition the scar area can be de-nervated resulting in the danger of over-heating the skin without the patient experiencing the sensation of pain as a warning sign. Because of this the operator/ treating physician is instructed to avoid the delivery of energy through the scar area when treating women with abdominal scars. Due to the difficulty in the identification of scars on MRI, this was near impossible to ensure and hence our exclusion of these women from treatment (see figure 1).

However due to the presentation of many women with either caesarean section or myomectomy scars, we identified an original method of highlighting transverse scars, which has improved our visualization of scar tissue and enabled us to treat patients who were previously excluded. With this method, scars are painted with a solution of nail varnish and paramagnetic iron oxide particles, providing an obvious artifact along the line of the scar, which can easily be avoided by appropriate positioning and angling of the ultrasound beam.

The aim of this study was to identify the effectiveness of this technique in allowing a safe and efficacious MRgFUS treatment.
Chapter 4 Figure 1: Treatment assessment scan performed prior to treatment with full bladder. The scar location not visible on MRI but is marked with a cod liver oil tablet (which shows up on scan but cannot be used during treatment due to heat bursting the capsule)
Chapter 4 Figure 2: A photograph of the same patient, showing an abdominal scar from a caesarean section
Patients and methods

Twenty five women who presented consecutively to the gynaecology clinic at St Mary’s Hospital, London with symptomatic uterine fibroids and an abdominal scar were treated with MRgFUS. All women had a screening MRI scan to determine technical suitability for MRgFUS treatment as assessed by a consultant radiologist. On the day of treatment care was taken to ensure that the pubic area was shaved clear of any hair to avoid the risk of air bubbles forming.

Several different solutions were tried and tested prior to achieving a solution which created an artefact easily visible on MR scan. The first solution tried was a nail varnish said to contain iron particles, the second was a mixture of gadolinium (a contrast agent in routine use at our department) and nail varnish to a ratio of 1:1 the third solution was Endorem (a contrast agent) mixed with nail varnish again to a ratio of 1:1 (See figure 3). This proved to be the most effective marker; creating the most artefacts. Endorem (Guerbet, Sulzbach) is a super-paramagnetic contrast agent for magnetic resonance imaging of the liver and spleen. The contrast agent consists of dextran-coated iron oxide particles with a size distribution between 120 and 180 nm and an iron concentration of 0.2 mol/l. Various different concentrations of Endorem to nail varnish solution were tried and tested to obtain the superior marker (see figure 4). Solution 1: consisted of 1 ml Endorem and 10ml of nail varnish, solution 2: 2ml of Endorem added to 10ml of nail varnish, solution 3: 5ml of Endorem to 10 ml of nail varnish. It was discovered that 4 mls of Endorem added to a 10ml bottle of nail varnish provided the best marking, in that a sufficient artefact was created on MRI whilst maintaining the consistency of the solution to allow easy coverage of the scar. The area of the scar was painted across its entirety with the iron oxide solution. All women were consented for the risk of skin burn and advised to inform the physician and nurse of any skin warming sensation experienced at any time throughout the procedure. Identification of the position of the scar was made on the MR images collated and the position was marked identifying it as a low energy density region (LEDR). Angulations of the beam as necessary to avoid the area were made. During the procedure the occurrence of any skin pain and frequency was noted. At the end of
the procedure, any redness, ulceration or changes to skin was also noted. Immediate treatment outcome was assessed by the non-perfused volume (NPV) achieved. All patients filled in the UFS-QOL prior and at 3 and 6 months post procedure.

Statistical analysis
Summary descriptive statistics were used for demographic data, QOL scores and volume measurements. Students t-test was used for comparison of SSS before and after treatment. Null hypotheses were rejected at a P level of less than 0.05.

Chapter 2 Figure 3: Photograph showing different markers being tested on a volunteer’s lower limb. The 1st marker identified by 1 cod liver oil tablet was nail varnish only. The 2nd is gadolinium, the 3rd Endorem.
Chapter 2 Figure 4: Various different concentrations were tried to identify the correct balance of contrast agent to nail varnish. It was identified that a concentration of 4mls of Endorem in a 10 ml bottle of nail varnish was the superior marker.
Results:

A total of 25 women underwent MRgFUS. The mean age of the women was 37 years (+/- 8; range 29-45). No subjects were post-menopausal. The mean body mass index (BMI) was measured as 24.87 (+/- 4.13; range 19-38) and the ethnic origin of the group was as follows; 17 Caucasian, 5 Black (African or Afro-Caribbean) and 3 Asian origin. Demographics and patient characteristics of this group are described in table 1 below.

Six patients presented with multiple fibroids and nineteen patients with a single fibroid. The average fibroid volume targeted was 740cc (range 48cc-840cc).

The primary presenting symptom was menorrhagia in 23 (92%) patients, with 2 (8%) patients presenting with pressure symptoms in the form of urinary frequency.
Chapter 4 Table 1: Patient Demographics

N=25

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<table>
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<tr>
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<tr>
<td><strong>Number of fibroids</strong></td>
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<td>Patients with a single fibroid</td>
<td>76%</td>
</tr>
<tr>
<td>Patients with multiple fibroid</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Clinical follow-up**

No incidences of skin pain were reported during treatment. Examination of the skin post treatment revealed no incidences of skin redness or any skin changes. The non-perfused volume (NPV) created in the targeted treatment region was calculated as a percentage of the total fibroid. The average NPV achieved was 65% (range 35-80%) which compared favourably with results from other studies. All women reached the 6 month follow up stage. The average baseline quality of life (QOL) score was 54.5 (range 34-91) at 3 months this was 41.2 (range 9-63) and at by 6 months the average QOL score had dropped by 64% to 34.7 (range 5-64, p<0.0001).
Discussion:

Following the first report of a full thickness burn in a woman following MRgFUS treatment (Leon-Villapalos, Kaniorou-Larai et al. 2005), despite continuous real-time MR imaging and thermal mapping, patients with abdominal scars have been excluded from treatment with MRgFUS. It was later understood that scar tissue is more fibrotic and less vascular which causes it to absorb more energy compared to normal abdominal tissue. Also as the scar area is to some extent de-nervated it results in a danger of over-heating the skin without the patient experiencing any sensation of pain as a warning sign. Scar identification on MR is difficult and therefore avoidance of the scar has been problematic.

Due to the recurrent nature of uterine fibroids however, this has posed a treatment dilemma for patients who seek a non-invasive treatment option following a previous myomectomy or other abdominal surgery. By direct visual observation of the scar, it was anticipated that complete avoidance of the scar could be achieved by various techniques, including bladder filling to lift the uterus above the scar creating a clear acoustic window (see figure 5).

Angulation of the beam could also achieve a clear beam pathway without going through the scar (see figure 6). By painting the scar completely with a paramagnetic iron oxide solution we have achieved a method by which an abdominal wall scar may easily be identified and avoided on MR imaging without affecting treatment outcome. All twenty five patients completed treatment without any adverse effects. One patient had a NPV of <40% due to the hyper-intensity of her fibroid causing poor thermal necrosis. This method of highlighting the scar provides the operator with complete control on the safety of treatment, without having to rely on the patient to relay sensations of skin pain. This method has allowed us to extend this non-invasive treatment to a significant subset of patients who previously had been excluded.
Chapter 4 Figure 5: Image showing abdominal scar easily visible on MR imaging, by filling the bladder the scar can be avoided completely.

Chapter 4 Figure 6: Image showing angulation of beam to avoid the scar (red arrow).
CHAPTER 5: MRgFUS FOR THE TREATMENT OF LARGE UTERINE FIBROIDS.
Summary

The objective of this study was to assess the feasibility and effectiveness of treating large uterine fibroids with MRgFUS following pre-treatment with GnRH agonists.

The hypothesis of this study was that by pre treating larger uterine fibroids with GnRH agonists, this would allow sufficient shrinkage of larger uterine fibroids, which could be maintained following treatment with MRgFUS.

This is a prospective study of women with fibroids in excess of 10cm in diameter who received Gonadotrophin Releasing Hormone (GnRH) agonist before MRgFUS treatment. Patients were recruited from the Gynaecology outpatient clinics and assessed for eligibility. Entry criteria were a set minimum fibroid symptom severity score (SSS) of 18 and confirmation of fibroid dimension >10cm based on screening MRI. All patients had a 3-month course of GnRH agonists followed by MRgFUS treatment. The primary outcome measurement was reported change in SSS as judged by the Uterine Fibroid Symptoms and Quality of Life Questionnaire (UFS-QOL).

Comparison was made at enrolment, treatment, 3, 6, 12 and 24 months post-treatment. Results: Fifty women were enrolled in the study. There was a 50% reduction in mean SSS at 6 months and this was maintained for 24 months post treatment. There was an average reduction in target fibroid volume of 21% overall at 6 months (p<0.01), 37% at 12 months and 34% at 24 months. No serious infective complications or emergency operative interventions were recorded.
**Introduction:**

Uterine Leiomyomas have both Oestrogen and Progesterone receptors and as such their growth and maintenance are sensitive to oestrogen and / or progesterone, with their effects being mediated by local peptide factors (Murphy, Kettel et al. 1993).

The depletion of these hormones during the menopause induces a significant regression of leiomyomas. A pseudo-menopause status can be created by treatment with gonadotrophin releasing hormone analogue treatment (GnRHa) treatment (Filicori, Hall et al. 1983).

GnRH is released from the hypothalamus and binds to specific receptors on pituitary gonadotrophs, resulting in stimulation of gonadotrophin biosynthesis which leads to subsequent modulation of ovarian activities.

GnRH agonist decreases oestrogen and progesterone secretion from the ovary and has been used in the treatment of some sex hormone-dependent cancers, including breast, prostatic, pancreatic, endometrial and ovarian cancers. Therapy of leiomyomas with GnRH agonist has been tried and has been shown to reduce leiomyoma volume (Adamson 1992; Watanabe, Nakamura et al. 1992). The reduction of tumour volume is associated with a decrease in cell proliferation and with an increase in cell loss by apoptosis. The molecular mechanisms involved however have not been fully clarified.

GnRH analogue administered once a month can result in approximately a 30 -50% (Adamson 1992) reduction in uterine volume and often an associated improvement in fibroid-related symptoms due to the accompanying amenorrhea. GnRHa treatment is limited for short term use due to unacceptable symptoms such as hot flushes and demineralization of bone with prolonged treatment. It is well known that on stopping GnRH treatment, there is often a rebound in size and a return of symptoms (Friedman, Hoffman et al. 1991). Thus to date GnRHa has been advocated as an adjuvant to surgery, both to reduce fibroid volume and to control bleeding.
The use of MRgFUS is limited in larger fibroids due to the treatment being volume dependent. By shrinking the overall uterine volume prior to treatment, we can make treatment of these larger fibroids more feasible.

The main hypothesis to be answered by this study is whether ablation of uterine fibroids with MRgFUS following three months of treatment with GnRHa therapy, will prevent the rebound in both volume and symptoms from the fibroid that is seen following treatment with GnRHa alone?
Patients and methods

Women with symptomatic uterine fibroids who presented to the Gynaecology clinics at St Mary’s Hospital, London, between April 2003 and October 2004 were recruited and followed up for 12 months by a previous gynaecology research fellow, O. Smart. Twenty-four month follow-up and statistics were performed by S. Zaher. All patients were informed about the benefits and potential risks and provided written informed consent to participate. Patient’s symptoms were assessed using a validated fibroid specific quality of life questionnaire, UFS-QOL (Spies, Coyne et al. 2002) and only women meeting the minimum symptom severity screening score of 21 points were included. Clinical entry criteria for this study dictated a minimum age of 18 years with no desire for future fertility. Women with a haematocrit < 25%, a positive pregnancy test, major medical disease or contraindication to MRI scanning were excluded from the study. (For full inclusion and exclusion criteria please see appendix).

Pre-treatment Imaging

All study participants underwent initial MR imaging of the pelvis in a 0.5T scanner (GE Medical Systems, Milwaukee, Wis) as detailed in Chapter 2: Materials and Methods. Only patients with largest diameter of the target fibroid being a minimum of 10cm were included.

Treatment preparation

GnRH agonist, Goserelin 3.6mg (Zoladex, AstraZeneca, UK), was administered as a course of 3 subcutaneous injections. The first injection was given on day one or two of the menstrual cycle with subsequent injections given twenty eight days later. MRgFUS was carried out two–three weeks following the last injection. On the day of treatment all patients were requested to shave their abdomen from the level of the umbilicus to the pubic symphysis, as experience from sister sites had identified the potential of air bubbles being trapped in the pubic hair with resultant skin burns. An intravenous cannula for IV analgesia and sedation and urinary
catheter were inserted. A pregnancy test was also performed, a positive pregnancy test being an exclusion criterion.

The MRgFUS procedure was performed as outlined previously in this thesis by O. Smart.

**Statistical analysis**

Summary descriptive statistics were used for demographic data, QOL scores and volume measurements. Wilcoxon Rank tests were used for comparison of SSS and measured volumes before and after treatment. Null hypotheses were rejected at a P level of less than 0.05.
Results:

Of the 50 women enrolled in the study, only one was unable to tolerate the procedure due to severe claustrophobia and did not undergo magnetic-resonance-guided focused ultrasound and was included in the screening failure group. The mean age of the participating women was 41 years (range 33-52 years). No subjects were postmenopausal, and only one was peri-menopausal. The mean body mass index was 24.87 (range 19-38), and the ethnic origin of the group was as follows: 24 white, 16 black (African or Afro-Caribbean), 3 Asian and 7 ‘other’ ethnic origin. 7 women had low transverse abdominal scars, of these, 3 were due to previous open myomectomy, 3 following Caesarean section and 1 as a result of ovarian cystectomy. One woman had been diagnosed with mild endometriosis but the remaining subjects had no history of additional gynaecological pathology.

Treatment outcomes

Thirty-eight of the 49 women completed MRgFUS treatment in one session and 11 subjects required a second visit to complete therapy. Mean treatment time was 183 mins (+/− 24; range 150-240) for the first treatment and 178 mins (+/− 27; range 135-210) for the second session with an average of 50 (+/− 20) sonications being delivered per patient. Total analgesic requirement during the procedure averaged 70 mg of Pethidine (range 0-100) and 7 mg of Diazepam (Range 0-10). All patients remained fully conscious and communicative throughout treatment.

The subjective assessment of change in symptoms for each patient, based on the UFS-QOL, is shown in figure 1. At enrolment mean symptom severity score was 61.82. On the day of treatment this had decreased by almost two-thirds (SSS = 22.44), which is explained by the amenorrhoea and reduced fibroid volume induced by 3 months of pre-treatment with GnRH agonist. Despite a small rise in symptom score, as would be expected following the return of menses, the mean SSS at 6, 12 and 24 months remained 50% lower than at enrolment (SSS =30.31).
Chapter 5 Figure 1: Shows the mean changes in QOL scores up to 24 months post treatment. This graph shows a substantial initial fall as described above followed by a continued symptom score reduction post FUS treatment and post cessation of GNRH treatment indicating prolonged improvement over this time course.
Chapter 5 Figure 2:

24 Month fibroid volume difference

- Fibroid Volume (cc)
- Patients

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|----------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Volume   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

- Screening
- 24 Months
The mean uterine volume at baseline was 1217 cm$^3$ (+/-601). Following treatment with 3 doses of GnRH agonists there was an average volume reduction by 38.5% to 724 cm$^3$ (+/-369). Following treatment with MRgFUS patients were scanned at an average interval of 6 months and 5 days (+/- 12 days). No evidence of oedema or soft tissue damage outside of the target fibroid was seen on follow up MR imaging. Contrast enhanced T1 weighted images demonstrated a mean non-perfused volume of 144 cm$^3$ (+/- 127) created within the target fibroid.

There was a significant reduction in volume of the target fibroid of 21% at 6 months and 37% at 12 months over the duration of the study (mean = 105 cm$^3$; p<0.01). By 24 months mean uterine volume was 419.04 cm$^3$ (p<0.001 range 69-1525 cm$^3$). Figure 2 compares volume reduction at baseline and 24 months post-procedure.

**Adverse Events**

Adverse events were monitored and reviewed at each study visit (treatment, 1 week, 3 months, and 6, 12 and 24 months). Two patients described lower back pain immediately after treatment, which persisted beyond 1 week but had resolved by 6 months. Small superficial skin burns (<2cm diameter) occurred in 2 patients and healed with minimal scarring. The only serious adverse event was a 5cm full thickness skin burn in a patient with a previous low transverse laparotomy scar mentioned earlier in this work. This event was pre-scar marking and prompted our investigation into overcoming this problem. This patient did not report any pain during the procedure due to a region of localised anaesthesia adjacent to the scar. Excision and direct closure of the area was carried out with a good cosmetic result at 6 months. Other adverse events documented were fainting during treatment (n=1), urticarial reaction to IV pethidine (n=1) and a report of sensory loss to a small area of skin in the right groin, which persisted beyond 6 months (n=1).
**Alternative treatments**

11 patients had alternative treatments, these included Myomectomy (n=2) Hysterectomy (n=4) Uterine Artery Embolisation (n=3) and percutaneous laser ablation (n=2). 3 of these were after 6 months post-treatment, 8 of the alternative treatments took place after 12 months post-treatment.

In total 26 patients completed 24 month follow-up, 9 did not consent to the longer-term follow up, 11 patients had alternative treatments and 3 were lost to follow up.
Discussion:

The management of uterine fibroids has undergone a revolution in the past few decades with better understanding of its impact on fertility and technical advances in endoscopy and radiologic embolisation techniques and also pharmaceutical alternatives such as gonadotrophin-releasing hormone agonist and progesterone intrauterine contraceptive devices. Much work is still needed to understand better molecular mechanisms and cellular biology before the arrest of tumour genesis can be achieved. We attempted to achieve a similar clinical effect by arresting fibroid growth by thermo-ablation of a hormonally pre-treated fibroid (see figure 3 and 4).

Chapter 5 Figure 3: Study patient 5. Left image shows a Sagittal view of a 10cm fibroid prior to treatment. Image on the right shows the same fibroid following 3 months treatment with GnRHa injections.
Chapter 5 Figure 4: Post treatment images of study patient 5. Left image shows a contrast enhanced image of the same fibroid immediately post treatment with MRgFUS. The image on the right shows the same fibroid 12 months post treatment, significantly smaller than at baseline.

The use of GnRH agonist pre-treatment is well established and routinely used by many surgeons prior to open or endoscopic surgery for uterine fibroids. This regulatory neuropeptide, when administered in a continuous fashion, creates a temporary menopausal state. It has been observed that in this hormonal milieu a significant reduction in fibroid volume occurs. Since fibroids rapidly re-grow to their original size within a few months of discontinuing GnRH agonists (Friedman, Hoffman et al. 1991), (see control case of ultrasound images figures 5-7 below) and longer-term administration is associated with significant morbidity, such as osteopenia, this type of drug cannot be used as a definite treatment for symptomatic fibroids.
However, as a time limited adjunctive therapy, it provides the technical advantages of smaller tumour size and also the additional benefit of reduction in vascular flow.

Chapter 5 Figure 5: Ultrasound image of control patient prior to GnRHa treatment. Size of fibroid pre-treatment measures 9.04cm
Chapter 5 Figure 6: Ultrasound image of control patient after 6 months of GnRHa therapy. Fibroid now measures 5.69 cm.
Chapter 5 Figure 7: Ultrasound image of control patient 1 year post cessation of GnRHa treatment. There has been a rebound in fibroid size to 9.91 cm.

When MRgFUS is performed large areas of coagulative necrosis can be achieved, in the shrunken fibroid, resulting in a prolongation of the symptomatic improvement seen in patients. This has allowed the technique of MRgFUS to be offered to women with larger fibroids. The time intensive nature of the procedure has meant that treatment of these women had previously been particularly lengthy and unsuccessful, with minimal shrinkage or non-perfusion achieved. (See figures 8-9).
Chapter 5 Figure 8: A Sagittal MR image of a giant fibroid uterus extending well above the umbilicus measuring 19.5 cm.
Chapter 5 Figure 9: A contrast enhanced image of the same patient in figure 8 post treatment with MRgFUS. The darkened central area corresponds to the ablation created within the fibroid. A massive volume of perfused fibroid tissue remains, indicating the complexity in treating large fibroids without pre-treatment with GnRHa injections.

We identified that by ablating the fibroid in patients pre-treated with a course of GnRH analogues, we can achieve long-term symptomatic improvement in patients of 24 months and beyond. We are also able to maintain the initial shrinkage that is often seen with GnRH analogues.
The main limitation of this study was that this study was initially planned with a 12 month follow up, as such not all of our recruited patients agreed to persist with follow up beyond the 12 month stage. Further work is under way to obtain longer term follow up results in our treated patients, unpublished data are optimistic, with some patients showing continued symptomatic relief beyond 36 months post-treatment.

In conclusion, we describe a non-invasive method which can be used to prolong the symptomatic relief afforded to patients following GnRHa administration, without actually having to continue administration of injections and hence any of the hormonal side-effects.
CHAPTER 6: MRgFUS FOR THE TREATMENT OF UTERINE FIBROIDS IN WOMEN DESIRING FUTURE PREGNANCIES.
Summary

The main aims of this study were to evaluate the safety of MRgFUS in the treatment of uterine fibroids in women desiring future fertility. Safety was determined by the evaluation of the incidence and severity of procedure related complications, including pregnancy, delivery and post-partum complications. This was a multicentre, international study (for participating sites please see appendix), pre-menopausal women who presented to the outpatient gynaecology clinic with symptomatic uterine fibroids and a desire to become pregnant within the next 12 months were recruited.

One hundred and sixteen women were recruited from five centres. There were sixty four reported pregnancies in sixty one women, with 30 completed deliveries. The mean time to conception was 8 months after treatment (range 4-11 months). The spontaneous abortion rate was 27%, with an elective pregnancy termination rate of 11%. The mean birth weight was 3.3kg, and the vaginal delivery rate was 64%. There were no reported cases of uterine rupture, premature labour, abnormal placentation or placental abruption. The preliminary fertility data are promising; with women treated with MRgFUS for their symptomatic fibroids being able to spontaneously conceive, carry and deliver safely.
Introduction

Uterine fibroids are the most common neoplasm of the female pelvis, increasing in incidence in the later reproductive years. A shift in cultural trends of women delaying pregnancy has resulted in many women presenting with symptomatic fibroids at a stage when preservation of the uterus is a priority. The national office of statistics reports a 74% increase in the number of conceptions in the 40-44 age group in 2004, when compared to 1988. This has resulted in a dilemma for the gynaecologist who is faced with providing an effective solution to his patient’s fibroid symptoms, whilst ensuring no detriment to her fertility. The current standard of practice remains surgical in the many forms of myomectomy (laparotomy, laparoscopy, hysteroscopy).

Despite myomectomy being the gold standard, few studies agree on the actual increase in pregnancy rates following surgery, this being described as anything from 44-81% however all report a fall in rate of pregnancy loss (Marchionni, Fambrini et al. 2004; Sinclair, Gaither et al. 2005; Seracchioli, Manuzzi et al. 2006).

Unfortunately fertility enhancement is not the only factor to be considered when recommending treatment but also the complications related to their removal. During myomectomy part of the uterine wall is severed in order to enucleate the fibroid. This damage to the wall is independent of the surgical technique used. Surgical sutures are placed in order to control bleeding and close the severed uterine wall, an ensuing fibrotic scar forms. In addition to the resulting relative weakness of the uterine wall post-surgery; which may result in the low but major risk of uterine rupture during pregnancy/labour; adhesion formation within the abdomen can also form resulting in mechanical infertility.

A further point to be considered is the risk of surgery-associated complications. Even if uncommon, intra-operative complications such as; bladder, bowel, ureteral injury, severe bleeding and unintended conversion to hysterectomy have been reported. Moreover, postoperative complications such as fistula or thrombosis and embolism may also occur (Altgassen, Kuss et al. 2006). The
minimal invasive treatment option of UAE has increased in popularity and reported pregnancies following treatment are plentiful. Although most pregnancies following UAE have good outcomes, the risk of preterm delivery, spontaneous abortion, abnormal placentation and postpartum haemorrhage, are increased following uterine artery embolisation compared to myomectomy. This may be due to the resultant ischaemia which not only occurs in the fibroid but the entire uterus. This ischaemia may result in chronic weakness of the pregnant uterus. Uterine rupture has been reported with both myomectomy and UAE (Lieng, Istre et al. 2004) (Vidal, Michel et al. 2008).

Although both myomectomy and UAE are seen as effective and safe treatment options for fibroids, the increase in pregnancy complications seen with UAE means that patients should be recommended myomectomy as the treatment of choice over UAE in those desiring future fertility.

With MRgFUS heat ablation is limited to the core of the fibroid and no damage to the surrounding uterine wall occurs. Real time monitoring of the volume of ablation enables limitation of the thermal damage to a distinct targeted region of the fibroid as shown in pathology specimens (Jolesz 2009) and MR contrast imaging. Accordingly there arises the hypothesis that MRgFUS may enable non-invasive treatment of uterine fibroids in women desiring pregnancy, without compromise to the integrity of the uterus or increase in pregnancy related risks.
Patients and methods

As described previously this was a multi-centre study. For the rest of this chapter we will describe the recruitment procedure, patient population and results of our centre’s involvement.

Pre-menopausal women presenting to the gynaecology clinic at St Mary’s Hospital between Aug 2005 and Aug 2006, who were seeking treatment for uterine leiomyomas and a desire to retain fertility were recruited into the study. A definitive diagnosis of a uterine fibroid(s) was confirmed both by clinical examination and MR imaging prior to enrolment. All MR images were reported by a consultant radiologist who evaluated size and location of uterine fibroids and overall pelvic anatomy. Patients were required to express a desire for pregnancy in the next 12 months post treatment. Clinical entry criteria for this study dictated a minimum age of 20 and a maximum of 40, for those planning to have egg donation the maximum age was 46. All women over the age of 38 required to be tested for normal ovarian function as judged by endocrinological evaluation. Patients with an abnormal cervical smear or any other gynaecological abnormality were excluded from the study. Couples who had failed to conceive one year after trying were asked to undergo tests for normal ovarian function and tubal patency, partners were asked to provide a semen analysis.

An absolute contraindication to treatment was the finding of loops of bowel or abdominal wall scars in the projected ultrasound beam pathway. All patients were informed about the benefits and potential risks and provided written informed consent to participate.

Study design

This was a prospective, phase II, non-randomised, multicentre study to evaluate the safety of MRgFUS in the treatment of uterine fibroids in women desiring future fertility. All patients were treated with MRgFUS and then followed
clinically for 12 months and/ or through future pregnancy to evaluate the change in their symptoms and the course of their pregnancies.

Treatment procedure:

Patients were screened for eligibility to the study. Those meeting the criteria were offered an informed consent to sign.

The MRgFUS procedure was performed as outlined in Chapter 2: Materials and Methods.

Follow-up

Follow-up visits were scheduled at 1 week, 3 months, 6 months and a final visit conducted either at 12 months, if the patient did not fall pregnant or 3 months after delivery or miscarriage, if she did. Patients were assessed for overall health related quality of life using the UFS-QOL, physical wellbeing, as well as device/procedure related adverse events that may have occurred during the follow-up period.

Patients were instructed not to conceive before three months after the last treatment procedure. All study participants were instructed to report their pregnancy as soon as possible. All patients who fell pregnant were followed up as per their local hospital’s policy of care for high risk pregnancies. An explanatory letter outlining the procedure was given to the patient and her obstetrician. Mode of delivery was determined by the treating obstetrician.

Statistical analysis

Summary descriptive statistics were used for demographic data, QOL scores and volume measurements. Student t-tests were used for comparison of SSS before and after treatment. Null hypotheses were rejected at a P level of less than 0.05.
Results

Study Population

Thirty two women enrolled in the study at our centre, the mean age was 38 years (+/- 4.6; range 23-46). All subjects were pre-menopausal. The mean BMI was measured as 24.87 (+/- 4.13; range 19-38) and the ethnic origin of the group was as follows; 7 Caucasian, 24 Black (African or Afro-Caribbean) and 1 other ethnic origin.

All women were keen to conceive, twenty four women were nulliparous, with 5 of these having previous miscarriages. Seven women were parous and one had 4 previous failed IVF treatments. No subjects had any history of additional gynaecological pathology.

Treatment outcomes

Twenty eight of the thirty-two women completed MRgFUS treatment in one session and 4 subjects required a second visit to complete therapy. Mean treatment time was 173 mins (+/- 30; range 143-203) for the first treatment and 145 mins (+/-27; range 118-172) for the second session with an average of 64 (+/- 20) sonications being delivered per patient. Total analgesic requirement during the procedure averaged 65 mg of Pethidine (range 0-100) and 8 mg of Diazepam (Range 0-10). All patients remained fully conscious and communicative throughout treatment.

Figure 1 below summarises pain experienced by patients at various time points during MRgFUS. They were asked to score pain on a scale between 0 and 4, where a score of 0 indicates no pain and a score of 4 indicates severe pain. This was recorded before, during and immediately after treatment. Of note is the finding that although the majority of patients described moderate pain during treatment, this had disappeared, in all but one case, by the time the patient reached the recovery area.
Chapter 6 Figure 1: Pain Experienced during treatment.

Clinical Follow up

Twenty nine women completed follow up to 12 months with no pregnancy. One woman became pregnant 5 months post treatment and miscarried at 12 weeks. One lady conceived 10 months post treatment delivering a healthy female infant at term and another underwent a successful IVF treatment with egg donation delivering at term a healthy male infant. These cases will be described in detail later. The results of the objective assessment of change in symptoms, based on the UFS-QOL, are shown below in figure 2. At enrolment mean symptom severity score was 66.4, this had almost halved at 3 months to 37.3, the mean SSS at 6 and 12 months was still 50% lower than at enrolment (SSS =30.31 and 28.2 respectively, p<0.002).
Chapter 6 Figure 2: This graph shows a substantial initial fall as described above followed by a continued symptom score reduction post FUS treatment, indicating prolonged improvement over this time course.

Adverse Events

Adverse events were monitored and reviewed at each study visit (treatment, 1 week, 3 months, and 6 and 12 months). Three patients described lower back pain immediately after treatment, which did not persist beyond 1 week. One woman developed a urine infection assumed to be catheter related and was placed on antibiotics. There were no other adverse events.
Uncomplicated Term Vaginal delivery following Magnetic Resonance guided Focused Ultrasound Surgery for Uterine Fibroids.

The objective of this case study was to describe an uncomplicated term vaginal delivery after MRgFUS for symptomatic uterine fibroids.

Case:
A 35 year old para 1+0, presented to the fibroid clinic at our hospital with a known diagnosis of fibroids made 3 years ago. The patient’s first pregnancy resulted in a premature delivery at 28 weeks (attributed to fibroids) of a 1.17kg female infant. She presented to our unit with a history of fibroid related menorrhagia and urinary pressure symptoms including frequency and nocturia. Symptoms were assessed using the uterine fibroid specific quality of life Questionnaire (UFS-QOL) (Spies, Coyne et al. 2002). The patient’s baseline score was 65. Severity of symptoms is directly related to the greatness of the score with a maximum score being 100.

In July 2006 radiological MRI assessment deemed she was suitable for treatment with MRgFUS. She enrolled in an ongoing clinical trial of MRgFUS for treatment of symptomatic fibroids, in women wishing to preserve their fertility. She gave informed consent pertaining to risk of skin burns, nerve irritation, unknown effects on pregnancy and fulfilled all eligibility criteria for the study.

The patient’s screening MRI (see figure 3) revealed an enlarged fibroid uterus with an inferio-superior diameter of 13.5 cm and a uterine volume of 646.5 cm$^3$. Five fibroids were identified, the largest being a fundal posterior intra-mural fibroid of 5cm, three other anterior intramural fibroids, and a low anterior wall fibroid of 4.5 cm which distorted the endometrial cavity posteriorly.
Chapter 6 Figure 3: T2 weighted sagittal image of study patient 31 prior to treatment

The patient had a pre-treatment course of 3 GnRH analogue (triptorelin 3.75mg) s/c injections, of which the first was given on the first day of the cycle and subsequent injections 28 days after the previous. She then underwent MRgFUS treatment in October 2006. Treatment time took 3 hours, the patient complained of abdominal cramps during treatment, which resolved at the end of the treatment episode. No adverse events occurred and the patient was discharged home with no complications. Immediate post-treatment contrast enhanced images revealed excellent results with approximately 90% non-perfusion of total fibroid volume achieved as calculated by volumetric analysis.
By 6 months post the procedure the patient had experienced almost complete resolution of her pre-treatment symptoms, with her UFS-QOL score now 24. The patient conceived 4 months later, with no antenatal problems noted at booking. All booking observations were normal. An anomaly scan performed at 20 weeks gestation revealed no abnormalities. Serial sonography at 28, 32, 36 and 40 weeks demonstrated appropriate fetal growth with cephalic presentation and an anterior placenta, which was not low-lying.

At 41 +6 weeks the patient was admitted for induction of labour as she was past her due date. Labour was augmented by artificial rupture of the membranes and lasted for 5 hours 8 minutes. Fetal monitoring throughout was reassuring, and an uncomplicated vaginal delivery of a healthy female infant with a birth weight of 3580gms was achieved. Apgar scores were 8 at 1 minute, 9 at 5 minutes and 9 at 10 minutes. In the institution at which the patient delivered, cord gases are not routinely done for non-distressed infants. No paediatrician was required at delivery.

6 months post delivery, the patient continues to have maintained symptomatic improvement, with a QOL score of 22. Contrast–enhanced MRI shows persistent non-perfusion of all fibroids, in addition there has been shrinkage in the overall uterine volume to 376.3 cm³ (See figure 4).
Chapter 6 Figure 4: Contrast enhanced image of the same patient (number 31) showing non-perfusion of all fibroids, and overall reduction in uterine volume.

In conclusion we describe the first U.K pregnancy and successful delivery in a woman who was part of a fertility trial and specifically treated with MRgFUS for symptomatic fibroids that had caused a previous premature delivery at 28 weeks.
The objective of this case study was to describe an IVF pregnancy and delivery after MRgFUS for symptomatic uterine fibroids.

Fibroids and in particular sub-mucosal fibroids are thought to reduce the implantation rates following IVF. A review of IVF outcomes in 24 women found a 70% decrease in pregnancy rate attributable to a 72 % decrease in implantation rate in women with sub-mucosal fibroids, when compared to infertile controls (129). This study has led to the recommendation by most reproductive specialists for the resection of sub-mucosal fibroids before proceeding with assisted reproductive technologies. The non-invasive nature of ExAblate whereby only the uterine fibroids undergo thermal ablation with no damage to healthy surrounding tissue suggests that MRgFUS should be a safe approach for women who want to preserve their fertility and perhaps may provide a non-invasive treatment alternative for this sub-set of women.

We describe the first IVF pregnancy following MRgFUS treatment for symptomatic uterine fibroids.

Case:

A 45 year old para 0+1, presented to the fibroid clinic at our hospital with a known diagnosis of fibroids. The patient had 4 previous IVF cycles, three from egg donations and 1 with her own egg. She had one pregnancy resulting in a first trimester miscarriage 2 years ago. She presented to our unit with a history of fibroid related menorrhagia and a desire to preserve her fertility. Symptoms were assessed using the uterine fibroid specific quality of life Questionnaire (UFS-QOL) (108). The patient’s baseline score was 72. Severity of
symptoms is directly related to the greatness of the score with a maximum score being 100.

In January 2007 radiological MRI assessment deemed she was suitable for treatment with MRgFUS, with an effective acoustic window to the fibroid.

The patient’s screening MRI revealed an enlarged fibroid uterus with an inferior-superior diameter of 9.4 cm due to a single anterior wall partially sub-mucosal fibroid measuring 9 x 6.2 x 7.1 cm, which had resulted in distortion of the endometrial cavity (See figure 5).

Chapter 6 Figure 5: pre-screening MRI of study patient 13 with a Sagittal view of the pelvis, showing an enlarged fibroid uterus with an anterior wall fibroid.
The patient was counselled on the unknown effects on pregnancy and underwent treatment in April 2007. Treatment time took 3 hours, the patient complained of abdominal cramps during treatment, which resolved at the end of the treatment episode. No adverse events occurred and the patient was discharged home with no complications. Immediate post-treatment contrast enhanced images revealed excellent results with approximately 90% non-perfusion of total fibroid volume achieved as calculated by volumetric analysis. The patient was advised not to conceive until 3 months after the procedure. She returned at 3 months for follow-up imaging and assessment of symptoms. Her 3 month follow up scan revealed significant shrinkage in the fibroid volume which now measured 5.1 x 4.3 x 3.5 cm, with no distortion of the endometrial cavity (see figure 6). In addition the patients’ symptoms appeared to have completely resolved with her UFS-QOL score now 14.

The patient underwent her IVF treatment in January 2008 becoming pregnant after the 1st cycle 10 months post her MRgFUS treatment. No antenatal problems were noted at booking. An anomaly scan performed at 20 weeks gestation revealed no abnormalities. Serial sonography at 28, 32, 36 and 40 weeks demonstrated appropriate fetal growth with cephalic presentation.
Chapter 6 Figure 6: Sagittal view of the pelvis of the same patient (number 13) 3 months post treatment, showing significant reduction in volume. Fibroid now measures 5.1 cm in inferio-superior dimension.

At 39+5 weeks the patient was admitted in spontaneous labour, due to a persistently sub-optimal cardiotocograph (CTG) which indicated fetal distress despite foetal blood gases within normal levels, the patient was delivered by emergency lower uterine segment caesarean section under spinal analgesia. This was uncomplicated with a 100ml blood loss reported in the delivery summary from her local obstetric unit. A vertex delivery of a healthy male infant weighing 3050gms was achieved. The cord gases were each of arterial pH of 7.36 and a venous pH of 7.28 with a base excess of -1.2 and -1.3. Apgars at 1 & 5 minutes were 9 and 10 respectively. No paediatric follow up was required.
Discussion

The complications of untreated leiomyomata in pregnancy are well-known and include placental abruption, premature labour and pain from red degeneration (Rice, Kay et al. 1989).

Traditional myomectomy remains the gold standard for fertility preserving fibroid treatments. This option remains in favour over newer minimal invasive techniques, where there are still concerns regarding the impact on fertility. A shift in cultural attitude that is noticeable is that many women no longer find surgical treatment of a benign condition acceptable.

MRgFUS is a non-invasive thermo-ablative technique, which combines the real-time thermal monitoring capabilities of MRI with the heat-generating properties of focused ultrasound waves. Delivery of concentrated sound energy (sonication) heats tissue within the focal area (about 1-2 cm³) to 60-85°C leading to thermal injury and subsequent necrosis and apoptosis (Lynn, Zwemer et al. 1942). It is an out-patient procedure with minimal sedation requirements and a speedy recovery time, allowing patients to return to work within 24 hours, compared to 10 days after UAE and 6 weeks with Myomectomy.

Over 4000 women with symptomatic uterine fibroids have been treated worldwide. Published studies have shown that up to 84.6% of women treated, experienced significant symptomatic improvement at 24 months post treatment follow up (Stewart, Gostout et al. 2007). Initial FDA guidelines recommended that only women who had completed their families undergo treatment. However with the advantage of consistently good safety and efficacy results being reported, multi-centre fertility studies were commenced.

The results from this multi-centre international study are reassuring in that a substantial percentage of patients are able to conceive after MRgFUS treatment of uterine fibroids, with a spontaneous abortion rate almost similar to the background rate at 28%. Most importantly, there were no cases of uterine rupture, pre-term
labour, placental abruption, abnormal placentation or fetal growth restriction, with a mean birth weight of 3.4Kg (see appendix for international results). MRgFUS treatment has the potential to deliver safe and effective treatment for uterine fibroid symptoms without damaging patient fertility or creating additional pregnancy related risks. Accordingly the Conformitee Europeene (CE) marking for the ExAblate system has been changed to include patients wishing to preserve their fertility.
CHAPTER 7: CONCLUSION AND FURTHER WORK
There is a growing body of data from clinical trials and clinical experience to validate the safety and efficacy of MRgFUS for the treatment of uterine fibroids. MRgFUS is a totally non-invasive outpatient procedure that is not associated with the typical surgical risks of bleeding, infection and has minimal recovery time (see figure 1). Additionally, the procedure allows women to address their symptoms whilst preserving the uterus. Consequently, MRgFUS is an alternative treatment option for suitable patients who have refused other interventions due to concerns about lost productivity, risks of surgical complications or future fertility.

Since uterine fibroids are most common among women during their prime working years, the impact of uterine fibroids on productivity is large. In the US it has been estimated that 9.9 million employed women suffer from clinically diagnosed fibroids (Wu, BirnBaum et al 2006) which implies approximately 2 million in the UK (Census) It has been suggested that the equivalent of 0.4-0.8 million work days are lost before surgery (Broder, Landow et al. 2000) and 0.6-1.4 million work days after surgery in the UK each year. Work absences are reported by 40% of women with symptomatic fibroids.
Chapter 7 Figure 1: Graph comparing effect of MRgFUS and TAH on return to normal activity.

Initial trials of MRgFUS were optimized for safety, and the clinical data from these trials demonstrate that the procedure is associated with a very low incidence of serious adverse events. Since MRgFUS was approved in 2004, additional trials have evaluated new screening methods or treatment parameters that may increase the efficacy of the procedure. For example additional improvements in treatment efficacy may be possible with improved selection criteria that better identify those UF patients for whom MRgFUS is likely to result in positive outcomes. For example our experience seems to suggest that fibroid signal intensity on T2-weighted MR images may be predictive of response to MRgFUS, with better results seen in fibroids with low or intermediate intensity, therefore by pre-treating high intensity fibroids with GnRHa to reduce vascularity we can improve treatment outcome. Also by removing restrictions on some margins such as desire to preserve fertility, size of fibroids, presence of abdominal scars and
allowing for a second treatment session result in a significant increase in the percentage of women for whom this treatment may be offered.

A key benefit of MRgFUS is that the procedure allows women to address fibroid symptoms while retaining their uterus. Although initial trials of MRgFUS prospectively excluded patients with plans for future fertility, case studies demonstrate that conception and delivery of full-term babies is possible after undergoing the procedure. Low birth-weight and stillbirths have not been reported in women who have become pregnant following MRgFUS (Rabinovici, David et al. 2010). Additional data from treated patients and the comparison of pregnancy rates and progression following MRgFUS or myomectomy should provide additional insight into fertility capacity following MRgFUS. Ethics approval for a RCT comparing myomectomy and MRgFUS has recently been applied for and obtained. Patient recruitment is due to start in January 2010.

Beyond the benefits associated with a non-invasive treatment for symptomatic uterine fibroids, a cost effectiveness analysis performed at the London school of Hygiene and Tropical Medicine evaluated the cost-effectiveness of adding MRgFUS to the arsenal of existing treatments for uterine fibroids. The results of this study suggested that a treatment strategy starting with MRgFUS is potentially more effective and less costly than current practice, however the cost per quality adjusted life year gained is sensitive to the cost of MRgFUS relative to other treatments, the age of the woman and the non-perfused volume relative to the total fibroids volume (Zowall, Cairns et al. 2008).

As an outpatient therapy, MRgFUS offers insurers reduced treatment costs. Additionally, the ability to offer patients a non-invasive treatment alternative may help hospitals attract uterine fibroid patients to their facilities. An internal review of fibroid treatments at our institution before and after introduction of an MRgFUS service indicated an increase in all fibroid treatment modalities. (see table below).
<table>
<thead>
<tr>
<th>Year</th>
<th>2001</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy (fibroids only)</td>
<td>76</td>
<td>32</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>45</td>
<td>79</td>
</tr>
<tr>
<td>UAE</td>
<td>11</td>
<td>175</td>
</tr>
<tr>
<td>FUS</td>
<td>n/a</td>
<td>73</td>
</tr>
</tbody>
</table>

Chapter 7 table 1: Comparison of treatment modality numbers pre and post introduction of MRgFUS in our unit.

In summary, MRgFUS appears to be a safe and effective approach to treating symptomatic uterine fibroids. The non-invasive procedure offers women a therapeutic option that avoids the potential risks and lengthy recover periods associated with hysterectomy, myomectomy and UAE. Early data suggest that MRgFUS is compatible with subsequent fertility and ongoing trials should help to clarify pregnancy rates, progression and risks following the procedure.

Continued clinical evaluation and experience should enable further refinement of patient selection and treatment parameters, resulting in improved efficacy. A retrospective review is currently underway aimed at identifying the percentage of targeted fibroid required to be treated for symptom maintenance at 12 months post treatment. A current figure of 40% non-perfusion post–treatment has been set by the manufacturer, however A UAE procedure is deemed successful only if there is >85% of non-perfusion achieved. By analysing retrospectively patients QOL scores at 12 months and correlating this with NPV percentages achieved post-treatment, we can determine what percentage of ablation is required to be created to ensure long-term maintenance of symptom improvement.
References


List of Appendices

- Appendix 1: UFS- QOL questionnaire
- Appendix 2: Inclusion/ exclusion criteria for GnRH study.
- Appendix 3: Inclusion/ exclusion for Fertility study.
- Appendix 4: Table of international pregnancy results.
- Appendix 5: Publications.
Appendix 1: UFS- QOL questionnaire
Appendix 2: Inclusion/ exclusion criteria for GnRH study.
Appendix 3: Inclusion/ exclusion for Fertility study
Appendix 4: Table of international pregnancy results
Appendix 5: Publications.
Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (√) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

<table>
<thead>
<tr>
<th>During the previous 3 months, how distressed were you by…</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>A great deal</th>
<th>A very great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heavy bleeding during your menstrual period</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>2. Passing blood clots during your menstrual period</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>3. Fluctuation in the duration of your menstrual period compared to your previous cycles</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>4. Fluctuation in the length of your monthly cycle compared to your previous cycles</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>5. Feeling tightness or pressure in your pelvic area</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>6. Frequent urination during the daytime hours</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>7. Frequent nighttime urination</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>8. Feeling fatigued</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
</tbody>
</table>
The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (√) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

<table>
<thead>
<tr>
<th>During the previous 3 months, how often have your symptoms related to uterine fibroids...</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Made you feel anxious about the unpredictable onset or duration of your periods?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>10. Made you anxious about traveling?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>11. Interfered with your physical activities?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>12. Caused you to feel tired or worn out?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>13. Made you decrease the amount of time you spent on exercise or other physical activities?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>14. Made you feel as if you are not in control of your life?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>15. Made you concerned about soiling underclothes?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>16. Made you feel less productive?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>17. Caused you to feel drowsy or sleepy during the day?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>18. Made you feel self-conscious of weight gain?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>19. Made you feel that it was difficult to carry out your usual activities?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>20. Interfered with your social activities?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
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<tr>
<td>21. Made you feel conscious about the size and appearance of your stomach?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
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<tr>
<td>22. Made you concerned about soiling bed linen?</td>
<td>[ ] 1</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
<td>[ ] 4</td>
<td>[ ] 5</td>
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<tr>
<td>Question</td>
<td>None of the time</td>
<td>A little of the time</td>
<td>Some of the time</td>
<td>Most of the time</td>
<td>All of the time</td>
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<tr>
<td>During the previous 3 months, how often have your symptoms related to uterine fibroids...</td>
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<tr>
<td>23. Made you feel sad, discouraged, or hopeless?</td>
<td></td>
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<tr>
<td>24. Made you feel down hearted and blue?</td>
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<tr>
<td>25. Made you feel wiped out?</td>
<td></td>
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<tr>
<td>26. Caused you to be concerned or worried about your health?</td>
<td></td>
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<tr>
<td>27. Caused you to plan activities more carefully?</td>
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<tr>
<td>28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?</td>
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<tr>
<td>29. Caused you embarrassment?</td>
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<tr>
<td>30. Made you feel uncertain about your future?</td>
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<td>31. Made you feel irritable?</td>
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<tr>
<td>32. Made you concerned about soiling outer clothes?</td>
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<tr>
<td>33. Affected the size of clothing you wear during your periods?</td>
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<tr>
<td>34. Made you feel that you are not in control of your health?</td>
<td></td>
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<tr>
<td>35. Made you feel weak as if energy was drained from your body?</td>
<td></td>
<td></td>
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<tr>
<td>36. Diminished your sexual desire?</td>
<td></td>
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<td>37. Caused you to avoid sexual relations?</td>
<td></td>
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</table>
Directions: Review the INCLUSION AND EXCLUSION CRITERIA below to determine the patient’s eligibility for entry into the study.

### PATIENT INCLUSION CRITERIA (✓ Yes if present, No if not present)

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Patient has given consent</td>
</tr>
<tr>
<td>2.</td>
<td>Patient is willing and able to attend all study</td>
</tr>
<tr>
<td>3.</td>
<td>Patient is a female of at least 18 years of age with a symptomatic uterine fibroid(s) who has completed her</td>
</tr>
<tr>
<td>4.</td>
<td>Patient presents with a uterine fibroid size of more than 300cc</td>
</tr>
<tr>
<td>5.</td>
<td>Clinically normal Pap smear within timing of national guidelines</td>
</tr>
<tr>
<td>6.</td>
<td>Raw score of 21 or greater on the UFS-QOL symptom severity screener.</td>
</tr>
<tr>
<td>7.</td>
<td>Patient is pre or peri-menopausal (within 12 months of last menstrual period).</td>
</tr>
<tr>
<td>8.</td>
<td>Patient is able to communicate sensations during the MRgFUS procedure.</td>
</tr>
<tr>
<td>9.</td>
<td>Uterine fibroids which are device accessible</td>
</tr>
<tr>
<td>10.</td>
<td>Tumour(s) clearly visible on no-contrast MRI</td>
</tr>
<tr>
<td>11.</td>
<td>The use or non-use of non-steroidal treatments for excessive vaginal bleeding such as anti-fibrinolytic agents (e.g. Tranexamic acid) or non-steroidal anti-inflammatory drugs (e.g. Mefenamic acid) should remain constant from three months pre-study and throughout the follow-up period.</td>
</tr>
</tbody>
</table>

*No answer to any of the above Inclusion Criteria disqualifies a patient from entry into the study.*

### PATIENT EXCLUSION CRITERIA (✓ Yes if present, No if not present)

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Patient is pregnant as confirmed by pregnancy test at time of screening</td>
</tr>
<tr>
<td>2.</td>
<td>Patient has had previous GnRH treatment</td>
</tr>
<tr>
<td>3.</td>
<td>Patient using hormone replacement therapy</td>
</tr>
<tr>
<td>4.</td>
<td>Patient using hormonal contraception</td>
</tr>
<tr>
<td>5.</td>
<td>Patient on dialysis</td>
</tr>
<tr>
<td>6.</td>
<td>Hematocrit is &lt; 25</td>
</tr>
<tr>
<td>7.</td>
<td>Patient has hemolytic anemia</td>
</tr>
</tbody>
</table>
PATIENT EXCLUSION CRITERIA (✓ Yes if present, No if not present)

8. Patient has unstable cardiac status including:
   ▪ Unstable angina pectoris on medication
   ▪ Documented myocardial infarction within 6 months of protocol entry
   ▪ Congestive heart failure requiring medication (other than diuretic)
   ▪ Currently taking anti-arrhythmic drugs
   ▪ Severe hypertension (diastolic BP>100 on medication)
   ▪ Presence of cardiac pacemaker
   
9. Patient has an ASA score of >2

10. Patient has severe cerebrovascular disease (multiple CVA or CVA within 6 months)

11. Patient is on anti-coagulation therapy or has an underlying bleeding disorder

12. Evidence of uterine pathology other than leiomyoma

13. Patient has an active pelvic infection or history of pelvic inflammatory disease

14. Patient has an undiagnosed pelvic mass outside the uterus.

15. Patient weight >110 kg

16. Subject with extensive abdominal scarring in an area of the abdomen directly anterior to the treatment area.

17. Subject with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices.

18. Known intolerance to the MRI contrast agent (e.g. Gadolinium or Magnevist).

19. Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 hours.)

20. Patient with an intrauterine contraceptive device anywhere in the treatment beam path.

21. Women who are breast feeding.

*A Yes answer to any of the above Exclusion Criteria disqualifies a patient from entry into the study.*

---

IF PATIENT HAS MET ALL INCLUSION/EXCLUSION CRITERIA AND SIGNED THE CONSENT FORM, THEN SCHEDULE FUS TREATMENT.

IF PATIENT DOES NOT MEET ALL THE INCLUSION AND EXCLUSION CRITERIA BUT YOU WISH TO ENTER THE PATIENT INTO THE STUDY, CONTACT InSightec BEFORE PROCEEDING.

---

Investigator’s Signature: [Signature]
Date: [Date]
Directions: Review the INCLUSION AND EXCLUSION CRITERIA below to determine the patient's eligibility for entry into the study.

PATIENT INCLUSION CRITERIA (✓ Yes if present, No if not present)

1. Subject with uterine fibroids, who desire pregnancy within 12 months and has the one of the following criteria:
   - Women 20-40 age.
   - Women age < 46 years old who plan to have egg donation.
   - Women above 38 should test for normal ovarian function as judged by endocrinological evaluation.
   - If the couple has failed to conceive for more than 1 year, the woman should test for normal ovarian function as judged by endocrinological evaluation, and the male must have adequate sperm test.
   - Women undergoing fertility treatment or plan to have sperm donation.

2. Use or non use of non-steroidal treatments for excessive vaginal bleeding such as antifibrinolytic agents (e.g. Tranexamic acid) or non-steroidal anti-inflammatory drugs (e.g. Mefanamic Acid) has been maintained for the three months prior to the planned date of the study procedure and the patient has agreed to maintain this use or non-use through the 6-month follow-up period.

3. Clinically normal PAP smear within timing of National Guidelines in the country of the clinical site.

4. Able and willing to give consent and able to attend all study visits

5. Able to communicate sensations during the MRgFUS procedure

6. Having uterine fibroids that are device accessible (i.e., positioned in the uterus such that they can be accessed without being shielded by bowel or bone).

7. Tumor(s) are clearly visible on non-contrast MRI.

8. Largest fibroid 8 cm in diameter or 12 cm if receiving GnRH

A No answer to any of the above Inclusion Criteria disqualifies a patient from entry into the study.

PATIENT EXCLUSION CRITERIA (✓ Yes if present, No if not present)

1. Patient is pregnant as confirmed by pregnancy test at time of screening

2. Uterine size >20 weeks as evaluated by US or MR.

3. Patients who are considered “high risk pregnancy” due to uterine factors (e.g. abnormal uterus, uterine scars, cerclage) except fibroids.

4. Patients with fibroid that is more than 50% sub-mucosal or with hysteroscopically resectable
PATIENT EXCLUSION CRITERIA (✔ Yes if present, No if not present)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
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</tr>
</tbody>
</table>

5. Patients with adenomyosis
6. Patient is on dialysis
7. Hematocrit is < 25
8. Patient has hemolytic anemia
9. Patient has unstable cardiac status including:
   - Unstable angina pectoris on medication
   - Documented myocardial infarction within 6 months of protocol entry
   - Congestive heart failure requiring medication (other than diuretic)
   - Currently taking anti-arrhythmic drugs
   - Severe hypertension (diastolic BP>100 on medication)
   - Presence of cardiac pacemaker
10. Patient has an ASA score of >2
11. Patient has severe cerebrovascular disease (multiple CVA or CVA within 6 months)
12. Patient is on anti-coagulation therapy or has an underlying bleeding disorder
13. Evidence of uterine pathology other than leiomyoma
14. Patient has an active pelvic infection or history of pelvic inflammatory disease
15. Patient has an undiagnosed pelvic mass outside the uterus.
16. Patient weight >110 kg
17. Subject with extensive abdominal scarring in an area of the abdomen directly anterior to the treatment area.
18. Subject with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices.
19. Known intolerance to the MRI contrast agent (e.g. Gadolinium or Magnevist).
20. Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 hours.)
21. Patient with an intrauterine contraceptive device anywhere in the treatment beam path.
22. Women who are breast feeding.
23. Five or more fibroids, bigger than 3cm diameter, each

A Yes answer to any of the above Exclusion Criteria disqualifies a patient from entry into the study.

---

IF PATIENT HAS MET ALL INCLUSION/EXCLUSION CRITERIA AND SIGNED THE CONSENT FORM, THEN SCHEDULE FUS TREATMENT.
IF PATIENT DOES NOT MEET ALL THE INCLUSION AND EXCLUSION CRITERIA BUT YOU WISH TO ENTER THE PATIENT INTO THE STUDY, CONTACT InSightec BEFORE PROCEEDING.

__________________________________________
Investigator’s Signature

__________________________
Date
<table>
<thead>
<tr>
<th>No.</th>
<th>Pt. ID</th>
<th>Demographics</th>
<th>Medical history</th>
<th>Delivery Complications</th>
<th>Newborn Complications</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>St. Mary's, England UF008-620</td>
<td>41 white 2 0 Yes 84 279 Intramural Early pregnancy bleeding Miscarriage Week 10 - - - None</td>
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<tr>
<td>2</td>
<td>Charite, Germany UF004-804</td>
<td>40 white 1 0 Yes 53 21 Intramural Bleeding during weeks 8 and 9 Vaginal Week 42 Male 3870 10,10 None</td>
<td>None None</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Charite, Germany UF004-805</td>
<td>34 white 2 0 Yes 11 43 Intramural None till miscarriage, bleeding Miscarriage Week 9 - - - Treated: Fibroids location: Intramural</td>
<td></td>
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<tr>
<td>4</td>
<td>Charite, Germany UF004-814</td>
<td>34 white 1 0 UNK 60 65 Intramural Chlamydia Caesarean Week 38 Female 3480 None</td>
<td>None None</td>
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<tr>
<td>5</td>
<td>Sheba, Israel UF002-612</td>
<td>44 white 3 1 UNK 69 293 2 Intramural, 1 subserosal None MA BW + D&amp;C Week 8 - - - Placenta residual that needed REVISIO (physical examination of the uterus for placenta residuals)</td>
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<tr>
<td>6</td>
<td>Sheba, Israel UF004-602</td>
<td>36 white 2 1 Yes 41 84 Focal fundi suspected diagnosis of persistent right umbilical vein Vaginal UNK Female 3050 UNK</td>
<td>None</td>
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<tr>
<td>7</td>
<td>Sheba, Israel UF004-606</td>
<td>28 african 4 4 Yes 34 230 Submucosal IUI (Intra Uterine insemination) Week 35 hospitalized due to PMC (premature contractions) and lumber Caesarean Week 38 Male 2656 9,10 due to fetus positioning Caesarean surgery scheduled. During surgery also underwent myomectomy. 3 hrs post surgery patient started to bleed Respiratory problems lasted several days post delivery. Referred to respiratory unit, with no specific findings.</td>
<td>None</td>
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<td>8</td>
<td>Sheba, Israel UF004-616</td>
<td>32 white 2 1 None 94 73 Intramural/Submucosal 10th week heavy bleeding referred for D&amp;C Miscarriage Week 10 - - - Hyteroscopy</td>
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<tr>
<td>9</td>
<td>ShinSuma, Japan UF007-73003</td>
<td>30 Japanese 0 0 UNK UNK 200 Intramural bleeding and FHM(-) Miscarriage Week 7 - - -</td>
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<tr>
<td>10</td>
<td>ShinSuma, Japan UF007-73035</td>
<td>41 Japanese 0 0 UNK UNK 950 Intramural Patient had the FUS Tx after her last ovulation and before her next period Abortion - - -</td>
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<td>11</td>
<td>ShinSuma, Japan UF007-73044/8</td>
<td>38 Japanese 1 0 UNK UNK 740 Intramural Temporary sign of miscarriage (bleeding) Caesarean week 41 +5/7 Female 3966 8,9</td>
<td>- - -</td>
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<td>Roszdrev, Russia</td>
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**Page 2 of 4**
<table>
<thead>
<tr>
<th>Case</th>
<th>Ethnicity</th>
<th>Race</th>
<th>Disease</th>
<th>Gestational Age</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Deliver</th>
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<td>35</td>
<td>White</td>
<td>4</td>
<td>None</td>
<td>47</td>
<td>488 submucosal</td>
<td>at week 20 arrived to ER with pain, fetus had no pulse. Underwent D&amp;C</td>
<td>Premature labor week 20</td>
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<td>31</td>
<td>Asian</td>
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<td>53</td>
<td>173 intramural</td>
<td>Vaginal week39+1</td>
<td>girl 3190</td>
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<td>30</td>
<td>African</td>
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<td>54</td>
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<td>None</td>
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<td>girl 3580, 1, 9@10, 9@</td>
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<td>41</td>
<td>White</td>
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<td>1 Gestosis</td>
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<td>297 submucosal</td>
<td>Myoma growth during 21st week of pregnancy lead to myomectomy</td>
<td>Caesarean week 36</td>
<td>girl 3410</td>
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<tr>
<td>36</td>
<td>White</td>
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<td>124 subserosal</td>
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**Notes:**

- **White**: White
- **Asian**: Asian
- **African**: African
- **Korean**: Korean
- **Charite, Germany**: Charite, Germany
- **Sheba, Israel**: Sheba, Israel
- **Bochum**: Bochum
- **Roszdrav, Russia**: Roszdrav, Russia
- **Trans**: Transmural
- **Intramural**: Intramural
- **Subserosal**: Subserosal
- **Submucosal**: Submucosal
- **Gestational Diabetes**: Gestational Diabetes
- **Abdominal pain, anemia**: Abdominal pain, anemia
- **Gestosis**: Gestosis
- **LTF**: LESION TERMINAL FUSIONS
- **Miscarriage**: Miscarriage
- **Abortion**: Abortion
- **Preterm Labor**: Preterm Labor
- **Premature Labor**: Premature Labor
- **Vaginal**: Vaginal
- **Caesarean**: Caesarean
- **D&C**: D&C
- **Miscarriage**: Miscarriage
- **Caesarean**: Caesarean
- **Abortion**: Abortion
- **Premature Labor**: Premature Labor
- **Week 38**: Week 38
- **Week 36**: Week 36
- **Week 39+1**: Week 39+1
- **Week 4**: Week 4
- **Week 5&10 bleeding. Week 14-15; hospitalization due to risk for miscarriage**: Weeks 5&10 bleeding, Week 14-15; hospitalization due to risk for miscarriage
- **Week 9**: Week 9
- **On-going**: On-going
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