

Intrauterine HIFU: A New Treatment for Uterine Fibroids

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Keywords: Uterine Fibroid, HIFU (High Intensity Focused Ultrasound).

Abstract: Uterine fibroids are the most common benign tumours among women of child-bearing age with a prevalence varying from 5.4% to 77%. The most common symptoms of uterine fibroids include: heavy menstrual bleeding, pelvic pressure or pain and infertility. Symptoms can be influenced by the location, size and number of fibroids. Fibroids are most often identified during a routine pelvic examination by a physician. Treatments may include temporary medical treatments, surgery or uterine artery embolization. As all of the methods above have considerable disadvantages, we propose a medical device using High Intensity Focused Ultrasound (HIFU) in a minimally procedure in which an ultrasound probe is inserted into the uterus to precisely ablate the fibroid and shrink it. Our new medical device proposal is aimed at improving clinical efficacy and patient satisfaction.

1 INTRODUCTION

We are a team of biomedical engineers, pharmacists and physicians including a gynaecologist who have met during the Clinmed 2018 Summer School organised by the EIT Health committee and the CIC-IT network (Clinical Investigation Centre - Technologic Innovation).

The Clinmed 2018 Summer School was an immersive experience with the opportunity to meet other students from various fields, assist to lectures and workshops. It aimed at understanding the unmet needs in healthcare industry and finally proposing a feasible technological innovation from initial concept till final development. Several teams were created and associated to a specific CIC-IT centre. Our team was located in Grenoble and supervised by Pr Alexandre Moreau-Gaudry. Our goal was to create an innovative medical device, in a two-week period, during the summer school.

We address a current problem in gynaecology, called uterine fibroids, which is widely known and concerns a majority of women around the world. The idea arose after interactions with healthcare professionals and surgeons at the University Hospital of Grenoble. The presentation of modern robots for

knee surgery kindled our interest on computer assisted medical procedures and out of our expertise we discovered the lack of efficient and less invasive treatment of uterine fibroids in women. To overcome important limits concerning sterilization and maintenance of medical devices, the sterilization and biomedical engineering department at the hospital increased our awareness of today's needs in health care industry. Since health care-associated infections are a non-negligible risk, we propose an innovation that will reduce surgical site infection and take full advantage of advanced computer technology to guide the physician to target the fibroid and to ablate it.

Uterine fibroid is the most common benign tumour among women. They occur in almost 70 % of Caucasian women and in more than 80 % of African American women by age 40 and a third of them are symptomatic (Baird et al, 2003) (Khan and al, 2014) (Stewart et al, 2017). Symptoms are heavy and long menstrual bleeding, acute and chronic pelvic pain, infertility, anaemia, urinary and digestive symptoms (constipation). Symptoms depend on the localization of the uterine fibroid as classified by the international FIGO system.

2 TREATMENT OPTIONS

2.1 Current Treatment Options

2.1.1 Medical Treatment

Medical treatments for fibroids are only symptomatic or temporary treatments. NSAIDs (non-steroidal anti-inflammatory drugs) are used to treat acute pelvic pain and tranexamic acid to treat heavy bleedings. Hormonal treatments (GnRH) can be used on a 3 to 6 months period or to prepare surgery.

Acetate ulipristal which induces apoptosis in fibroid cells and therefore reduce significantly the fibroid size. This treatment is indicated before surgery or for women in whom surgery is not suitable. However, this treatment has been reviewed recently because of reported cases of liver injury and hepatic failure.

2.1.2 Surgical Treatment

Nowadays we can consider three main types of surgeries: hysteroscopy, myomectomy and hysterectomy (Chanelles et al, 2010).

Hysteroscopy is a quick and safe procedure, however it is only applicable for fibroids which are reachable from the cavity.

Myomectomy; the local removal of the fibroid is not always possible since it depends on the localization of the fibroid. It can weaken the uterus muscle and may lead to a preventive caesarean section in case of a future pregnancy.

A final option is the hysterectomy which is the total removal of the uterus. Today, uterine fibroid is the main indication for hysterectomy.

This surgery may be complicated by urinary and digestive per-operative wounds. Furthermore, many women refuse hysterectomy out of sensible personal reasons.

2.1.3 Non Invasive Treatment

Other treatments which are less invasive than surgery exist to treat fibroid. The uterine artery embolization is performed by radiologists, however the inflammation and necrosis induced by the embolization lead to painful recovery. Furthermore, a pregnancy is not possible after a uterine artery embolization.

Radiofrequency ablation (RFA) is another option to treat fibroids, it is quite new and not well evaluated yet.

2.2 HIFU Technology

2.2.1 Definition

High Intensity Focused Ultrasound, known as HIFU, is an innovative technology which could promote an alternative in fibroid treatment (Donnez J, 2016) (Marret et al, 2010).

Ultrasounds are vibrations delivered by an external transducer with a very high frequency. The produced waves deliver energy as they travel through tissues.

However, by increasing the intensity of the waves and focusing them, HIFU technology deposits large amounts of energy into tissues, which leads to the ablation of cells in a focal point

Two main mechanisms are involved: the thermal effect and the acoustic cavitation. With regard to the thermal effect, the absorption of ultrasounds energy into the tissues in a few seconds (with each pulse) causes a sharp increase in temperature higher than 70°C, which leads to cell damage. The cavitation effect is induced by the interaction of HIFU and micro-bubbles in the sonicated tissue, it enhances cell membrane permeability and leads to tissue ablation. Both of these mechanisms lead to the destruction of the cells by a coagulative necrosis.

2.2.2 Medical Application

Since 2000, HIFU technology is well known in various medical fields. Dermatologists use HIFU technology to treat wrinkles, it is nowadays considered as a safe and effective procedure to improve skin elasticity (Ko et al, 2017). HIFU technology is also used to treat localized prostate cancer where a probe is introduced into the rectum next to the prostate, so that the urologic surgeon can target and ablate the cancer (Gelet and al, 2009). HIFU technology has been tested on fibroids; it has demonstrated high efficacy, however, there are considerable limitations as shown below. The procedure is as follows: the patient is laying on the abdomen on a surgical table. The HIFU transducer is situated underneath the table. The procedure is supervised by an MRI machine which controls the heat produced by the HIFU waves (Marret et al, 2010).

External HIFU technology efficacy is controlled by two main factors: the acoustic intensities and the focalization of the ultrasound waves. Power converters are used to increase and obtain efficient acoustic intensities (the main goal is to obtain a power of 100W/cm²). Focalization of the ultrasounds is possible thanks to the use of several transducers at the

same time. The total energy released is around 7500 joules which is equivalent to a heat of 70°.

One of the main advantages of HIFU is the theoretic preservation of fertility.

However, the HIFU technique used to date is limited by its external use, due to the following reasons: risk of bowel perforation of the digestive tract, risk of skin lesion, costly associated MRI and no reimbursement, contraindications such as abdominal scars, localization of the fibroid (next to the spine, intracavitary, sub-mucosal, retro-versed in the posterior wall of the uterus) and obesity (Marret et al, 2010) (Bohlmann et al, 2014) .

3 THE MEDICAL DEVICE

We propose an innovative medical device inserted directly into the uterus through the vagina. The probe combines imaging ultra sounds to target the fibroid with HIFU to ablate and shrink it.

As illustrated, the medical device is divided into three parts: the two functions probe, the stabilizing arm, and the machine. The probe is the only part of the device that needs to be sterile. Once the probe is inserted into the uterine cavity, the surgeon can fix the probe and leave the operative field. Then, he can manage the fibroid ablation from the computer.

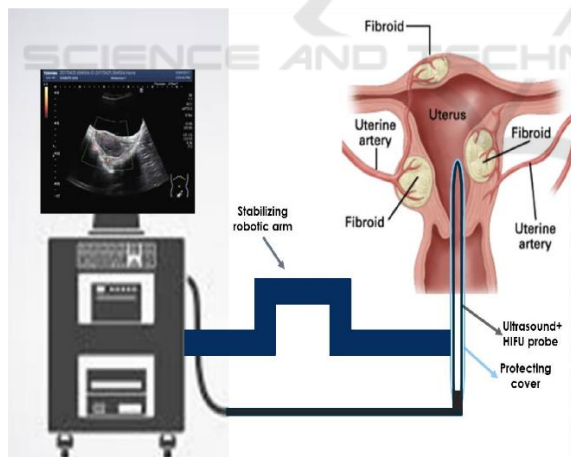


Figure 1: Schematic illustration of the device.

3.1 The Probe

The probe will be made of stainless steel and will include the imaging ultrasound device and the HIFU transducer.

3.1.1 The Imaging Ultrasound

It consists of an ultrasound device which allows precise real-time mapping and 3D reconstruction of the organ including the fibroid. The treatment and imaging process are interleaved to allow visual tracking of the ablation.

This can be achieved by elastography and the change of the speed of ultrasound waves due to temperature change (Rueff & Raman, 2013) (Tavakkoli & Sanghvi, 2011).

3.1.2 The Transducer

In the same probe a transducer is included which allows HIFU ablation of the targeted tissue. The ablation of the targeted tissue can be achieved due to the thermic and the mechanic effect of HIFU (Donnez J, 2016) (Rueff & Raman, 2013) leading to a coagulative tissue necrosis. The transducer is located laterally and is approximately 6 cm long and 1 cm wide. As explained above, we need several transducer units to focalize the ultrasounds.

We will target the same goals as the external HIFU technology: obtaining a power of 100W/cm², a total energy release of around 7500 joules which is equivalent to a heat of 70°. This is a challenging objective as we need to miniaturise the technology currently used for HIFU technology. A first step would be to try to adjust the frequency, the range and the throb of the ultrasound waves. A second step would be to work on various probe components to find the one which maximises HIFU technology.

The transducer will be made of hard ceramic piezoelectric material (e.g. titanium, nickel), that characterized with low dielectric losses and biocompatibility. This means that the probe can be driven to higher frequencies and voltages, without causing self-heating of the transducer (Vijaya, 2013).

For the time being, our device is limited to laterally located fibroids, but we plan to create a device which will reach any localization in the future.

Alternatively, we consider two different types of HIFU transducer, one located laterally and one located on top of the probe.

As illustrated below, we have planned to create a probe with ceramic, within the probe, we need to insert several transducers, the amplifier and the driver pulse. The challenge is to obtain a 1 cm wide probe to respect the uterine cervix.

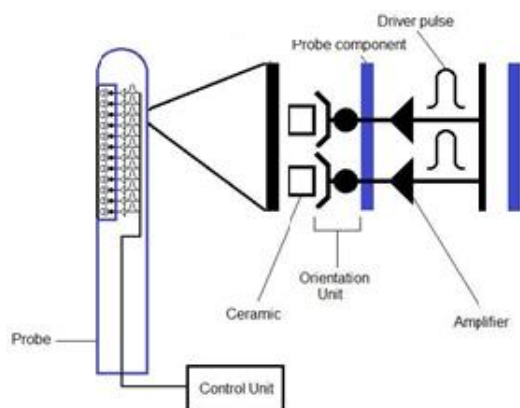


Figure 2: Schematic illustration of the probe.

3.1.3 The Protective Cover

Due to the fact that the probe is inserted into a sterile environment, it has to be covered with a sterile disposable cover made of transparent and biocompatible material which allows the transduction of ultrasounds.

To allow the transduction of the ultrasounds, the cover will be filled with and covered in conductive gel.

To define the exact composition of the cover material, the first lead is the plastic which is already used for intra uterine cannulas (used in case of aspiration curettage). Other sterile, latex-free covers which are on the market are made of polyethylene but are limited in our case due to the fragility and therefore high risk of infection.

3.2 The Machine

3.2.1 The Screen

The screen allows the visualization of a 3D image of the target and a colour code during the treatment in accordance to the efficacy of the ablation (turning red to green once the tissue is successfully ablated).

3.2.2 The Software

Contouring of the fibroid is done by the surgeon and its precise localization in the uterus can be achieved by the software. The energy and power level of the HIFU pulses will be managed by the software.

3.2.3 The Arm

Since the treatment time may be long depending on the fibroid size, the probe will be connected to a stabilizing arm once it is set in place by the surgeon.

3.3 User Guide

A user guide will be provided with the device.

We recommend a gynaecologic positioning for the patient for a better use of the probe.

A disinfection of the vagina and the use of an operative field are necessary to reduce the risk of infection.

A dilatation of the cervix to 11 mm is necessary to insert the probe with its sterile cover.

Once the probe is in place, the surgeon uses the probe to target the fibroid. The probe is then stabilized by the arm and the HIFU ablation may start.

The patient should be fasting and we recommend the placement of a urinary catheter to protect the bladder.

Since the procedure is minimally invasive, the patient is free to leave the same day without hospitalization. It is expected that the recovery phase will not take more than a few days, which is why sick leave at work is kept at a minimum.

3.4 Advantages and Limitations

3.4.1 Advantages

With our device it is possible to avoid MRI control during the HIFU ablation which therefore reduces the cost of the operation.

It will be possible to treat fibroid in any localization in the uterus since the probe is inserted in close contact to the target. We will be able to treat fibroids up to the size of 10 cm.

Contrary to HIFU external use, the risks of skin irritation and bowel perforation can be considerably decreased. Furthermore, the treatment of obese women and women who already underwent abdominal surgery, leading to scar tissue, is not a restriction.

Compared to external HIFU we are closer to our target and can therefore increase ultrasound frequency. This way the sound waves are absorbed faster (low penetration depth due to absorption) which could increase the speed of treatment.

The patient will undergo general or epidural anaesthesia during the procedure.

As the uterus is in the pelvis, the impact of the patient breathing movements should be non-significant. The bladder is kept empty thanks to the urinary catheter. Finally, the stabilizing arm maintains the probe in the good position.

3.4.2 Limitations

There are still limitations which are common with all the current surgical treatments such as infections (endometriosis, vaginitis, urinary active infection) and malignant cervix tumour.

Furthermore, patients with uterine malformation, fibroids with a size over 10 cm and fibroids localized too close to the digestive tract should not be treated with our device.

Hyper sensibility to components of our device is a contraindication.

4 DEVELOPMENT PLAN

4.1 Risk Analysis

Our device is classed as a IIb medical device.

Risk assessment is very important as it is considered as an integral part of an occupational health and safety management plan. We have created a table which gives an overview of the risks for our medical device according to the new guidelines (ISO 14971). We used a severity colour code (red is extreme severity, yellow moderate severity and green is low severity):

Table 1: Risk analysis.

	Frequent	Likely	Occasional	Rare
Catastrophic		infertility miscarriage	Electric hazard, Uterine synechia perforation	Death, anaphyl- -actic shock Haemor- -rhage
Critical	Damage to organs Software issues		surgical site infection	Failure
Significant	Pelvic pain,		Hypersensi- -tivity to component, loss of blood	Breach of sterile cover, scar tissue
Minor	Nausea and vomiting	Fever after surgery		

4.2 Essential Requirements

4.2.1 Biocompatibility

The probe must pass all the biocompatibility tests and allow the focused ultrasound waves to pass through the cover.

We will use a special designed piezoelectric ceramic material that will address our requirements regarding safety and efficacy.

4.2.2 Risk of Infection

To keep the infection level as low as possible; we propose a one-time use sterile cover filled with sterile conductive gel. After use, the probe and the robotic arm must be disinfected.

4.2.3 Risk of Electrical Hazards

To reduce the risk of electrical hazards, we will use insulated electric wires and backup power supply to ensure continuity and stress free surgical procedures.

4.2.4 Safety and Usability

Every device will come with a safety and usability manual to ensure that the involved person is well trained to conduct the procedure (workshops to train the physicians in technical and software knowledge are envisioned).

4.2.5 Software Requirements

We will guaranty the maintenance of the software regularly. It will be our responsibility to upgrade the software with the latest cybersecurity precautions to ensure information protection.

4.3 Usability Evaluation

4.3.1 Effectiveness

Our device offers an effective way of treating fibroids in the uterus, it is less invasive than surgical treatments and therefore there is less risk of infection.

4.3.2 Satisfaction

We will propose a detailed usability manual to help physicians integrate easily with the new product. As gynaecologist surgeons know how to use an endovaginal (or transvaginal) ultrasound probe, we assume the learning curve will be fast. However, it is essential to train gynaecologist surgeons about HIFU

technology, this may be possible through workshop sessions.

The procedure will be performed by the gynaecologist surgeon, this is an innovative added value: the surgeon can schedule directly the procedure on the surgery program, there is no more need for a radiologist (as for external HIFU technology.) As there is only one physician involved; the procedure organization is faster, the risk of medical error decreases and the patient trust increases.

Intrauterine HIFU use may lead to cost savings in terms of hospitalization (ambulatory hospitalization) and sick leave period (we recommend a one week sick leave whereas a three weeks sick leave is often needed after hysterectomy, myomectomy or uterine artery embolization).

Furthermore, it offers a psychological satisfaction to the patient (not losing the uterus and chances of retaining fertility, no scar). HIFU technology is more efficient than medical treatment and less invasive than surgical treatment. The procedure is under general or epidural anaesthesia, this allows the procedure to be safe and painless.

4.3.3 Efficiency

Using an internal delivery of the HIFU technology may require less time than the external HIFU use.

Moreover, with our device, there is no need for a radiologist; the user of the device is the gynaecologic surgeon.

Finally, the ambulatory hospitalization makes the procedure easier and quicker.

4.4 Clinical Trial

We will conduct the necessary pre-clinical and clinical tests (e.g. *In vitro* proof-of-concept test for HIFU transducer) by accredited laboratories, involving the required notified body with regard to our medical device class.

4.4.1 Phase 1: In Vitro

We plan to study HIFU treatment efficacy on fibroma cell culture. As for the safety test, we will study the toxicity on myometrial and endometrial cell culture.

As we want our technique to be used for women with infertility due to fibroid, we will be extremely focused on the impacts of HIFU on the endometrial tissue.

4.4.2 Phase 2a: In Vivo

We will test our device on animal models (healthy sheep whose uterus have many similarities with human uterus). We plan to obtain and study histologic sampling post HIFU treatment to study the long term effects on tissues (study of the tissue after 3 days, 14 days, 2 months, 6 months, and finally after 1 year).

For each animal 4 treatment sites will be tested (lateral, fundus, sub-mucosal, sub-serosal).

Other animal models are limited in our case, such as horses (commonly concerned by fibroma, but too expensive), ruminants (less expensive, but very rare fibroma cases), rats (not comparable to humans due to their size)

4.4.3 Phase 2b: Human Trials – Safety and Efficacy

Our primary outcome will be the reduction of symptoms according to the UFS-QOL scale and patient satisfaction (opinion survey).

Our secondary outcome will be the reduction in menstrual blood loss (using the PBAC score), the decrease of the fibroid size (MRI 6 month after the procedure).

Concerning the study population; the included subjects will be women over 42 years old or women older than 30 years with tubal ligation. Further patients include those suffering from significant fibroid symptoms for more than 3 months, uterine fibroid FIGO classification type 1 to 7 or uterine fibroid over 10 cm of size.

Subjects to be excluded are subjects with an urgent need for surgery, pregnant women, less than 18 years old women, patient with a desire for pregnancy, patients with severe endometriosis, pelvic or uncontrolled systemic disease, history of lower abdominal surgery and MRI contraindication.

So far, the exact number of patients is not known but we estimate a total of 60 patients.

As for the trial follow-up we plan to evaluate the success of the treatment with a MRI at 6 months to measure the remaining fibroid tissue. We will control the endometrial tissue by performing a hysteroscopy.

4.4.4 Phase 3: Human Trials – Comparison

We will study subjects with fibroma suitable for external and internal HIFU (Fibroma type 4 to 6 with an anterior localization), who are older than 18 years old.

We will lead a prospective randomized study; however, it won't be possible to double-blind the study.

5 CONCLUSION

Intrauterine HIFU technology is the answer to a real need for women.

Our device is promising, not only on a technical point of view but also regarding the business and marketing approach. Once this step is achieved, we plan to improve our medical device by creating an adjustable wide-angle probe and an automated guidance arm to increase precision of HIFU treatment of fibroids in every localization.

More indications will allow to expand our technology, for instance endometrial hyperplasia or patients with malign endometrium tumour who are contraindicated to surgery.

ACKNOWLEDGEMENTS

This work received funding from EIT-Health campus call (Project Grant Agreement n°18497).

We would like to thank the EIT Health committee and its partners for organising the Clinmed 2018 Summer School where we had the chance to meet and develop our project. This was a rewarding experience.

This would not have been possible without the CIC-IT from Grenoble and we would like to thank Pr Alexandre Moreau-Gaudry, Isabelle Marque, Laura Cotarla and the whole team.

We devote a special thanks to the University Hospital of Grenoble for welcoming us in the different departments we have visited. We warmly thank Dr François Istasse from the gynaecology department who answered our various questions about uterine fibroids.

We would also like to thank Pr Frederic Patat and Pr Jacques Felblinger who answered to our technical questions about HIFU technology and helped to feature our project.

Finally, we would like to thank Adria Maceira who besides giving us marketing advices, supported us and added to our project a special team spirit!

REFERENCES

Baird et al, D., 2003. High cumulative incidence of uterine leiomyoma in black and white women : ultrasound evidence.. *Am J Obstet Gynecol*.

Bohlmann et al, M., 2014. High intensity focused ultrasound ablation of uterine fibroids - potential impact on fertility and pregnancy outcome. *Geburtshilfe Frauenheilkd.* .

Chanelles et al, O., 2010. Fibromes - la chirurgie. *Recommandations CNGOF*.

Donnez J, D. M., 2016. Uterine fibroid management : from the present to the future. *Hum Reprod Update*.

Gelet and al, A., 2009. Transrectal High-Intensity Focused Ultrasound: Minimally Invasive Therapy of Localized Prostate Cancer.. *Journal of Endourology*.

Khan and al, T., 2014. Uterine fibroids - current perspectives. *Int J. Women Health*.

Ko et al, E., 2017. Safety of non-invasive body tightening with high-intensity focused ultrasound (hifu).. *Skin res technol.*.

Marret et al, H., 2010. Thermodestruction des fibromes utérins par ultrasons focalisés : une alternative?. *Recommandations CNGOF*.

Rueff, L. and Raman, S., 2013. Clinical and technical aspects of mr-guided high intensity focused ultrasound for treatment of symptomatic uterine fibroids. *Semin Intervent Radiol.*.

Stewart et al, E., 2017. Epidemiology of uterine fibroids : a systematic review.. *Obstetric. Gynecol.*.

Tavakkoli, J. and Sanghvi, N., 2011. *Therapeutic Ultrasound: Mechanisms to Applications..* s.l.:s.n.

Vijaya, M., 2013. *Piezoelectric Materials and Devices: Applications in Engineering and Medical Sciences.* s.l.:CRC press.

Yoshizawa et al, S., 2017. Enhancement of high-intensity focused ultrasound heating by short-pulse generated cavitation.. *Appl Sci*.

Yu An et al, C., 2017. An ultrasound imaging-guided robotic hifu ablation experimental system and accuracy evaluations, applied bionics and biomechanics.. *Appl Bionics Biomech.*.

APPENDIX

Competitors analysis :

GA = General anaesthesia

H = Hospitalization

SL = Sick leave

SSI = Surgical site infection

A = Anaemia

I = Infertility

FU = Final user, can be Gynecologist (G) or Radiologist (R) O = Occurrence

Type of treatment	Total cost				Side effects and Risks				Usability		Recidive	Fibroma
	GA	H	SL	Cost	Pain	SSI	A	I	Time	FU	O	Types
GnRH Analogue	-	-	-	- but only 3 months use	-	-	-	+		G	+++	0-7
Hysteroscopy	+	-	+	-	-	+	+	-	<1h	G	+	0,1,2
Hysterectomy	+	+	+	+	+	++	+	+	1h or more	G	-	0-7
Myomectomy	+	++	+	++	++	++	+	-	0,5 - 3h	G but not easy	++	4-7
Embolization	-	-	-	+/-	+	-	-	+	<1h	R	+	1-7
HIFU External use	-	-	-	+MRI 6000€	-	-	-	-?	>2h	R	+	3-7 Anterior
HIFU internal use	+	-	-		-	+	-	-?	<1h	G	+	1-5