QUALITY OF LIFE AND SYMPTOMATOLOGY AFTER HIGH INTENSITY FOCUSED ULTRASOUND TREATMENT FOR UTERINE FIBROIDS

Dr Melissa van der Merwe

Student number: 927551

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology.

Johannesburg, 2020

Declaration

I, Melissa van der Merwe, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed

Signed at Johannesburg

On this date

Acknowledgements

Dr. Amy Wise – Thank you for your patience and perseverance! I value your guidance, input and support.

Presentations arising from this project

None

Abstract

Uterine leiomyomas (ULs) are the most frequently occurring benign tumours of the female genital tract in premenopausal women. A higher prevalence of larger and multiple ULs is found in African women, which are typically more symptomatic. Women affected by ULs may display numerous types of symptoms impacting one's quality of life. A novel non-surgical modality explored for the treatment of ULs is the ultrasound guided high-intensity focused ultrasound (USgHIFU). In 2002, Spies *et al*, developed the Uterine Fibroid Symptom and Health Quality of Life (UFS-HQOL) questionnaire (8 symptom questions and 29 HQOL questions) in order to act as a self -administered tool for the evaluation of differences in symptom severity and health related quality of life in patients. The aim of this study was to determine if the USgHIFU treatment applied on a South African population improved the symptoms and quality of life perceived by patients.

This study was a retrospective analysis of prospectively collected data collected from 116 women from 1 October 2015 to September 2016 at Chris Hani Baragwanath Academic Hospital gynaecological department. Patients were interviewed before and at 6-months post treatment, using the UFS-HQOL questionnaire to identify the various symptoms and gauge the severity thereof.

The study consisted of women with mean age 34.95 ± 5.97 years with mean weight of 67.67 ± 0.64 kg and 35.34% being overweight. A total of 87% of women at baseline exhibited some form of dysmenorrhea, in comparison to 73% of women at 6-months. The UFS subscale (heavy bleeding during menstrual periods; fatigue; pelvic pressure; urination frequency) showed a mean score for symptom severity of 25.5 ±16.4 at the initial stage, improving to 15.5 ± 9.3 at the 6 months post treatment (higher scores highlight a greater number of symptoms and greater distress). The HRQL aspect (concern; activities; energy/mood; control; self-consciousness; sexual function) provided patterns of perceived improvement in all

aspects at month 6 (total HRQL score of 77± 16.9, change mean score 35.8 and effect size of 1.8).Therefore the questionnaire was able to detect and record the improvement of the health quality related and associated aspects of the lives of women 6 months post USgHIFU treatment.

Table of Contents

Declaration i

Acknowledgements ii

Presentations arising from this project iii

Abstract iv

Table of Contents vi

List of Abbreviations x

List of Figures xii

List of Tables xiii

1 Chapter: Literature Review 1

1.1 Introduction 1

1.2 Incidence of uterine leiomyomas 3

1.3 Risk factors for uterine leiomyomas 4

1.3.1 Age 4

1.3.2 Race 4

1.3.3 Hormones 5

1.3.4 Reproduction 6

1.3.5 Obesity 8

1.3.6 Lifestyle 9

1.4 Clinical Presentation 9

1.5 Diagnosis and Management 11

1.5.1 Medical Management 11

1.5.2 Surgical management 12

1.5.3 Non- surgical management 13

1.6 Treatment outcomes 18

1.7 Definition of the Term ‘Quality of Life’ 20

1.7.1 Health 20

1.7.2 Psychological 20

1.7.3 Physical limitation 21

1.7.4 Sexual function 21

1.8 Uterine leiomyomas: A South African Perspective 21

2 Chapter: Aims and Objectives 23

2.1 Problem statement and Aim 23

2.2 Objectives 23

3 Chapter: Methods and Materials 24

3.1 Study Design 24

3.2 Study Period 24

3.3 Study Site and Context of Study 24

3.4 Study Population 25

3.4.1 Inclusion Criteria 25

3.4.2 Exclusion Criteria 25

3.5 Study Methods 26

3.5.1 UFS-QOL 27

3.5.2 Dysmenorrhea score 29

3.5.3 Fertility 29

3.6 Data analysis and Interpretation 29

3.6.1 Body mass index calculation 30

3.6.2 UFS-QOL 30

3.7 Ethics 31

4 Chapter: Results 32

4.1 Patient demographic data 32

4.2 Dysmenorrhea and fertility data 32

4.3 UFS-QOL results 34

5 Chapter: Discussion 37

5.1 General overview 37

5.2 Study symptom outcome: dysmenorrhea 38

5.3 The UFS-QOL patient evaluation of outcomes following HIFU treatment 40

5.3.1 UFS or symptom severity subscale (SSS) 41

5.3.2 HRQL 42

5.4 Limitations 44

6 Conclusion 44

7 Chapter: References 46

8 Chapter: Appendices 51

8.1 Appendix A 51

8.2 Appendix B 54

8.3 Appendix C 55

8.4 Appendix D 57

8.5 Appendix E 58

8.6 Appendix F 59

List of Abbreviations

3D	Three-dimensional
AUB	Abnormal uterine bleeding
BMI	Body mass index
BWHS`	Black Women's Health Study
CE	Conformite Europeene
CHBAH	Chris Hani Baragwanath Academic Hospital
DMPA	Medroxyprogesterone acetate
DNA	Deoxyribose Nucleic Acid
DPT	Dermatopontin
ECM	Altered Extracellular Matrix
ER-α	Oestrogen receptor-α
FDA	Food and Drug Administration
GnRH	Gonadotropin-releasing hormone
HIFU	High intensity focused ultrasound
HRQL	Health related quality of life
IGF-1	Insulin-like growth factor-1
Kg	kilogram
M	meter
MRgHIFU	Magnetic Resonance-guided High-Intensity Focused ultrasound
MRI	Magnetic resonance imaging
NPV	Non-perfused volume
PR	Progesterone receptor
RFA	Radiofrequency ablation
SD	Standard Deviation
SERM	Selective oestrogen receptor modulators

SF-36	Short Form-36
SHBG	Sex hormone binding globulin
SPRM	Selective progesterone receptor modulators
TGF-β3	Transforming growth factor-β3
UAE	Uterine artery embolization
UFS-QOL	The Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire
UK	United Kingdom
ULs	Uterine leiomyomas
USA	United States of America
USgHIFU	Ultrasound-guided High-Intensity Focused Ultrasound

List of Figures

Figure 3.1 UFS-QOL symptom severity scoring (36). 28

Figure 3.2 UFS-QOL health-related quality of life subscales scoring guide (36). 28

Figure 4.1 Bar chart of dysmenorrhea scores of patients at the initial phase of HIFU treatment (n=108) and at the six-month post HIFU treatment (n=102) follow-up. 33

Figure 4.2 Patient fertility responses at the initial phase of HIFU treatment (N=116). 33

Figure 4.3 Overall (untransformed) mean and standard deviation scores for UFS and QOL subscales of study population at the initial baseline (blue) and six-month (red) post treatment stages (n=105). 34

List of Tables

Table 4.1 UFS-QOL transformed scores at baseline initial stage and six-month post treatment stage. 36

1 Chapter: Literature Review

1.1 Introduction

Uterine leiomyomas (ULs) or uterine fibroids are a frequently found type of benign tumour of the female genital tract in premenopausal women (1). Fibroids are of Mullerian duct origin and are defined as monoclonal tumours of the smooth muscle compartment or myometrium of the uterus, appearing histologically as benign neoplasms. These forms of neoplasm consist entirely of disordered smooth-muscle cells which are buried in abundant quantities of extracellular matrix (2).

The exact aetiology of uterine fibroids remains unknown but various molecular and cytogenetic studies by a variety of cohorts internationally have shown ULs originate at a cellular level (1, 3, 4). It is believed however, that some evidence supports the opinion that each fibroid originates through the marked modification of a single somatic stem cell of the myometrium when under the influence of ovarian hormones (2). The transformation and alteration of the myometrium is not an unusual occurrence and during the reproductive years of a woman, it normally undergoes changes in size and cellular properties such as during pregnancy. During pregnancy the uterus undergoes changes in the cellular phenotype of these cells which result in hypertrophy of the myometrial smooth muscle. Leiomyomas share certain characteristics with parturient myometrium, such as increased production of extracellular matrix (ECM) components as well as peptide and steroid hormone receptor expression. ECM is known to provide the vital support for intracellular connectivity and is involved in the regulation of intracellular communication. However, unlike parturient myometrium, uterine leiomyomas, continue to grow and are not subjected to regression processes via apoptosis. In general UL characteristically show increased proliferation of disordered smooth muscle cells, the deposition of the altered ECM with a less vascularization

network and disorganized structure, as well as the enhanced responsiveness to sex steroid hormones like progesterone and oestrogen (3).

A defining feature lies with the overproduction of ECM. The ECM is characterised as disorganized and fibrous in nature as well as having a protein profile distinctive in collagens, fibronectin and proteoglycans. Studies have shown that the causes of the increased activation of the ECM production pathways involve those with transforming growth factor-β3 (TGF-β3), CD24, and insulin-like growth factor-1 (IGF-1) (2,4). Within the UL, the organisation of collagens is thought to be affected by decreased levels of levels of the ECM proteoglycan dermatopontin (DPT), and also contribute towards to altered TGF-β signalling (2,4).

ULs may occur as single predominant mass or alternatively as a cluster of many smaller fibroids. The location and size of the UL will result in specific associated clinical manifestations. UL are divided into three major forms: submucous fibroids; intramural fibroids; and subserous fibroids (2).

Fibroids which extend in to the submucous layer extend into the uterine cavity which may result in endometrial integrity disruption, implantation issues, as well as the contraction capacity of the myometrium which stops menstrual bleeding from the endometrial blood vessels. The formation of these fibroids will result in excessive or irregular bleeding, infertility, and recurrent pregnancy loss (2). An intermediary group include intramural fibroids which reside in the myometrial wall. Large subserous fibroids, which grow out into the peritoneal cavity exerts pressure in so much that it is perceived by the patient as pelvic discomfort (2).

Depending on the size and location, a variety of symptoms may arise which may include bleeding disorders, infertility, pelvic pain, dysmenorrhea (painful menstruation) and pelvic pressure symptoms (1).

1.2 Incidence of uterine leiomyomas

Uterine leiomyomas are the most common form of benign tumor found in women. The frequency of the condition is underestimated as ULs can provide no symptoms or symptoms may develop more subtly remaining undiagnosed (5).

ULs were first described in 1793 at St George's Hospital London, England, and current studies continue to highlight the ongoing plight of women suffering from ULs. Okolo in 2008 reported that up to 25% of all women and up to 30-40% women over the age of 40 years presented with clinically apparent fibroids (1). Stewart *et al* in 2017 in their review of uterine fibroids, highlighted that over 70% of women suffered from UL by the onset of menopause and that the incidence of ULs ranged from 5.4% to 77% in women of reproductive age (5). An online self-reported prevalence study conducted across eight countries (Brazil, Canada, France, Germany, Italy, South Korea, UK and USA) with women of reproductive age (15-49 years) who have experienced menstrual bleeding and had a confirmed diagnosis of UL, provided prevalence data which ranged from 4.5% within the UK to 9.8% in Italy (6).

Between 20–40% of reproductive age women may experience ULs however, their prevalence rates vary amongst races (1). In about 50% of these women, ULs lead to symptoms (7).

It is important to note that the variability of the data relating to the reported incidence and prevalence studies, are greatly impacted by the method of diagnosis (pelvic examination, ultrasound evaluation, hysterectomy), clinical data (medical record reviews, screening, self-reporting), health status (access to health practitioners and gynecological focused facilities) as well as the population studied (6,7,8). The true incidence and therefore impact on women health, specifically in South Africa, remain unknown until suitable population-based research is conducted.

1.3 Risk factors for uterine leiomyomas

The large number of undiagnosed patients with ULs, present at times limited evidence in relation to risk factors especially those affecting country specific population groups (5). Certain risk factors have been identified, explored and published.

1.3.1 Age

It has been shown that age is considered a significant risk factor with the greatest magnitude (approximately up to 10 fold) for the development of ULs (5). In general the occurrence of ULs in women do not occur before puberty, and have a tendency to increase with age throughout the reproductive years subsequently declining during the postmenopausal years (5, 8, 9). In studies conducted from women hospitalized for UL in the USA, highlighted a patient age reaching a peak at 45-49 years and then declining between 50-54 years of age (8). Similar trends were noted and supported through data evaluated from Israel and the UK (5).

1.3.2 Race

Overall, uterine leiomyomas are three to five times more common in African women than in Asians and Caucasians (10, 11). African women suffering from ULs are often more symptomatic and have larger and multiple tumours. These women are of a younger age at diagnosis and at hysterectomy (10, 11).

When evaluating race, Black women are at most risk when compared to White and Asian women. In fact it has been shown that Black women have almost three times the age-specific cumulative incidence of White women (8). Numerous studies have confirmed that the lifetime risk of UL (the cumulative risk of developing a UL by the age of 50) Black women was greater than 80% when compared to White woman at nearly 70% (8, 9). The Black Women's Health Study (BWHS) of Slone Epidemiology Centre at Boston University, USA, is a

prospective cohort study of 60 000 Black women of the age range 21-65 years which provides important and useful epidemiological data and their associated risk factors when suffering from UL (9). Overall Black women are diagnosed early in life, often suffer from multiple and larger UL, experience more severe symptoms, are of a much younger age at diagnosis and at hysterectomy, when compared to other ethnic groups (1, 9). It has been hypothesized that the racial divergence of varied expression of UL is based on estrogen biosynthesis differences as well as estrogen metabolism in a genetically mediated manner (9). Various genetic role players in the development and occurrence of uterine leiomyomas, have of late been identified and characterized (9). Some genetic role players that are thought to be involved in the occurrence of uterine leiomyomas include the gene linked to fumarate hydratase (an enzyme which potentially plays a role in White women suffering from ULs but are not associated with other signs or symptoms); chromosomal changes (e.g. trisomy 12); alterations of genes (e.g. MED12, HMGA2), alterations of protooncogenes (e.g. p27 and p53), disruption to signalling pathways (e.g. P13K-AKT-MTOR) and finally epigenetic mechanisms (DNA methylation and histone modifications) (1-3, 9).

1.3.3 Hormones

It is well known that both oestrogen and progesterone play a major role in the growth of ULs (1, 2, 4, 8). This is reflected in the prevalence and occurrence of ULs during active ovarian activity whilst most leiomyomas shrink after menopause. Local hormone concentrations and hormone receptors in uterine tissue differ between UL and healthy myometrial tissue (4). UL tissue have been found to contain high concentrations of oestradiol, progesterone receptor (PR), aromatase and also oestrogen receptor-α (ER-α) (4).

Biologically powerful oestrogen and oestradiol induce the production of PR via the ER-α which is mediated by aromatase. Aromatase catalyses the formation of oestrogen in the ovaries (which then circulate to the leiomyoma) as well as converting androstenedione, from

the adrenal gland or ovaries, to oestrogen locally in the leiomyoma (2). This subsequently stimulates the PR via the ER-α. The increased number of PR results in an increased responsiveness of UL tissue to progesterone secreted by the ovaries. The enhanced activity of progesterone and PR result in increased cell proliferation and survival, decreased cell apoptosis, enhanced extracellular-matrix formation and hence increased tumour growth (2). The result of progesterone signalling through its receptor, plays a critical role in the clonal expansion of fibroid stem cells, which have been genetically altered, into fibroids which present clinically and also to increase the growth of ULs by affecting both stem cells and differentiated UL cells (2).

1.3.4 Reproduction

Reproductive factors include those which increased risk of UL incidence (i.e. time since last birth and premenopausal status) and also those factors which take the form of protection (i.e. parity, oral contraceptives, injectable contraceptives) (5). The chances of developing ULs have been shown to increase by 2-3 fold in women who last gave birth 5 or more years ago compared with women who gave birth more recently hence suggesting that the time period since last giving birth plays a role in UL development (5, 9). Also it was found that in certain registry studies, premenopausal women were at approximately 3-5 times higher risk of developing symptomatic ULs versus postmenopausal women (5).Similarly studies have also shown that the risk of developing UL increases with an earlier age at menarche which then consequently leads to a longer history of menstrual cycling and consequently increased mitotic myometrium activity, which is reaches a peak during the luteal phase of the cycle (1, 8). After menopause, pathologic evaluation of hysterectomy UL specimens found that there was a reduction in both the size and number of ULs in postmenopausal women versus premenopausal women (8).

Bearing offspring has shown an association with decreased risk of developing ULs. A 20-50% reduction in risk has been noted when comparing parous with nulliparous women, and also it has been suggested that the risk of developing ULs will decrease with increasing parity (5, 8). Pregnancies that end spontaneously preterm or are incomplete seem to be unrelated to risk (8). In cases of nulliparity, it has been hypothesized that the correlation between never having given birth and the incidence of ULs is primarily due to the continuous oestrogen secretion being uninterrupted by pregnancy and lactation in a women's reproductive life (1). Other contributory factors include maternal age at the first birth (where women of an older age at first term birth have a lower associated risk of UL development); interpregnancy interval (a longer interval increases the risk of UL); fertility (direct correlation between diagnosed infertility and presence of UL especially in women of younger ages < 25 years). There is no definitive association with breastfeeding (8).

The use of oral contraceptives and UL development has generated a wide range of findings with no clear emerging patterns (1, 8). Studies have investigated and evaluated associations between UL development and types of contraception, contraception component potency, types of progestin or oestrogen formulation, duration of use, as well as onset of use (1, 8). In cases relating to the injectable contraception medroxyprogesterone acetate (DMPA), studies conducted in Thailand and repeated by the BWHS cohort, identified that between 40-50% women using DMPA were less likely to suffer from ULs, than those women who never used this form of contraception (5, 8). Though information relating to the exact nature of association remains unclear, it is important to note that oral contraceptives still forms part of an effective treatment plan for various menstrual disorders associated with ULs and its use continues to be sanctioned in women who merit it (1).

1.3.5 Obesity

The development of UL has been associated with obesity. A woman with a body mass of 70 kg or greater is three times more at risk of developing UL compared to a woman with a body mass of less than 50 kg. Furthermore, when evaluating women with larger BMIs presenting with ULs relative to the general population, 50% vs. 25% were likely to be obese and 16% vs. 7.2% severely obese (1).

A body mass index (BMI Kg/m^2) in certain cases, has been associated with moderate increased risk and in other cases, none at all (8, 9). A positive connection between UL risk and BMI amongst Black women versus White women has been shown, in addition to a non-linear relationship of UL risk which increased with overweight women then decreasing slightly among the more heavier of women (8). It is hypothesized that obesity impacts as a risk factor through a variety of hormonal and inflammatory mechanisms. Obesity results in an increase in the adrenal androgen to estrone conversion, as well as a reduced production of sex hormone binding globulin (SHBG) within the liver, resulting in the decreased circulating levels of SHBG. These lower levels of circulating SHBG then biologically impacts on UL development by potentially increasing the bioavailability of circulating estrogens and androgens (8). Central obesity promotes insulin resistance and this state of hyperinsulinemia may directly or indirectly influence the development of fibroids through the promotion of myometrial smooth muscle cell proliferation and also increases circulating levels of ovarian hormones (9). Furthermore, components of metabolic syndrome i.e. elevated blood pressure, hyperlipidemia, insulin resistance and central obesity with more pronounced proinflammatory effects, all are factors associated with higher UL risk (9). A combination of metabolic and physiological factors of obesity including insulin resistance, diabetes mellitus and hypertension, as well as the action of increase IGF-1 activity and increased androgen levels, all contribute towards the mediation of increased risk of UL development (1).

1.3.6 Lifestyle

Evaluation of risks related to smoking, alcohol consumption, caffeine consumption and diet have been evaluated through various studies and cohorts (8). Smoking has been founds to have a moderate protective effect in women experiencing a 20-50% lower occurrence in those who currently smoke (or previously smoked) versus those who had never smoked (1, 8). It is hypothesized that components within tobacco may inhibit aromatase which then subsequently impacts on the metabolism of estradiol to the less potent forms of estrogen (8).

Increased alcohol consumption has been associated with increased endogenous levels of estradiol and oestrogen thereby leading to certain positive associations between alcohol and risk of UL development (8). Similarly caffeine and coffee consumption are shown to have some relationship with increased levels of early follicular phase estradiol and potentially may enhance the production of sex steroids (8). Plant based diets or an increased intake of fruits and vegetables as opposed to meat, has been found to have a protective effect on women versus those women who eat larger amount of meat. This is primarily due to the increased bioavailability of endogenous hormones through diet (8).

1.4 Clinical Presentation

Although leiomyomas are not life threatening, they can be severely debilitating and affect one's quality of life. Most leiomyomas are asymptomatic resulting in some women not even being aware they are suffering from UL. However 25% of women affected by ULs, exhibit symptoms that impact on activities of daily living and exhibit severe symptoms which require treatment (12). Women are affected by various sizes, types, location and number of leiomyomas. Consequently women will display numerous types of symptoms and many women affected display more than one symptom (13, 14).

Abnormal uterine bleeding (AUB) is the most common symptom, which normally consists of uncontrolled menstrual bleeding which left untreated can result in life threatening anaemia (13, 14). Approximately 60% of women with symptomatic ULs may experience a form of prolonged bleeding (15). The exact mechanism of leiomyoma associated AUB is thought to be linked with the increased endometrial surface area, vascular dysregulation and as well as endometrial haemostasis interference (16).

Pelvic pain is commonly described as being cramping in nature with 75% of symptomatic women reporting this symptom and a smaller proportion of women reporting backache and leg pain (15). Pelvic pain has been found to be suggestive of degeneration, distortion, possible associated adenomyosis and endometriosis (16). In the event of larger fibroids, women may present with additional symptoms including pelvic pressure, dysfunction of the bowels and urinary frequency, and urinary urgency (16). Professional medical physical evaluation of leiomyoma size and location, as well as the patient own self- assessment, noted signs of incontinence which impacted on overall quality of health (15).

Infertility and leiomyomas are thought to be associated with the size of the fibroid as well as the location, especially submucosal and intramural myomas which result in the distortion of the uterus. Various mechanisms have been suggested to explain the pathogenesis and link with infertility. A combination of physical changes (e.g. distortion of uterine cavity), functional changes (e.g. increased contraction of the uterus and endometrial function impairment), changes to the local hormonal conditions as well as paracrine molecular changes, incidents of intracavitary inflammation, and finally mechanical blockage of tubal ostia which may interfere with sperm or embryo transport through the fallopian tubes, are all suspected to play some role with fertility (15, 17). In addition, leiomyomas have been shown to significantly impact and affect obstetric outcomes e.g. with preterm delivery (< 37 weeks), primary caesarean section, breech presentation and lower birthweight infants (18).

1.5 Diagnosis and Management

Detection and precise evaluation of the number, size and location of ULs is now possible due to advances in imaging and endoscopic methods (10). Diagnosis can be by clinical examination, ultrasonography, hysteroscopy, or magnetic resonance imaging (MRI) (17). A physical pelvic exam may reveal the presence of an enlarged uterus or mass and a blood test for haemoglobin levels may allow for the identification of anaemia. Ultrasound screening is the gold standard method for a cost effective, easy, and immediate confirmation for the presence of leiomyomas. Recent developments in 3D imagining have resulted in 3D ultrasound allowing for evaluation of myometrial pathology, as the technology is able to reconstruct the coronal plane of the uterus (17). Diagnostic hysteroscopy does not require anaesthesia and is normally performed in an outpatient setting resulting in the ability to differentiate between intracavitary myomas and large endometrial polyps (17). Lastly MRI is able to provide information on the number of ULs, their size, degree of vascularization, endometrial cavity and serosal surface placement, as well as the identifying the boundaries with normal myometrium (17).

Treatment of fibroids depends on the type of symptoms, size, location, the women's desire for fertility, access to treatment, and also the physicians experience (14). Successful treatment aims to provide relief of symptoms, sustained reduction of leiomyomas, maintenance of fertility if desired while avoiding harm (14). There are medical, surgical and radiological options available for the treatment.

1.5.1 Medical Management

Medical management options for UL often have a moderate impact on the patient and/or associated adverse effects. However novel therapies are currently being evaluated and developed especially those at gene and receptor level which potentially may result in

improved long term effectiveness (16). Standard recommended therapies for UL include gonadotropin-releasing hormone (GnRH) (normally preoperative treatment to shrink in size the UL prior to surgery); GnRH analogues are occasionally used for temporary symptomatic relief as well as the reduction of fibroid size preoperatively; levonorgestrel-releasing intrauterine system or Mirena for the treatment of AUB; nonsteroidal anti-inflammatory drugs e.g. typical anti-inflammatories and prostaglandin inhibitors; oral contraceptives (used to treat atypical bleeding); selective progesterone receptor modulators (used to decrease the size of UL as part of a preoperative plan and also in women approaching menopause); tranexamic acid (part of antifibrinolytic therapy); aromatase inhibitors (prevent growth of ULs through the blockage of aromatase activity; selective oestrogen receptor (SERM e.g. Raloxifene) and selective progesterone receptor modulators (SPRM e.g. ulipristal acetate and mifepristone) (14, 16, 19, 20). The decision on which course of medical treatment to follow, commonly is prescribed by specific symptomology exhibited by the woman i.e. women who present with UL associated AUB (e.g. may be treated with oral contraceptives or the Mirena) and women who display more severe complex combination of symptoms associated with UL (e.g. may be treated with SPRMs).

1.5.2 Surgical management

The most effective treatment of ULs is the removal of the uterus i.e. hysterectomy (21). A hysterectomy provides a definitive solution to symptoms and results in immediate improvement in quality of life in those women not wanting to preserve fertility. Before surgery is undertaken, it is recommended that the needs and expectations of the patient are evaluated, the competency of the surgeons, the availability of various techniques at a facility and the application of obstetric and gynaecological guidelines are assessed (17, 21). Surgical strategy options include hysterectomy and myomectomy.

A hysterectomy can be performed by various routes i.e. abdominal, laparoscopic, or vaginal. Vaginal hysterectomy may be the chosen preferred technique (dependent on the size of the myomatous uterus) as it provides several advantages which includes a shorter time in surgery, reduced blood loss incidents, minimal hospitalisation times, and a reduced time of physiologic ileus due to postoperative gut dysmotility (14, 16).

Women who wish to retain their uterus and hence fertility may opt for a myomectomy to remove the ULs (22). This surgical option is primarily aimed at those patients who present with submucosal leiomyomas less than 3 cm and when more than 50% of the leiomyoma is intracavitary (14). Two forms of myomectomy are performed in order to remove the leiomyoma: (i) laparoscopy which is associated with reduced postoperative pain, less risk of postoperative complications e.g. fever, and shorter hospitalisation time; and (ii) the open surgical technique (14). It has been reported however that there is a 15%-33% recurrence of ULs in women who have undergone a myomectomy and furthermore 10% of women may eventually even require a hysterectomy within 5-10 years (14, 16).

Myolysis or Radiofrequency ablation (RFA) allows for the removal of ULs using a focused beam of energy which originates from either an electric current, radiofrequency or a cryoprobe . However this is not mainstream treatment for fibroids (23, 24).

1.5.3 Non- surgical management

New and varied options to traditional surgical techniques have been evaluated in recent years. Surgery is invasive and expensive thereby potentially significantly impacting a health care system of a country. The chosen form of therapy will often be considered in proportion against the untreated disease condition costs, ongoing or repeated medical investigations costs and as well as the specific treatment modality availability and costs (18). More conservative and less invasive techniques have become increasingly popular especially in woman desiring fertility or those not fit for surgery (25).

1.5.3.1 Uterine artery embolization

Uterine artery embolization (UAE) is a technique which involves the introduction of an embolic agent via angiography resulting in the occlusion of the fibroid vascular supply, resulting in UL atrophy (21, 25).

UAE is an interventional radiologic procedure involving occluding agents injected into either one or both of the uterine arteries limiting the blood supply to the entire area i.e. uterus and leiomyomas. Women who wish to preserve their uterus or avoid surgical procedures due to personal preference or risk of medical comorbidities, may decide on this medical intervention method (14, 16, 17). Benefits of the UAE include a decreased hospitalisation days, decreased time to resuming normal activities and a decreased likelihood of blood transfusion time (14). The most common complications and long term contraindications are post procedure discomfort, post-embolization syndrome characterized by fever and pain, allergy to the contrast media, physical vaginal expulsion of the tumour tissue, loss of ovarian function, active uterine or adnexal infections, and renal insufficiency (14, 16, 17). The success of the UAE depends on the size of the uterus (a 20 weeks and larger uterus in size may not provide a clinically significant reaction) as well as the type and number of leiomyomas (single submucosal or subserosal ULs respond better to surgery) (16). It has been suggested that between 15%-33% of patients would require future surgical intervention within 18 months to five years of UAE (14, 17).

1.5.3.2 High-Intensity Focused Ultrasound (HIFU)

Conservative treatments involving a focused energy delivery system have been developed and tested over the past ten years (Energy sources include radiofrequency, electricity, supercooled cryoprobes and most recently ultrasound focused ablation techniques (either magnetic resonance-guided i.e. MRgFUS or high frequency ultrasound guided transcutaneous focused) (16,17). Many of these techniques are new however and they lack the supportive

medical evidence and long term data to adequately evaluate their risks and benefits to the patient (16, 17).

High-intensity focused ultrasound (HIFU) was first introduced in 1942 by Lynn *et al* who suggested using extracorporeal focused ultrasound energy for tissue destruction. However, only in the 1980s has more scientific interest and technical expertise been invested into the use of this non-invasive surgical technique on the management of solid cancerous tumours and uterine fibroids (26, 27).

HIFU is a non-invasive technique which involves a beam of ultrasound waves produced by piezoelectric or piezoceramic transducers, which is focused at one point. This is typically one to five mm (diameter wise) and 10 to 50mm (length wise) (26, 28, 29).The focused ultrasound energy raises and maintains a 60°C and higher temperature within the targeted tissue for one second or longer to cause coagulative necrosis of the targeted tissues and immediate cell death without damaging the surrounding vital tissues and organs (26, 28).

Mechanical effects involved a combination of cavitation, microstreaming and radiation forces produced by the high intensity acoustic pulses (28). The coagulative necrosis leads to a reduction in the fibroid size over time and improvement in associated symptoms as the fibroid shrinks in size (29).

During the ablation process of the localised area the HIFU beam must be constantly monitored. This can be achieved using magnetic resonance i.e. magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU) or using ultrasound i.e. ultrasound-guided HIFU (USgHIFU) (28, 30). Different manufactures have introduced various instruments for fibroid treatment however not all devices have been formally sanctioned for use by medical regulatory bodies. This is in part due to the fact that ongoing studies are still underway in order to assess the long term efficacy and safety aspects of these techniques for fibroid management (16). In the USA, the Israeli Insightec ExAblate MRgHIFU instrument is an

approved technique for fibroid treatment by the Food and Drug Administration (FDA), similarly the United Kingdom (UK) developed Sonalleve MRgHIFU instrument has received formal Conformite Europeene (CE) marking and lastly the Chinese JC HIFU USgHIFU instrument has been installed and used at the Queen Mary Hospital since 2012 for fibroid treatment. The latter USgHIFU instruments and similar systems from other Chinese manufacturers still have not received FDA approval. At the South African Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, the ultrasound guided HIFU is used. It has been suggested that the use of the USgHIFU system in relation to the MRgHIFU system, is a cheaper mode of treatment and also requires shorter treatment times (26).

Limitations of the HIFU technique include: production of tissue burns occurring between the targeted tissue area and the transducer, associated injuries such as nerve damage or bowel injuries arising from scattered or reflected high-intensity ultrasound waves; variation of absorbed energy and excessive energy absorption by tissues resulting in unpredictable distribution of cell death; high patient exclusion rates; the requirements of expensive magnetic resonance instrument; targeting of only a single fibroid during a treatment; and the central ablation of fibroids even though numerous ULs tend to grow peripherally (16, 26, 28).

HIFU is indicated in woman with symptomatic ULs wishing to avoid surgery or to remain fertile. The effect of HIFU on fertility and fecundability is unclear since there is a lack of large scale ongoing investigations resulting in continuous data (31, 32). Patient selection criteria for HIFU therapy is dependent on the expertise of the particular medical facility. In general however, HIFU treatment is offered to premenopausal women with symptomatic fibroids and/or adenomyosis (26). Most protocols exclude women with uteri more than a 20 week gestational size, a large myoma (greater than 10 cm in diameter), women with greater than 5cm subcutaneous abdominal tissue, pregnant women, any major medical disease or

any contraindications for MRI (33). Patients with previous abdominal surgery are a relative contraindication but these should be individualised as scar tissue has a high ultrasound absorption when compared to normal skin tissue, potentially resulting in pain and thermal skin damage (33). ULs targeted in areas where the focused ultrasound treatment beam would pass through bowel or bladder may also be reason for exclusion if the bowel cannot be deflected away with a degassed water balloon (34). Limited data also suggests that ultrasound-guided HIFU when used for treatment of uterine fibroids does not impact on ovarian reserves (11). HIFU seems to be promising to patients who desire fertility, however further long term studies still need to be done (31). For the purpose of this study, patients were selected according to the guidelines and protocols established by the Department of Obstetrics and Gynaecology at Chris Hani Baragwanath Academic Hospital (CHBAH) (refer to inclusion criteria 3.4.1).

Once screening has been conducted, pre-treatment planning is critical in order to allow for adequate tumour coverage, mimic the sonication, identify the depth of target tissue, identify the proximity of the affected tissue to the sacrum , assess the potential presence of a bowel loop along the sonication path, and finally the adequate consideration of coagulation, desiccation and vapour formation during the transmission of ultrasound energy which could lead to harmful side effects in the patient (26, 28).

The HIFU procedure is conducted whilst the patient is under intravenous conscious sedation which then allows for active engagement of medical personnel with the patient to obtain real time responses and also minimizing patient movement. Post treatment management includes the administration of analgesic medication, allowing the patient to lay prone for approximately an hour and the cooling of the urinary bladder using cold saline solution (26).

1.6 Treatment outcomes

In general, the choosing of a management strategy for uterine leiomyomas is dictated to by the age of the patient, the desire to preserve fertility, the avoidance of radical surgical methods, cost of therapies, availability of novel and traditional therapeutic measures and technologies, and finally the experience and expertise of medical professionals and facilities (16, 18). The choice of therapy chosen by patients will however be primarily for the alleviation or total disappearance of symptoms associated with ULs. Whilst a hysterectomy would eventually alleviate all UL symptoms, most women are opposed to this option due to the undesirable comorbidities experienced. Hence the choice of an alternative, less invasive procedure to hysterectomies is becoming more favourable. However not all alternate therapies would result in the relief of UL symptoms. Hence in order to make an informed and educated choice to an alternate therapy, sufficient medical evidence and clinical findings into the therapy effectiveness would need to be evaluated as well the evaluation of a patient reported outcome to evaluate and assess the reduction in symptoms (18, 35).

Most studies have focused on clinical findings and assessments conducted by medical professionals on patients before, during and after the various stages of treatment. These include aspects relating to the reduction in fibroid volume, fibroid size, subsequent symptom resolution, and also the rate of re-intervention for persistent or recurrence of symptoms (26, 32). Physical measurements include the longitudinal, anteroposterior, transverse dimensions of the fibroid taken to calculate the fibroid volume and monitor any changes in size. Other indicators of treatment efficacy include the percentage of UL or adenomyotic volume ablated (NPV) during HIFU, highlighting the improvement of symptoms and also reduction in the volume of the fibroid (26).

An equally important aspect is the assessment of the impact of treatment made by the patient themselves. The patient would evaluate the impact of the UL on their own quality of life as

well as any quality of life improvements made after UL treatment. Over the last ten years further emphasis has been placed, investigated and assessed on the women's health-related quality of life (HRQL) in relation to ULs (15). Health-related quality of life measures include the Short Form-36 (SF-36) and the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) (15). The SF-36 is a questionnaire which is a generic measure of the HRQL and consists of 8 subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (35). It is also the most commonly used quality of life measurement of studies, including those specific to fibroid-related quality of life (15). In 2002, Spies *et al*, developed the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire in order to act as a tool for the detection of differences in symptom severity and health related quality of life in patients suffering from ULs specifically (15, 35-37). The UFS-QOL questionnaire has been cited to been used in numerous studies of women suffering with ULs regardless of the treatment modality (35). It is a reliable and validated tool for women suffering with ULs and has also been shown to be extremely responsive to treatment for ULs and forms a useful outcome measure for uterine-sparing uterine fibroid treatments (35). The questionnaire consists of eight symptom questions, and 29 HRQL questions with six subscales or domains – concern, activities, energy/mood, control, self-consciousness, and sexual function (15, 36). Scores are achieved for both scales ranging from 0 to 100, are assessed using specific calculations and results interpreted to the developers recommendations (15, 36)

The objective of the UFS-QOL questionnaire overall aims to be a reliable measure of the impact and potential improvement of the medical interventions utilised for the treatment of UL, from a patient perspective. Subsequent interpretation and usage of this data can contribute towards the overall success of clinical trials, comparison between cohort studies, as well as further long term based research efforts (15, 35, 36)

1.7 Definition of the Term ‘Quality of Life’

The non-invasive technique HIFU had been introduced and diversely implemented for treatment of uterine fibroids at the South African Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg in 2015. Although HIFU has been proven to be a safe and effective procedure, there was minimal data highlighting and reflecting its effectiveness on a local South African population.

In this study, we used the term ‘quality of life’ to refer to the patient’s satisfaction of general improvement in their post-treatment condition compared to their pre-treatment condition regarding their psychological, emotional and physical well-being.

Quality of life is difficult to quantify as there is no defined progression or biochemical measure. Although quality of life is subjective, clinical parameters have shown to be in keeping with subjective findings. The success of treatment cannot only be judged on the objective findings alone such as shrinkage of the UL but also on the objective and subjective symptoms. The effects of ULs on quality of life include those aspects pertaining to personal health; psychological wellbeing; lifestyle limitations; and sexual dysfunction.

1.7.1 Health

Fibroid related symptoms can severely effect health related quality of life. Patient experience debilitating symptoms such as: menorrhagia (with or without anaemia), dyspareunia, lower back pain, pregnancy complications, labour, and reproductive problems e.g. infertility.

1.7.2 Psychological

Studies have found that women suffering from fibroids experienced sadness, self-reported depression, anger and frustration. A women's psychological distress while living with fibroids is a major component when assessing quality of life.

1.7.3 Physical limitation

For many women fibroids become a painful condition that significantly alters their lives. Symptoms can have an impact on the patients' abilities to complete activities of daily living.

1.7.4 Sexual function

The symptoms themselves that accompany fibroids may get in the way of sexual intercourse. Intercourse may become uncomfortable or even painful. The psychological burden also adds to sexual dysfunction.

A preliminary study to evaluate the therapeutic effect and safety of ultrasound guided high-intensity focused ultrasound treatment conducted at the teaching facility Chris Hani Baragwanath Academic Hospital (CHBAH) gynaecological department on a local population suffering from symptomatic ULs was conducted (38). The study, a first of its kind with regards to treatment modality as well as study conducted on South African Black female population group, demonstrated that USgHIFU treatment could be well tolerated and safely applied to women suffering from ULs. This was despite the involvement of a small number of enrolled patients and extended follow-up of clinical symptoms. This study however did not focus on the patient's perspective on the improvement of symptoms nor the quality of life aspects.

1.8 Uterine leiomyomas: A South African Perspective

Only a handful of studies have been conducted on a uniquely South African base of patients suffering from ULs. Earlier studies of these women, have evaluated various therapeutic hormonal treatment modalities (39-41), issues of fertility (42, 43), genetic mutations (44, 45), as well as surgical interventions (38, 46-48). Recently only two studies, published to date, have been sourced specifically evaluating and reporting on the efficacy and safety aspects in

relation to the USgHIFU treatment modality (38, 47). Both studies involved the co-operation between engineers and medical practitioners from both China and South Africa and the implementation of an USgHIFU system JC200; Haifu Medical Technology Co., Chongqing, China. The technique was used on a local Johannesburg, South Africa based Black population of symptomatic UL sufferers. The study by He *et al* in 2018, evaluated the UL rate of shrinkage, relief of symptoms, and improvement aspects relating to quality of life, whilst Zhang *et al* in 2017 evaluated the therapeutic, effect and safety of the technique (38, 47). Both of these studies have shown positive outcomes and have shown that the USgHIFU technique provides feasible and effective medical outcomes in a safe manner.

2 Chapter: Aims and Objectives

2.1 Problem statement and Aim

HIFU was introduced to Chris Hani Baragwanath Academic Hospital (CHBAH) in October 2015. Most studies to date had been conducted in China and Hong Kong, where HIFU for uterine leiomyomata was used extensively. The population that South Africa serves, however, differs drastically from that of China, and these factors include ethnicity, culture, obesity and spectrum of symptomatology. Hence the patient awareness and perception of the impact and effectiveness of HIFU treatment on a local population remains unknown. This therefore formed the basis of a pilot study at CHBAH, wherein women were provided with a patient self-evaluation survey of HIFU treatment administered and monitored at regular intervals post treatment. The pilot nature of the study formed part of a feasibility approach within the department in order to assess the efficiency of the HIFU treatment program within the department. The aim of this study was to determine if HIFU improved the quality of life as well as changes in symptoms of patients, before and six months post HIFU treatment at the Chris Hani Baragwanath Academic Hospital, evaluated and perceived by patients utilising a uterine leiomyomata symptoms and health related quality of life questionnaire (UFS-QOL).

2.2 Objectives

2.2.1 To determine the change in the quality of life after HIFU treatment

2.2.2. To determine the change in symptoms after HIFU treatment

3 Chapter: Methods and Materials

3.1 Study Design

This study was a retrospective analysis of prospectively collected data which was designed to assess a leiomyomata affected patients' satisfaction with the HIFU procedure by answering an established validated survey before and after the HIFU procedure was conducted under medical supervision.

3.2 Study Period

Patient selection and data collection was conducted from 1 October 2015 to end September 2016. During this time patients were evaluated before treatment and six months post treatment.

3.3 Study Site and Context of Study

This study was carried out at the Department of Obstetrics and Gynaecology, Chris Hani Baragwanath Academic Hospital (CHBAH). The HIFU section is a specialised unit located within the Department of Obstetrics and Gynaecology. The CHBAH is affiliated with the University of the Witwatersrand and is situated in Soweto, South Africa. It is a referral centre that treats mainly high-risk conditions. At the time of the study in 2016, it was the only hospital in the country with HIFU facilities and therefore served the general population group of interest. The HIFU technique was applied the JC200 focused Ultrasound tumour therapeutic system from the Chongqing HAIFU medical technology company, China. This study did not involve the medical examination of patients, but rather evaluation of their departmental medical files and answers to the questionnaires.

3.4 Study Population

The study population consisted of 116 women who fit the prescribed criteria for HIFU treatment. HIFU treatment was administered as per CHBAH Gynaecological departmental procedures

Potential HIFU treatment candidates were initially screened for age, uterine size, abdominal subcutaneous tissue and the presence of symptomatic fibroids. Before HIFU treatment was commenced, patients were subjected to a Magnetic Resonance Imaging scan (MRI), MRI suitability screening (fibroid location and accessibility) and fibroid mapping. If the inclusion criteria were met, patients were then admitted a day before the procedure and were then normally discharged the day after, provided there were no complications.

3.4.1 Inclusion Criteria

Suitable HIFU treatment patients were identified according to departmental HIFU treatment guidelines, as follows:

- Patient age must have been less than 50 years old or premenopausal
- Patient must have had a uterine size maximum 18 weeks
- Patient must have had less than 5cm of abdominal subcutaneous tissue
- Patient must have had symptomatic uterine leiomyomata requiring treatment
- Patients may not have undertaken the HIFU treatment for fertility sparing reasoning
- Patients must have been to lie prone for at least 1 hour during the procedure

3.4.2 Exclusion Criteria

The following patients were excluded (according to departmental HIFU treatment guidelines), from this study:

- Patients who had contraindications to the MRI scan
- Patients who had asymptomatic uterine leiomyomata

- Patients who were obese i.e. > 5cm abdominal subcutaneous tissue
- Pregnant patients
- Patients who had metal foreign bodies in the treatment pathway (e.g. IUCD or Filshie clips)
- Patient who exhibited any major co morbidities (e.g. cancer; clotting disorders)
- Patients who received an abnormal pap smear during the previous 12 months
- Patients who suffered from pelvic inflammatory disease

A control group was not applicable to this study as the study design did not include a comparative study between two groups (treated and non-treated) nor was the medical impact on treatment evaluated.

3.5 Study Methods

This was a retrospective study of patient (identified as per inclusion criteria) information sourced from hospital records. Patients were interviewed prior and post the HIFU treatment, and disclosed various symptoms and gauging the severity thereof.

As per standard departmental practice, all patients identified for HIFU treatment were requested to complete a Uterine Fibroid Symptom and Health Related Quality of Life questionnaire (UFS-QOL) (refer to Appendix A). Patients completed the UFS-QOL before the HIFU treatment and at one, three- and six-month post treatment intervals in order to evaluate symptoms of uterine fibroids and their impact on HRQL from a patient's perspective. Only data from the initial assessment and six-month assessment were included and evaluated in this study, as the focus of this study was the evaluation of long term (i.e. six-month post treatment) improvements.

The questions in the questionnaire were asked in the preferred home language of the patient, by the same HIFU nursing sister before and after the treatment. All response answers were maintained in the patient medical files in the HIFU room in the Department of Obstetrics and Gynaecology at CHBAH. Patient information was kept confidential and a study number was automatically assigned to each patient by the HIFU software when treatment was commenced.

In addition to the UFS-QOL, patients were evaluated to assess their dysmenorrhoea symptoms (adapted from the UFS-QOL Spies *et al* 2002) as well as their fertility status.

3.5.1 UFS-QOL

The uterine fibroid symptoms and health related quality of life questionnaire (UFS-QOL) is an international established and validated questionnaire designed by Dr James B. Spies and colleagues from the Department of Radiology, Georgetown University Hospital, Washington DC, USA (36, 49).

The questionnaire was originally developed to provide and assess the impact of symptom status and health related quality of life of leiomyomata, from a patients' perspective. The UFS-QOL consisted of 37 questions or items, which were divided into two parts: a symptom severity scale (8 items) and a health-related quality of life scale (29 items covering 6 domains). Response options were presented as five-level Likert scales which ranged from "not at all" to "a very great deal" for the symptom severity items and "none of the time" to "all of the time" for the symptom frequency and health-related quality of life items.

3.5.1.1 Symptom severity subscale

The symptom severity subscale was based on the answers of items 1-8. A summed raw score from the items was calculated and the following formula used to transform the value into a percentage i.e. 0-100 point scale:

Transformed score =

(actual raw score – lowest possible raw score) / possible raw score range x 100

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Figure 3.1 UFS-QOL symptom severity scoring (36).

3.5.1.2 Health-related quality of life (HRQL) subscale

The health-related quality of life subscale was divided into 6 individual domains or subscale scores: Concern (items 9+15+22+28+32); Activities (items 10+11+13+19+20+27+29); Energy/mood (items 12+17+23+24+25+31+35); Control (items 14+16+26+30+34); Self-conscious (items 18+21+33); Sexual function (items 36+37).

All subscale scores as well as the total HRQL (calculated from the sum of the 6 subscale scores) was transformed into a percentage scale i.e. 0-100 point using the following formula:

Transformed score =

(highest possible score – actual raw score) / possible raw score range x 100

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores	29, 145	116

Figure 3.2 UFS-QOL health-related quality of life subscales scoring guide (36).

[Formulas, highest and lowest possible raw scores, possible raw score ranges were based off the UFS-QOL scoring manual of appendix B in (36)]

3.5.2 Dysmenorrhea score

A question was posed to patients to evaluate their level of dysmenorrhea experienced. Response answers were presented as a five-level Likert scale which ranged from “none of the time” or score of 1 to “all of the time” with a score of 5. The scoring system was based and adapted from the original UFS-QOL questionnaire developed by Spies, Coyne *et al* 2002.

3.5.3 Fertility

The fertility status of patients was defined as those patients who have struggled or are struggling to conceive after two years of regular sexual intercourse. The answer was in the form of a categorical yes and no.

3.6 Data analysis and Interpretation

Patient medical files and information were assessed and the respective data from the UFS-QOL surveys was recorded onto data sheet (see appendix B). Patient details remained confidential and subsequently recorded in a register kept by the researcher. Appendix B was the original data collection sheet used for patient information acquisition and reflected all the data that was originally gathered from patients and entered into the patient files and databases. However this study focused only on the inclusion of certain patient data required in order to answer the objectives set out by the researcher and hence subsequent interpretation

Data was transferred, tabulated, categorized to Microsoft® Excel. Analysis was also performed using the statistical data analysis add-on program in Microsoft® Excel. Relevant data recorded and included in this study were as follows: patient demographics (age; weight (kg); height (m); body mass index (BMI) (kg/m ^{2}); treatment date and diagnosis), dysmenorrhoea score, fertility status, the symptom severity subscale and health-related quality of life subscales. Descriptive statistics (mean, standard deviations) was utilised to assess

information in relevant categories and categorical data was presented as proportions or frequencies.

3.6.1 Body mass index calculation

BMI was calculated and threshold values evaluated according to weight classifications cited on the website Physiology web(50). BMI and corresponding weight classification categories were as follows: BMI <18.5 (Underweight); BMI 18.5-24.9 (Normal); BMI 25.0-29.9 (Overweight); BMI 30.0-39.9 (Obese); BMI ≥ 40.0 (extremely obese).

3.6.2 UFS-QOL

Patients with missing raw subscale analyses items (one or more) were excluded from the evaluation during the transformation processing of UFS-QOL scoring. Evaluation and interpretation of data was conducted as per the developers of the questionnaire (36).

3.6.2.1 Symptom severity

The symptom severity subscale score is inversely related i.e. higher scores indicate greater symptom severity and lower scores indicate minimal symptom severity. Scores were subsequently transformed into a percentage as cited in 3.5.1.1.

3.6.2.2 Health quality of life

The HRQL total score was calculated by summing the individual subscale (domain) scores and excluding the symptom subscale. The HQOL subscale scores are directly related with higher HRQL subscale scores indicating better HRQL Each subscale and total HRQL score was then transformed into a percentage as cited in 3.5.1.2.

3.6.2.3 Effect sizes

A mean and standard deviation for each UFS-QOL subscale was determined and effect sizes calculation applied. Effect size is a quantitative measure of change that standardises the comparison between groups (35). Change scores for the UFS-QOL were calculated from baseline to month six. The effect size was calculated as follows: the difference between baseline to month six divided by the standard deviation of baseline scores of patients. The effect size was interpreted and defined as small (0.20), moderate (0.50), or large (0.80) (35).

3.7 Ethics

Written consent was originally obtained from all HIFU treated participants to record and assess their data for any future research studies that may occur (see appendix C). This written consent protocol formed part of the initial agreement to participant in the HIFU treatment program but did not involve the participation of this researcher. The data mined from the original database was collected during the course of this study and was retrospective.

Permission to conduct this study and utilise the data (i.e. the use of data accumulated during the course of the HIFU treatment) was obtained from the University of the Witwatersrand's Human Research and Ethics Committee (HSREC) and ethics clearance certificate M161132 was obtained (see appendix D). The data collected during the course of this study was retrospective

The designated representative of the Chief Executive Officer at Chris Hani Baragwanath Academic Hospital was approached and written permission obtained to conduct this study (see appendix E).

4 Chapter: Results

4.1 Patient demographic data

This study evaluated 116 female patients who had a mean age of 34.95 years (± SD 5.97 years) and were all Black. Only 100 of the study population patients had complete records of both height and weight. The mean height of the 100 patients was 1.62m (± SD 0.07m) and the mean weight was 67.67 Kg (± SD 0.64 Kg).

Overall, 100 of the 116 patients (86.21%) had their BMI calculated 16 (13.79%) had missing data. Of these patients 35.34% (n=41) were classified as overweight, 34.48% (n=40) were classified as within the normal range, 14.66% (n=17) were classified as obese and 1.72% (n=2) were classified as underweight. The overall mean BMI for these patients was 25.77 kg (SD ± 0.42 kg) with a mean weight of 67.67 kg (SD±1.06 kg) and a mean height of 1.62m (SD ± 0.01 m).

4.2 Dysmenorrhea and fertility data

The dysmenorrhea scores were assessed at the initial and six-month phase of the patient care. Not all patients assessed their dysmenorrhea scoring before the HIFU procedure (6.9%, n=8) and after HIFU procedure scores (12.1%, n=14) for the severity of dysmenorrhea they experienced. The overall remaining patient results were tabulated and presented in figure 4.1. Individuals initially (n=108) reported effects of dysmenorrhea most of the time (42.59%), some of the time (22.22%), none of the time (12.96%), little of the time (11.11%), and all of the time (10.19%). At the six-month assessment post treatment, individuals (n=102) reported effects of dysmenorrhea some of the time (34.31%), little of the time (32.35%), none of the time (26.47%), most of the time (5.88%) with no individuals reporting all of the time.

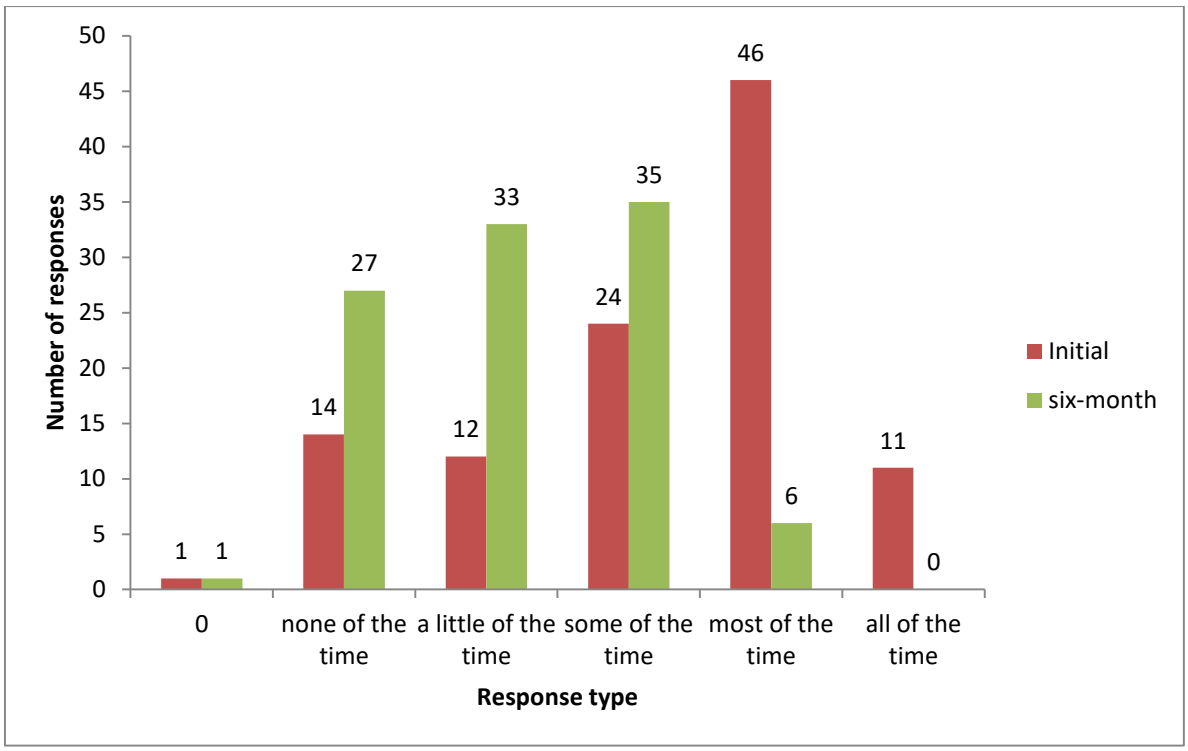

Figure 4.1 Bar chart of dysmenorrhea scores of patients at the initial phase of HIFU treatment (n=108) and at the six-month post HIFU treatment (n=102) follow-up.

Patient fertility status was assessed at the initial phase of HIFU treatment only. Patient responses are presented in figure 4.2.

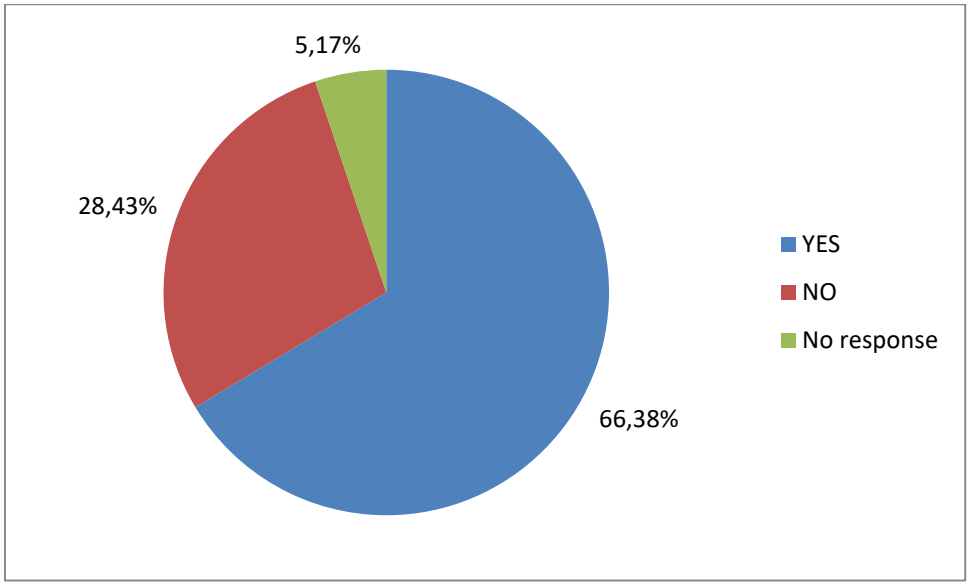

Figure 4.2 Patient fertility responses at the initial phase of HIFU treatment (N=116).

4.3 UFS-QOL results

Of the 116 patients assessed in the study, 10 patients had missing UFS-QOL data at their six-month follow-up assessment and one had missing subscale score data. This resulted in a sample of 105 patients.

A summary of the mean UFS (symptom severity) and QOL (concern, activities, energy/mood, control, self -conscious and sexual function) subscales of the questionnaire at the baseline initial stage and six-month post treatment stage is presented in the figure 4.3. The overall mean HRQL at the baseline stage for individuals was 97.3 (SD ±22.8) and at the six-month post treatment stage was 55.7 (SD ±19.6).

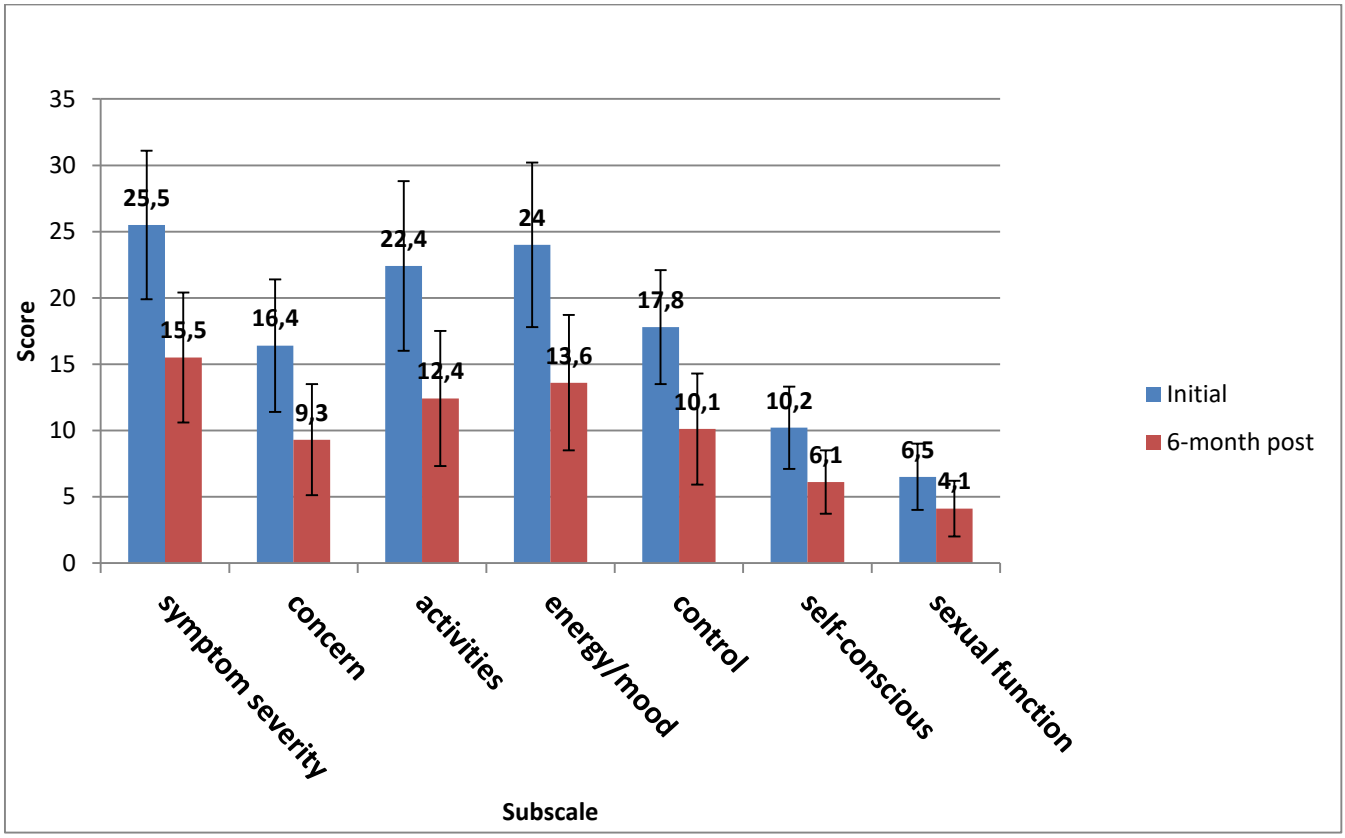

Figure 4.3 Overall (untransformed) mean and standard deviation scores for UFS and QOL subscales of study population at the initial baseline (blue) and six-month (red) post treatment stages (n=105).

The mean change scores reflected in all domains (Symptom Severity and HRQL) within the UFS-QOL, highlighted patient improvement from baseline to the six-month point. No statistical evaluation could occur as the only time period i.e. baseline to six-month was recorded.

The Symptom Severity had a score of -31.3 with a large effect size from baseline to six-month of -1.8.

The total HRQL score demonstrated an overall score of 35.8 with a large effect size at the six-month point of 1.8. The means scores for the individual HRQL subscales ranged from 30 for Sexual Function to 38.3 for Control. All individual HRQL subscales had established large effect sizes from baseline to month, they ranged from 0.9 for Sexual Function to 1.8 for the Control subscale (Refer to Table 4.1). Outcomes of the questions before HIFU and six-month post HIFU treatment were interpreted and evaluated according to previous studies and no tests of significance were conducted (35, 36).

Table 4.1 UFS-QOL transformed scores at baseline initial stage and six-month post treatment stage.

UFS-QOL SUBSCALE	BASELINE N=105 MEAN	BASELINE N=105 SD	SIX-MONTH N=105 MEAN	SIX-MONTH N=105 SD	MEAN CHANGE SCORE	SIX-MONTH EFFECT SIZES
Symptom Severity	54.8	17.6	23.5	15.4	**-31.3**	**-1.8**
Concern	43.1	24.8	78.5	21	**35.4**	**1.4**
Activities	45.1	22.9	80.6	18.1	**35.5**	**1.6**
Energy/mood	39.4	22	76.4	18.3	**37**	**1.7**
Control	36.1	21.7	74.4	21	**38.3**	**1.8**
Self-consciousness	39.8	26.1	74	19.6	**34.2**	**1.3**
Sexual Function	43.3	31.8	73.3	26.5	**30**	**0.9**
TOTAL HRQL SCORE	41.2	19.7	77	16.9	**35.8**	**1.8**

5 Chapter: Discussion

5.1 General overview

Much insight has been gained by medical professionals into the incidence, etiology and epidemiology of ULs with certain factors, including race (Black), age (pre-menopausal) and obesity (obese), being definitively associated with increased risk of UL development (1, 4, 5, 8, 9). Obesity has been shown to be a risk factor due to either the involvement of either hormonal or inflammatory mechanisms, whilst age plays a role in the natural history of fibroids and with its growth in time, individuals are diagnosed in greater numbers in older age (9). A 2-3 fold incidence of fibroids has also been shown in Black women and they have been shown to be diagnosed earlier in life, suffer from multiple and larger fibroids and exhibit more severe symptoms, compared to other race groups (5, 8, 9).

This study population consisted of women with a mean age of 35 years old, were all Black, with 35.34% being overweight and 14.66% obese. They formed the "typical" group of women affected by ULs identified in other international and African based studies (1, 3, 6, 11, 51), highlighting the increased incidence of ULs in Black women typically in their mid-30s and potentially influenced through a combined genetic and racial factors. Data and statistics from a uniquely Black South African profile of UL sufferers have also been reported (38, 44, 47).

Early modern genetic investigations on South African females supported the risk factors of age and the impact of the genetic component on the development of ULs in the local women population (44, 45). A study conducted at Groote Schuur and Tygerberg hospitals, Cape Town, South Africa between 2009 and 2012 of UL affected women, consisted of 36 women with symptomatic ULs with a mean age of 38 years overall and 72% of participants being Black (48). More recent studies conducted at CHBAH of UL sufferers included one study of 26 Black patients with a mean age of 34 years and a mean weight 66.5 kg (38) whilst a second

study reported on 81 Black patients with a mean age of 35 years, average weight of 68.4 kg and average BMI of 26.3 (47). Similar outcomes was seen in this study, with patients having an average weight of 67.7 kg and average BMI of 25.8 (i.e. overall overweight).

The women in this study population therefore, underline the previous findings of studies relating to ULs as an important factor of morbidity for reproductive-age Black women who are also overweight (38, 47).

5.2 Study symptom outcome: dysmenorrhea

The inclusion of the HIFU technique forms part of many suggested and accepted algorithms for the management of uterine leiomyomas worldwide (14, 16, 18, 52-54). The HIFU technique offers a novel non-invasive surgical technique, which is perceived as a safe and effective form of relief to the effects of uterine leiomyomas. When evaluating the effectiveness of the HIFU treatment, due consideration must be given to the fact that ultrasound-guided HIFU technique remains non FDA approved as of 2018 (55), as well as that most studies conducted using the ultrasound-guided HIFU had reported only on the short term effectiveness of uterine fibroid treatment, whilst data for long term effects remain uncertain (56, 57). Previous studies conducted reported on the success of the HIFU treatment given to UL afflicted women by evaluating a range of physical and safety clinical outcomes (26, 55, 58).

The outcomes of this study however, hoped to contribute towards these physical and safety results by providing patient evaluated perceived changes in symptomology and quality of life aspects associated with suffering from a UL. Dysmenorrhea was the only UL symptom evaluated by patients in this study.

Abdominal pain or dysmenorrhea, described mostly as cramping in nature, has been widely reported in UL sufferers (1, 5, 14, 15). Dysmenorrhea impacts and has an effect on comfort, functionality of an individual's day-to-day activities, as well as their psychological well-being (1, 5, 6).

An international internet-based study reported that 50.2% of UL diagnosed women compared to 47.2% women who did not have a diagnosis of ULs, suffered from cramping during their menstrual period (6). Also a review article by She *et al* (2016) specifically reported that pain symptoms are reduced by more than 50% in patients who have undergone HIFU (28). A study on Nigerian UL sufferers over a 25 year period, showed that 18.9% of women recorded dysmenorrhea as a symptom (51).

Dysmenorrhea is also a known recorded symptom of South African UL sufferers, however it has not been extensively reported on in relation to USgHIFU treated patients. An early study conducted on Black South African women living in Johannesburg, South Africa in 1972, found that 26.8% (n=101 fibroid sufferers) versus 2.5% (n=116 control women) reported to suffer from dysmenorrhoea (59). A recent study conducted by Zhang *et al* in 2017, reported that 69.2% of their 26 patients suffered from dysmenorrhea, however they did not report on the status of the patient dysmenorrhea symptoms post USgHIFU treatment (38). A second study by He *et al* (2018) did not report on any UL symptomatology (e.g. dysmenorrhea), in the studied population, but rather focused and evaluated on issues related to clinical safety and efficacy (47).

In the current study, dysmenorrhea was assessed at the initial stage (n=108) of the study as well as six-month post treatment evaluation (n=102). Individuals were asked to score their level of discomfort associated with dysmenorrhea as one of the following: 1 = none of the time, 2= a little of the time, 3= some of the time, 4= most of the time, and 5= all of the time.

This study identified 87% (n=94) of patients at the baseline stage of the study, reported some form of a dysmenorrhea severity symptom i.e. a score of ≥ 2, in comparison to 73% (n=75) of individuals who reported similarly at the six-month post treatment stage. Approximately 43% of individuals initially reported they suffered “most of the time” at the start of the study, however six-month post treatment a majority of women now reported only “some of the time” (34%) or “none of the time” (33%). There was therefore a definite shift of opinion of UL sufferers, from that of suffering “most of the time” to suffering “some of the time”, as well as improvement in the number of patients who stated that they did not suffer from any symptoms of dysmenorrhea.

From the self-evaluation recorded data relating to dysmenorrhea in this study, dysmenorrhea remains a frequently reported symptom of South African UL sufferers, but can be perceived to be less frequently reported post USgHIFU treatment. The scoring system relating to dysmenorrhea, though still to be validated, provides a scale of severity which when applied, may aid clinicians with efficacy information relating to various treatment modalities.

5.3 The UFS-QOL patient evaluation of outcomes following HIFU treatment

The subjective self-assessment of well-being using the UFS-QOL tool, before and after the application of UL treatment modalities, ultimately provides and contributes towards the overall assessment of success and effectiveness of the particular treatment (15, 35-37, 60).

The UFS-QOL questionnaire is simple, brief, able to be self-administered and most importantly provides meaningful and usable scores to assess the effectiveness of therapeutic interventions by assessing any changes in symptom distress and the impact on health-related quality of life changes in women (36).

In the current study, large mean change scores in all subscales of the UFS-QOL were noted demonstrating the degree of improvement of symptoms overall as well the severity of symptoms, six months post HIFU treatment from a strictly patient perspective. This was corroborated by reviewing the large effect sizes that were determined for all subscales.

5.3.1 UFS or symptom severity subscale (SSS)

The UFS or SSS assessed aspects relating to both menorrhagia (i.e. heavy bleeding during menstrual periods) and bulk-related symptoms (i.e. feeling fatigued, feeling tightness or pressure in the pelvic region as well as the frequency of urination felt during daytime and night times) using a transformed percentage scale, wherein a large score would indicate a worse symptom and greater impact on a symptom distress (36). Multiple research and clinical cohorts have reported on the outcomes of treatment modalities using SSS data.

The mean baseline symptom severity scores (evaluation period prior to commencement of UL treatment modality) obtained in a variety of international studies have been reported and ranged from 64.8 (SD± 20.0) (60); 61.5 (SD ±14.7) (35); 61.7 (SD ± 15.2) (61); 51.6 (IQR 42.2-65.6) (62); as well as a local South African Black women study 56.3 (SD ±16.7) (47). The women in this study reported a baseline symptom severity score of 54.8 (SD ±17.6) which is comparable to those reported as well as to the known SSS mean score of approximately 40 which typically is seen in women who suffer from symptomatic ULs versus healthy women, who register a score of approximately 20 (61, 63).

Post treatment (at typically six-month and twelve-month assessment after treatment for UL) symptom severity scores, after the application of various UL treatment modalities, all displayed improvements: International studies of 14.8 (SD14.0) (Non-HIFU treatments) (60); 33.9 (SD ± 19.0) (MRgFUS treatment) (35); 37.7 (SD ± 21.2)(MRgFUS treatment) (61); 15.6 (IQR 6.3-35.9) (non-HIFU treatment) (62); and a local study 20.6 (SD ±14.2) (USgHIFU)

(47). The patients in this study showed an improvement after their USgHIFU treatment and recorded a symptom severity score of 23.5 (SD ±15.4) six months after the procedure.

Not all studies reported on the mean change score for SSS, which reflects an official improvement of symptom severity of individuals and also it is accepted that a standard 10-point improvement (as reflected in clinical data from validation studies) is considered significant (47, 61). In this study a mean change score of -31.3 and an effect size of -1.8 was determined, which compared favourably with international studies which reported a SSS mean change score -43.7 and effect size -2.18 (60) and -27.8 with effect size -1.87 (35). The SSS mean change score in this study population after USgHIFU treatment at the six-month assessment, was similar or larger than that compared to international studies of women of African descent (60, 62) and of previous local studies (47) therefore reaffirming the effectiveness of USgHIFU treatment on Black South African women.

5.3.2 HRQL

The HRQL aspect of the questionnaire dealt with 29 items comprising 6 domains: concern, activities, energy/mood, control, self-consciousness and sexual function (36). A high HRQL subscale score indicates a better indication of health related quality of life (35, 36). The HQOL score of the current study participants at baseline stage was 41.2 (SD± 19.7). This was very similar to a previous South African study of women who underwent USgHIFU treatment for ULs, showed a baseline QOL score of 41.3 (SD ± 21.2) (47); whilst a study of American women undergoing treatment with MRgFUS for ULs had a baseline HRQL score of 46.8 (SD± 18.3) (35) with a second American study of women undergoing various other forms of surgical treatments having a HRQL of 40.8 (SD ± 22.1) (60).

Individually, the domains which seemed to most impact women's lives at the beginning of the study was control (36.1± 21.7), energy/mood (39.4 ±22) and self-consciousness (39.8 ± 26.1).

This is in keeping with findings made in other studies (35, 36, 60). The control subscale asked questions related to feelings of controls over ones' health, life, and future uncertainty whilst the energy/mood subscale includes aspect dealing with fatigue. Finally, aspects of self-consciousness include the effects of the bulk symptoms on health-related quality of life including the related appearances of the stomach as well as bloating. Spies *et al* noted in their validation of the UFS-QOL questionnaire that the subscales of concern and control appear to be the most affected by symptoms followed by the activities and self-consciousness subscales (36). Likewise the study by Harding *et al* in the USA based study found that subscales self-consciousness (39.3 ±26.8), concern (45.8 ± 26.2), and activities (46.9 ± 21.4) (35). To my knowledge, no other South African studies provided details of the individual subscale scores in women suffering from ULs.

Patterns of perceived improvement were seen in all changes of the mean scores for all subscales six months post treatment in the current study, with a total HRQL score of 77 (SD ± 16.9) at month six and a calculated change in mean score of 35.8 overall (with an effect size of 1.8). Similar findings were seen in other cohorts at the six months post treatment stage. In the earlier South African study, the QOL score at six-months post treatment was 73.4 (SD ± 19.2) but with no reported mean change scores or effect sizes (47); the Harding *et al* study in their MRgHIFU treated American population showed a total HRQL score of 70.5 (SD ± 20.6) and a mean change score of 24.0 (with an effect size of 1.30) (35); and the final American study with multiple surgical interventions, reported a HRQL mean change score of 42.7 (with an effect size of 1.96) (60). Overall, the questionnaire seemed to be able to detect and record the improvement of in the quality health related aspects of women's lives 6 months post USgHIFU treatment.

5.4 Limitations

The translation of the UFS-QOL questionnaire was conducted verbally by the sister in charge of the HIFU unit. The translated version was not validated before use, and hence issues of inference and interpretation would need to be a considered as part of the answers provided and data recorded.

The study suffered from a number of participants who failed to complete all aspects (i.e. in one or more quality of life questions) of the questionnaire at both pre and post treatment stages and hence their data had to be omitted from the study. It is recommended that in future the UFS-QOL questionnaire form part of the regular treatment protocol applied to all patients undergoing USgHIFU within the treatment unit and also that answers to questionnaire be capture electronically and filed.

Limitations in the evaluation of the true statistical meaning of the data over multiple stages of assessment must be considered in future. Data was only gathered at the baseline and 6-month phase of the treatment stages and hence it was difficult to ascertain continued improvement over an extended period of time evaluated at regular intervals.

No control or benchmark groups were utilised within this study and hence the no comparative effectiveness of the USgHIFCU technique could be made.

6 Conclusion

The current study highlights the patient perceived and self-assessed improvement in the severity of symptoms and various health related quality of life aspects of women who suffer from ULs pre- and post USgHIFU treatment. This therefore contributes positively towards the

evidence for the efficacy of the utilisation of USgHIFU treatment on South African Black women and helps to advocate it as a safe option in the treatment modality for ULs.

7 Chapter: References

1. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):571-88. DOI: 10.1016/j.bpobgyn.2008.04.002 [Accessed on 2 August 2016]

2. Bulun SE. Uterine fibroids. N Engl J Med. 2013;369(14):1344-55. DOI: 10.1056/NEJMra1209993 [Accessed on 3 February 2019]

3. Catherino WH, Eltoukhi HM, Al-Hendy A. Racial and ethnic differences in the pathogenesis and clinical manifestations of uterine leiomyoma. Semin Reprod Med. 2013;31(5):370-9. DOI: 10.1055/s-0033-1348896 [Accessed on 3 February 2019]

4. McWilliams MM, Chennathukuzhi VM. Recent Advances in Uterine Fibroid Etiology. Semin Reprod Med. 2017;35(2):181-9. DOI: 10.1055/s-0037-1599090 [Accessed on 3 February 2019]

5. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017;124(10):1501-12. DOI: 10.1111/1471-0528.14640 [Accessed on 16 May 2019]

6. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012;12:6. DOI: 10.1186/1472-6874-12-6 [Accessed on 10 April 2019]

7. Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. Br J Obstet Gynaecol. 1990;97(4):285-98. DOI: 10.1111/j.1471-0528.1990.tb01804.x [Accessed on 18 August 2016]

8. Wise LA, Laughlin-Tommaso SK. Epidemiology of Uterine Fibroids: From Menarche to Menopause. Clin Obstet Gynecol. 2016;59(1):2-24. DOI: 10.1097/GRF.0000000000000164 [Accessed on 13 March 2019]

9. Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and Risk Factors of Uterine Fibroids. Best Pract Res Clin Obstet Gynaecol. 2018;46:3-11. DOI: 10.1016/j.bpobgyn.2017.09.004 [Accessed on 3 February 2019]

10. Buttram VC, Jr., Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36(4):433-45. DOI: 10.1016/s0015-0282(16)45789-4 [Accessed on 2 August 2016]

11. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med1996. p. 483-90. Available from https://pubmed.ncbi.nlm.nih.gov/8829060/ [Accessed on 10 March 2018]

12. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013;209(4):319 e1- e20. DOI: 10.1016/j.ajog.2013.07.017 [Accessed on 4 March 2019]

13. Al-Hendy A, Myers ER, Stewart E. Uterine Fibroids: Burden and Unmet Medical Need. Semin Reprod Med. 2017;35(6):473-80. DOI: 10.1055/s-0037-1607264 [Accessed on 3 February 2019]

14. De La Cruz MS, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician2017. p. 100-7. Available from https://pubmed.ncbi.nlm.nih.gov/28084714/ [Accessed on 10 February 2019]

15. Fortin C, Flyckt R, Falcone T. Alternatives to hysterectomy: The burden of fibroids and the quality of life. Best Pract Res Clin Obstet Gynaecol. 2018;46:31-42. DOI: 10.1016/j.bpobgyn.2017.10.001 [Accessed on 3 February 2019]

16. Vilos GA, Allaire C, Laberge PY, Leyland N, Special C. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2015;37(2):157-78. DOI: 10.1016/S1701-2163(15)30338-8 [Accessed on 13 March 2019]

17. Donnez J, Arriagada P, Donnez O, Dolmans MM. Emerging treatment options for uterine fibroids. Expert Opin Emerg Drugs. 2018;23(1):17-23. DOI: 10.1080/14728214.2018.1446943 [Accessed on 4 March 2019]

18. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016;22(6):665-86. DOI: 10.1093/humupd/dmw023 [Accessed on 3 February 2019]

19. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2001(2):CD000547. DOI: 10.1002/14651858.CD000547 [Accessed on 4 September 2016]

20. Zapata LB, Whiteman MK, Tepper NK, Jamieson DJ, Marchbanks PA, Curtis KM. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception. 2010;82(1):41-55. DOI: 10.1016/j.contraception.2010.02.011 [Accessed on 10 September 2016]

21. van der Kooij SM, Hehenkamp WJ, Volkers NA, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010;203(2):105 e1-13. DOI: 10.1016/j.ajog.2010.01.049 [Accessed on 2 August 2016]

22. Hart R, Molnar BG, Magos A. Long term follow up of hysteroscopic myomectomy assessed by survival analysis. Br J Obstet Gynaecol. 1999;106(7):700-5. DOI: 10.1111/j.1471-0528.1999.tb08370.x [Accessed on 10 September 2016]

23. Kim CH, Kim SR, Lee HA, Kim SH, Chae HD, Kang BM. Transvaginal ultrasound-guided radiofrequency myolysis for uterine myomas. Hum Reprod. 2011;26(3):559-63. DOI: 10.1093/humrep/deq366 [Accessed on 10 September 2016]

24. Goldfarb HA. Laparoscopic coagulation of myoma (myolysis). Obstet Gynecol Clin North Am. 1995;22(4):807-19. DOI: 10.1016/s0889-8545(00)80032-7 [Accessed on 10 September 2016]

25. Moss JG, Cooper KG, Khaund A, Murray LS, Murray GD, Wu O, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG. 2011;118(8):936-44. DOI: 10.1111/j.1471-0528.2011.02952.x [Accessed on 10 August 2016]

26. Cheung VYT. High-intensity focused ultrasound therapy. Best Pract Res Clin Obstet Gynaecol. 2018;46:74-83. DOI: 10.1016/j.bpobgyn.2017.09.002 [Accessed on 13 May 2019]

27. Lynn JG, Zwemer RL, Chick AJ, Miller AE. A New Method for the Generation and Use of Focused Ultrasound in Experimental Biology. J Gen Physiol. 1942;26(2):179-93. DOI: 10.1085/jgp.26.2.179 [Accessed on 15 August 2016]

28. She WH, Cheung TT, Jenkins CR, Irwin MG. Clinical applications of high-intensity focused ultrasound. Hong Kong Med J. 2016;22(4):382-92. DOI: 10.12809/hkmj154755 [Accessed on 10 March 2019]

29. Jeong JH, Hong GP, Kim YR, Ha JE, Lee KS. Clinical Consideration of Treatment to Ablate Uterine Fibroids with Magnetic Resonance Imaging-guided High Intensity Focused

Ultrasound (MRgFUS): Sonalleve. J Menopausal Med. 2016;22(2):94-107. DOI: 10.6118/jmm.2016.22.2.94 [Accessed on 15 August 2016]

30. Fan HJ, Zhang C, Lei HT, Cun JP, Zhao W, Huang JQ, et al. Ultrasound-guided high-intensity focused ultrasound in the treatment of uterine fibroids. Medicine (Baltimore). 2019;98(10):e14566. DOI: 10.1097/MD.0000000000014566 [Accessed on 4 March 2019]

31. Cheung VY, Lam TP, Jenkins CR, Cheung GK, Chan SS, Choi WK. Ovarian Reserve After Ultrasound-Guided High-Intensity Focused Ultrasound for Uterine Fibroids: Preliminary Experience. J Obstet Gynaecol Can. 2016;38(4):357-61. DOI: 10.1016/j.jogc.2016.02.006 [Accessed on 31 October 2016]

32. Ren XL, Zhou XD, Zhang J, He GB, Han ZH, Zheng MJ, et al. Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: imaging and histopathologic evaluation. J Ultrasound Med. 2007;26(2):201-12. DOI: 10.7863/jum.2007.26.2.201 [Accessed on 4 February 2019]

33. Hillis SD, Marchbanks PA, Peterson HB. Uterine size and risk of complications among women undergoing abdominal hysterectomy for leiomyomas. Obstet Gynecol. 1996;87(4):539-43. DOI: 10.1016/0029-7844(95)00478-5 [Accessed on 16 August 2016]

34. Fan TY, Zhang L, Chen W, Liu Y, He M, Huang X, et al. Feasibility of MRI-guided high intensity focused ultrasound treatment for adenomyosis. Eur J Radiol. 2012;81(11):3624-30. DOI: 10.1016/j.ejrad.2011.05.036 [Accessed on 16 August 2016]

35. Harding G, Coyne KS, Thompson CL, Spies JB. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health Qual Life Outcomes. 2008;6:99. DOI: 10.1186/1477-7525-6-99 [Accessed on 3 February 2019]

36. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300. DOI: 10.1016/s0029-7844(01)01702-1 [Accessed on 13 May 2019]

37. Williams VS, Jones G, Mauskopf J, Spalding J, DuChane J. Uterine fibroids: a review of health-related quality of life assessment. J Womens Health (Larchmt). 2006;15(7):818-29. DOI: 10.1089/jwh.2006.15.818 [Accessed on 3 February 2019]

38. Zhang C, Jacobson H, Ngobese ZE, Setzen R. Efficacy and safety of ultrasound-guided high intensity focused ultrasound ablation of symptomatic uterine fibroids in Black women: a preliminary study. BJOG. 2017;124 Suppl 3:12-7. DOI: 10.1111/1471-0528.14738 [Accessed on 13 March 2019]

39. Van der Spuy ZM, Fieggan AG, Wood MJ, Pienaar CA. The short-term use of luteinising hormone-releasing hormone analogues in uterine fibroids. Horm Res. 1989;32 Suppl 1:137-40. DOI: 10.1159/000181329 [Accessed on 3 February 2019]

40. Venkatachalam S, Bagratee JS, Moodley J. Medical management of uterine fibroids with medroxyprogesterone acetate (Depo Provera): a pilot study. J Obstet Gynaecol. 2004;24(7):798-800. DOI: 10.1080/01443610400009543 [Accessed on 13 May 2019]

41. Newton CL, Riekert C, Millar RP. Gonadotropin-releasing hormone analog therapeutics. Minerva Ginecol. 2018;70(5):497-515. DOI: 10.23736/S0026-4784.18.04316-2 [Accessed on 3 February 2019]

42. Benecke C, Kruger TF, Siebert TI, Van der Merwe JP, Steyn DW. Effect of fibroids on fertility in patients undergoing assisted reproduction. A structured literature review. Gynecol Obstet Invest. 2005;59(4):225-30. DOI: 10.1159/000084513 [Accessed on 3 February 2019]

43. Matjila MJ, Hoffman A, van der Spuy ZM. Medical conditions associated with recurrent miscarriage-Is BMI the tip of the iceberg? Eur J Obstet Gynecol Reprod Biol. 2017;214:91-6. DOI: 10.1016/j.ejogrb.2017.05.003 [Accessed on 10 April 2019]

44. Makinen N, Heinonen HR, Moore S, Tomlinson IP, van der Spuy ZM, Aaltonen LA. MED12 exon 2 mutations are common in uterine leiomyomas from South African patients. Oncotarget. 2011;2(12):966-9. DOI: 10.18632/oncotarget.370 [Accessed on 16 May 2019]

45. Amant F, Dorfling CM, de Brabanter J, Vandewalle J, Vergote I, Lindeque BG, et al. A possible role of the cytochrome P450c17alpha gene (CYP17) polymorphism in the pathobiology of uterine leiomyomas from black South African women: a pilot study. Acta Obstet Gynecol Scand2004. p. 234-9. Available from https://pubmed.ncbi.nlm.nih.gov/14995917/ [Accessed on 18 May 2019]

46. Prollius A, de Vries C, Loggenberg E, du Plessis A, Nel M, Wessels PH. Uterine artery embolisation for symptomatic fibroids: the effect of the large uterus on outcome. BJOG. 2004;111(3):239-42. DOI: 10.1046/j.1471-0528.2003.00019.x [Accessed on 13 March 2019]

47. He M, Jacobson H, Zhang C, Setzen R, Zhang L. A retrospective study of ultrasound-guided high intensity focussed ultrasound ablation for multiple uterine fibroids in South Africa. Int J Hyperthermia. 2018;34(8):1304-10. DOI: 10.1080/02656736.2017.1421323 [Accessed on 6 February 2019]

48. Lawson AC, C; Olarogun, J; Legge, D; Patel, M; Beningfield, S; Dyer, S. Uterine artery embolisation for uterine leiomyomas. South African Journal of Obstetrics and Gynecology. 2014;20(1):18-21. DOI: 10.7196/SAJOG.798 [Accessed on 13 May 2019]

49. Onubi OJ, Marais D, Aucott L, Okonofua F, Poobalan AS. Maternal obesity in Africa: a systematic review and meta-analysis. J Public Health (Oxf). 2016;38(3):e218-e31. DOI: 10.1093/pubmed/fdv138 [Accessed on 14 June 2018]

50. no author Body Mass Index (BMI) Calculator 2008 [updated 26 August 2016. Available from: https://www.physiologyweb.com/calculators/body_mass_index_calculator.html.

51. Okogbo FO, Ezechi OC, Loto OM, Ezeobi PM. Uterine Leiomyomata in South Western Nigeria: a clinical study of presentations and management outcome. Afr Health Sci. 2011;11(2):271-8. Availble from https://pubmed.ncbi.nlm.nih.gov/21857861/ [Accessed on 23 June 2019]

52. Ji Y, Hu K, Zhang Y, Gu L, Zhu J, Zhu L, et al. High-intensity focused ultrasound (HIFU) treatment for uterine fibroids: a meta-analysis. Arch Gynecol Obstet. 2017;296(6):1181-8. DOI: 10.1007/s00404-017-4548-9 [Accessed on 3 February 2019]

53. Donnez J, Donnez O, Dolmans MM. The current place of medical therapy in uterine fibroid management. Best Pract Res Clin Obstet Gynaecol. 2018;46:57-65. DOI: 10.1016/j.bpobgyn.2017.10.008 [Accessed on 4 March 2019]

54. Dolmans MM, Donnez J, Fellah L. Uterine fibroid management: Today and tomorrow. J Obstet Gynaecol Res. 2019;45(7):1222-9. DOI: 10.1111/jog.14002 [Accessed on 3 February 2019]

55. Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M. High intensity focused ultrasound: The fundamentals, clinical applications and research trends. Diagn Interv Imaging. 2018;99(6):349-59. DOI: 10.1016/j.diii.2018.03.001 [Accessed on 4 March 2019]

56. Zhang L, Zhang W, Orsi F, Chen W, Wang Z. Ultrasound-guided high intensity focused ultrasound for the treatment of gynaecological diseases: A review of safety and efficacy. Int J Hyperthermia. 2015;31(3):280-4. DOI: 10.3109/02656736.2014.996790 [Accessed on 3 February 2019]

57. Cheung VYT, Lam TPW, Jenkins CR, Lam SW, Cheung GKI, Chan SSY, et al. Efficacy and safety of ultrasound-guided high-intensity focused ultrasound for uterine fibroids: a preliminary experience. J Obstet Gynaecol. 2019;39(6):833-9. DOI: 10.1080/01443615.2019.1581740 [Accessed on 3 April 2019]

58. Duc NM, Keserci B. Emerging clinical applications of high-intensity focused ultrasound. Diagn Interv Radiol. 2019;25(5):398-409. DOI: 10.5152/dir.2019.18556 [Accessed on 3 March 2019]

59. Rubin A, Ford JA. Uterine fibromyomata in urban Blacks. A preliminary survey of the relationship between symptomatology, blood pressure and haemoglobin levels. S Afr Med J. 1974;48(49):2060-2. Available from https://pubmed.ncbi.nlm.nih.gov/4421296/ [Accessed on 29 October 2020]

60. Coyne KS, Margolis MK, Bradley LD, Guido R, Maxwell GL, Spies JB. Further validation of the uterine fibroid symptom and quality-of-life questionnaire. Value Health. 2012;15(1):135-42. DOI: 10.1016/j.jval.2011.07.007 [Accessed on 3 February 2019]

61. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006;85(1):22-9. DOI: 10.1016/j.fertnstert.2005.04.072 [Accessed on 02 November 2020]

62. Mariara C, Obura T, Hacking N, Stones W. One year symptom severity and health-related quality of life changes among Black African patients undergoing uterine fibroid embolisation. BMC Res Notes. 2017;10(1):240. DOI: 10.1186/s13104-017-2558-0 [Accessed on 02 November 2020]

63. Spies JB, Warren EH, Mathias SD, Walsh SM, Roth AR, Pentecost MJ. Uterine fibroid embolization: measurement of health-related quality of life before and after therapy. J Vasc Interv Radiol. 1999;10(10):1293-303. DOI: 10.1016/s1051-0443(99)70235-6 [Accessed on 02 November 2020]

8 Chapter: Appendices

8.1 Appendix A

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

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.

During the previous 3 months, how distressed were you by...	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycle	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐	☐	☐	☐	☐
10. Made you anxious about traveling?	☐	☐	☐	☐	☐
11. Interfered with your physical activities?	☐	☐	☐	☐	☐
12. Caused you to feel tired or worn out?	☐	☐	☐	☐	☐
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐	☐	☐	☐	☐
14. Made you feel as if you are not in control of your life?	☐	☐	☐	☐	☐
15. Made you concerned about soiling underclothes?	☐	☐	☐	☐	☐
16. Made you feel less productive?	☐	☐	☐	☐	☐
17. Caused you to feel drowsy or sleepy during the day?	☐	☐	☐	☐	☐
18. Made you feel self-conscious of weight gain?	☐	☐	☐	☐	☐
19. Made you feel that it was difficult to carry out your usual activities?	☐	☐	☐	☐	☐
20. Interfered with your social activities?	☐	☐	☐	☐	☐
21. Made you feel conscious about the size and appearance of your stomach?	☐	☐	☐	☐	☐
22. Made you concerned about soiling bed linen?	☐	☐	☐	☐	☐

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

8.2 Appendix B

Datasheet

Baseline data:

Date:

Study number:

Date of procedure:

Age:

Parity: Gravidity:

Height: Weight: BMI:

Main symptoms Y/N:

Pain:

Pressure (bladder frequency or constipation):

Heavy bleeding (Menorrhagia):

Infertility Y/N:

Number of fibroids

Uterine volume

MRI findings:

Location of fibroids: (A/P/F/L)

Type of fibroid Number of uterine fibroids

Volume of uterus (cm3).{Longitudinal (D1), AP(D2),transverse(D3)}.

Volume of uterine fibroids (cm3).

MRI T2 signal intensity of fibroids: (Hyper/Iso/hypo intensity)

8.3 Appendix C

Consent form: Use of clinical information

Collection of data and questionnaire for study and research purposes

Good morning, I am Dr…….

The doctor has explained why you have been referred for High intensity focused ultrasound (HIFU) treatment for your fibroids and what this procedure entails.

This is a new procedure in South Africa and it has been used in other countries for more than 15 years. However, the long-term effects in South Africa are unknown.

With time as the fibroid scar attempts to heal, it will start shrinking in size. As the fibroids shrink in size, it has been shown to reduce symptoms in women.

Before the procedure, the information from your MRI, medical information and the questionnaire is entered into a clinical database. The database allows us to audit our work and review our treatment outcomes.

The questionnaire will be done before the procedure and again at 1,3,6 and 12-month intervals by the same sister. This allows us to determine the change in symptoms in a uniform manner. It also provides information regarding the standard of care as well as the outcome of treatment.

Both the clinical data, questionnaire information in the database is also used for research purposes.

Research will only be performed after approval from the Human research ethics committee of the University of the Witwatersrand has been obtained. Any research performed using this data will be completely anonymous, that is, your identity will never be revealed.

We would like your permission to use the questionnaire and enter your MRI information and clinical data. The clinical data includes age, parity, gravidity, race, hemoglobin level, contraception use, body mass index, co morbidities, pap smear result and previous surgeries. The MRI data includes location and number of fibroids, abdominal wall thickness, volume of uterus, volume of uterine fibroids, T1 and T2 signal intensity.

Your treatment will not be different whether you agree to the information being put into the clinical database or not. There will be no benefit to you for being in the study and you may at any stage withdraw your consent to the use of your data.

The risks of the procedure have been explained to which include skin burn, nerve or bowel injury.

Should you wish to contact us regarding this consent then please phone the HIFU clinic at 011 933 0368

Informed consent

1. I hereby confirm that I have been informed by the doctor about the collection of data pertaining to my diagnosis, treatment and follow up.
2. I have read, received and understood the above written information regarding research using my medical information
3. I am aware that the results of the study, including personal details regarding my age, date of birth, initials and diagnosis will be anonymously processed into a study report.
4. In view of the requirements of research, I agree that the data collected during the study can be processed in a computer system.
5. I may at any stage withdraw my consent and participation in the study.
6. I have had sufficient opportunity to ask questions and will participate in the study

Patient signature: _____

Date: _____

8.4 Appendix D

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr M van der Merwe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M161132

NAME: (Principal Investigator)	Dr M van der Merwe
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Quality of life and symtomatology after high intensity focused ultrasound for uterine fibroids
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr H Jacobson
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	16/05/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

8.5 Appendix E

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 2nd November 2018

TITLE OF PROJECT:

The change in quality of life after high intensity focused ultrasound treatment for uterine fibroids

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Melissa van der Merwe

Department: Obstetrics & Gynaecology

Supervisor : Dr H Jacobson

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand,
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 2/11/2018

Approved/Not Approved
Hospital Management
Date:

8.6 Appendix F

22830375_M_vd_Merwe_Feb2020_Turnitinv5.docx

ORIGINALITY REPORT

6%	%	6%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Gale Harding. "The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL)", Health and Quality of Life Outcomes, 2008 Publication	1%
2	Dora Pavone, Sara Clemenza, Flavia Sorbi, Massimiliano Fambrini, Felice Petraglia. "Epidemiology and Risk Factors of Uterine Fibroids", Best Practice & Research Clinical Obstetrics & Gynaecology, 2018 Publication	1%
3	Fernandez Hervé, Ardaens Katty, Queval Isabelle, Solignac Céline. "Impact of uterine fibroids on quality of life: a national cross-sectional survey", European Journal of Obstetrics & Gynecology and Reproductive Biology, 2018 Publication	1%
4	Chelsea Fortin, Rebecca Flyckt, Tommaso Falcone. "Alternatives to hysterectomy: The burden of fibroids and the quality of life", Best Practice & Research Clinical Obstetrics & Gynaecology, 2018 Publication	1%

Biology, 2018
Publication

4	Chelsea Fortin, Rebecca Flyckt, Tommaso Falcone. "Alternatives to hysterectomy: The burden of fibroids and the quality of life", Best Practice & Research Clinical Obstetrics & Gynaecology, 2018 Publication	1 %
5	Paul Christopher Lyon, Vic Rai, Natalia Price, Aarti Shah, Feng Wu, David Cranston. "Ultrasound-Guided High Intensity Focused Ultrasound Ablation for Symptomatic Uterine Fibroids: Preliminary Clinical Experience", Ultraschall in der Medizin - European Journal of Ultrasound, 2019 Publication	1 %
6	C Zhang, H Jacobson, ZE Ngobese, R Setzen. "Efficacy and safety of ultrasound-guided high intensity focused ultrasound ablation of symptomatic uterine fibroids in Black women: a preliminary study", BJOG: An International Journal of Obstetrics & Gynaecology, 2017 Publication	1 %

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		