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Pregnancy outcomes post high intensity focused ultrasound at Chris Hani Baragwanath Academic Hospital

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Pregnancy outcomes post high intensity focused ultrasound at Chris Hani Baragwanath Academic Hospital

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UNIVERSITY OF THE
WITWATERSRAND,
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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, 2025

DECLARATION

I, Khanya Makhatheng Montsho, declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine MMed at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: 

Date: May 2025

DEDICATION

This MMed is dedicated to my loving children, Mogaka and Motse Montsho and to my husband Goitseone Montsho for the continuous support. I also extend my gratitude to my mother and sisters for their continuous cheer leading.

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ABSTRACT

Background: High-intensity focused ultrasound (HIFU) is a promising non-invasive treatment for uterine fibroids, offering effective management while preserving fertility.

Objective: This study assessed the effects of HIFU on pregnancy outcomes in women with uterine fibroids at the Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa.

Methods: A retrospective descriptive study was conducted on 160 reproductive-aged women who underwent HIFU treatment between October 2015 and June 2022. Women intending to conceive post-treatment were included, whereas those with contraceptive use or hysterectomy after HIFU were excluded. The primary outcome was pregnancy status, and secondary outcomes included miscarriage, delivery, and neonatal outcomes. Statistical analyses were performed using STATA version 15.0, with chi-square tests to analyse pregnancy rates ($p < 0.05$).

Results: The pregnancy rate after HIFU was 33.8% (54/160) with 59 pregnancies. The spontaneous pregnancy and delivery rates were 94.4% and 73.3%, respectively. There were 13 miscarriages (21.7%) and three ongoing pregnancies (5.0%). Among the 44 live births, 8 (18.2%) were preterm, and 2.3% were early and late neonatal deaths. The average age of women who conceived was 32.3 years, significantly younger than those who did not (36.2 years). Pregnancy rates were higher in women without chronic illnesses (38.1%) than in those with a history of chronic diseases (21.4%).

Conclusion: While HIFU may be an alternative treatment for women with fibroids wishing to preserve their fertility, this study underscores the need for further research with larger samples to strengthen the evidence on HIFU's efficacy in this regard.

Keywords: Uterine fibroids, high-intensity focused Ultrasound (HIFU), Pregnancy

Presentations and publications from this study

Presentations: The Wits O&G Annual Women's Health Research Symposium (5th February 2025)

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LIST OF ABBREVIATIONS

CHBAH: Chris Hani Baragwanath Academic Hospital

Fibroids: Uterine Fibroids

HIFU: High intensity focused ultrasound

HSG: Hysterosalpingogram

IQR: Inter-quartile range

MRgFUS: Magnetic Resonance guided focused ultrasound

MRgHIFU: Magnetic Resonance Imaging guided High intensity focused ultrasound

UAE: Uterine artery embolization

USgHIFU: Ultrasound-guided high intensity focused ultrasound

Pregnancy outcomes post High Intensity Focused Ultrasound at Chris Hani Baragwanath Academic Hospital

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ABSTRACT

Background: High-intensity focused ultrasound (HIFU) is a promising non-invasive treatment for uterine fibroids, offering effective management while preserving fertility.
Objective: This study assessed the effects of HIFU on pregnancy outcomes in women with uterine fibroids at the Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa.
Methods: A retrospective descriptive study was conducted on 160 reproductive-aged women who underwent HIFU treatment between October 2015 and June 2022. Women intending to conceive post-treatment were included, whereas those with contraceptive use or hysterectomy after HIFU were excluded. The primary outcome was pregnancy status, and secondary outcomes included miscarriage, delivery, and neonatal outcomes. Statistical analyses were performed using STATA version 15.0, with chi-square tests to analyse pregnancy rates ($p < 0.05$).
Results: The pregnancy rate after HIFU was 33.8% (54) with 59 pregnancies. The spontaneous pregnancy and delivery rates were 94.4% and 73.3%, respectively. There were 13 miscarriages (21.7%) and 3 ongoing pregnancies (5.0%). Among the 44 live births, 8 (18.2%) were preterm, 2.3% were early and late neonatal deaths. The average age of women who conceived was 32.3 years, significantly younger than those who did not (36.2 years). Pregnancy rates were higher

in women without chronic illnesses (38.1%) than in those with history of chronic illnesses (21.4%).

Conclusion: HIFU may be an alternative treatment for women with fibroids wishing to preserve their fertility. Early screening and treatment are recommended to enhance conception chances, although further research with larger samples is needed to strengthen the evidence on HIFU's efficacy in this regard.

Keywords: Uterine fibroids, high-intensity focused Ultrasound (HIFU), Pregnancy

BACKGROUND

Uterine fibroids, also known as myomas, are the most prevalent gynaecological condition, affecting nearly 70% of women in their reproductive years [1]. These fibroids develop through a complex interplay of factors, including reproductive, hormonal, genetic, and racial influences and environmental factors [1–3]. Although they are benign tumours, about one-third of individuals diagnosed, experience symptoms such as heavy menstrual bleeding, painful periods, pelvic discomfort, and complications in pregnancy, like infertility and repeated miscarriages [4–6]. For those experiencing symptoms or fertility issues related to uterine fibroids, a range of treatment options is available.

The treatment of uterine fibroids depends on symptom severity, fibroid size and location, and the desire to preserve fertility. Treatment options range from medical therapies to surgical interventions and minimally invasive techniques [7–9]. Pharmaceutical interventions such as gonadotropin-releasing hormone (GnRH) agonists and selective progesterone receptor modulators (SPRMs) provide transient alleviation of symptoms; however, their utilization may be unsuitable for women desiring to conceive, owing to their effects on reproductive function and ovulation [8,9]. Invasive surgery techniques include hysterectomy and myomectomy. A hysterectomy involves the total removal of the uterus, leading to the inability to conceive in the future. [9,10]. Surgical myomectomy, considered the gold standard for fertility preservation, effectively removes fibroids and restores uterine function but carries risks of scarring and uterine rupture during pregnancy [9,10].

Recent advancements in minimally invasive techniques, such as uterine artery embolization (UAE) and high-intensity focused ultrasound (HIFU), have expanded the available options for women seeking to preserve their uteruses [9–11]. These methods focus on shrinking fibroids and relieving symptoms while protecting the uterus and shortening recovery time compared to surgical intervention [9,10]. However, HIFU, a non-invasive option, thermally ablates fibroids without the surgical risks and helps preserve ovarian tissue, reducing the chance of ovarian failure—an essential factor for women aiming to maintain their fertility associated with other methods [12–16]. Conversely, UAE, which restricts blood supply to fibroids, might pose an increased risk of ovarian insufficiency and adverse pregnancy outcomes, making it less ideal for women who intend to be pregnant in the future [17,18].

Substantial research on HIFU has been conducted mainly in Asia, Europe, and North America [15,16,19,20]. These studies highlight a significant gap in our understanding of HIFU safety, efficacy, and effects on pregnancy outcomes within African communities. The biological and clinical fibroid burden may vary in Africa compared to the aforementioned regions [2,19,21].

Current evidence indicates that HIFU is feasible, safe, and effective for managing symptomatic and multiple uterine fibroids in South Africa [21,22]. However, additional research is necessary to understand the effects of HIFU treatment on fertility and pregnancy outcomes in this region. This research addressed this gap by assessing the effects of HIFU treatment on pregnancy outcomes in women with uterine fibroids.

METHODOLOGY

A retrospective descriptive study with interviews was conducted involving women of reproductive age with symptomatic uterine fibroids who underwent HIFU therapy at the Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa. The study received approval from the Human Research Ethics Committee (HREC) Medical at the University of Witwatersrand. Authorization to access patient records and perform the study was secured from the head of the Obstetrics and Gynaecology Department and the Medical Advisory Committee at CHBAH, respectively.

The medical records of 551 women who underwent HIFU treatment between October 2015 and June 2022 were retrieved from the Obstetrics and Gynaecology Clinic of CHBAH. Medical records were reviewed to extract patient contacts, who were then reached by telephone and invited to join the study. Those who agreed to participate indicated a desire for pregnancy after HIFU treatment and were not using contraceptives. Exclusion criteria encompassed individuals who did not respond to follow-up telephone calls and those who reported a history of hysterectomy or contraceptive use after HIFU treatment. The flowchart (Figure 1) delineates the exclusion criteria, and the final sample size used for the analysis.

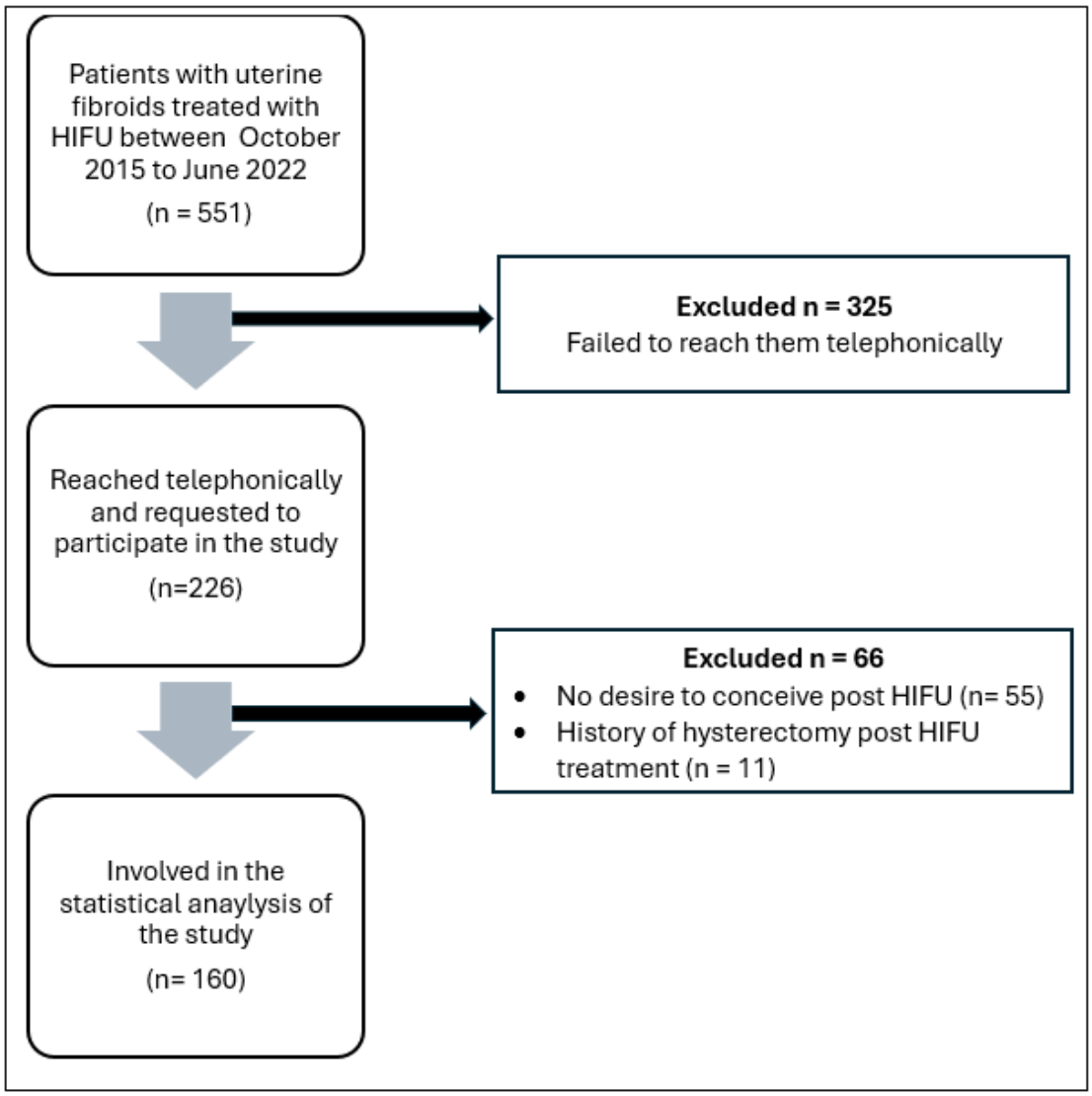


Figure 1. Flow chart showing the exclusion criteria

Data were collected using a paper-based, pre-developed questionnaire in English. The interviews were conducted telephonically due to Covid-19 restrictions. Data collected included age at the time of treatment, primary reason for HIFU, history of chronic illness, obstetric history including gravidity and parity before HIFU, history of uterine surgeries, pregnancy approach, and pregnancy outcomes (pregnancy status, history of miscarriage post-HIFU, and delivery information).

Pregnancy status after HIFU treatment was the primary outcome of this study, and secondary outcomes included a history of miscarriage, delivery information (preterm or full-term), and neonatal outcomes (alive or dead). The other variables were used as independent variables. The de-identified collected data were then captured using Research Electronic Data Capture (REDCap) web application, a password-protected research database.

Treatment procedures

Prior to HIFU ablation treatment, all patients presenting at CHBAH, Johannesburg, South Africa underwent contrast-enhanced magnetic resonance imaging (MRI) to evaluate the fibroids and ascertain their number, size, location, and volume [22]. The methodological details pertaining to the pretreatment procedures involving contrast-enhanced MRI, preparation for HIFU treatment, and HIFU ablation treatment protocol have been previously documented in a study conducted by He et al. among patients who underwent HIFU treatment at CHBAH [22], which serves as the identical study site for the present investigation. The HIFU procedure utilized the Model JC Focused Ultrasound Tumour Therapeutic System JC200 HIFU, Chongqing Haifu (HIFU) Tech Co., Ltd., Chongqing, China), with microwave emission output power adjusted to 200-400W [22]. This was performed under ongoing real-time ultrasound supervision while patients remained under intravenous conscious sedation [22]. Patients were monitored for four hours post-treatment, prior to discharge. Post-treatment instructions included the use of contraceptives for three months and abstinence from sexual intercourse until after menstruation [22].

Statistical analysis

Data were exported from REDCap to STATA version 15.0 for data cleaning, organisation, and statistical descriptive analyses. Measures of central tendency and dispersion were used to summarize continuous variables like age. In normally distributed data, results are shown as the mean with standard deviation (SD). When data is not normally distributed, findings are reported as the median and range. Categorical variables are presented as absolute values and percentages. A T-test analyses the differences in mean ages based on pregnancy status at the time of treatment. The difference in pregnancy rates by independent variables was analysed using the Chi-square test, with statistical significance determined at $P < 0.05$.

RESULTS

Characteristics of the participants who received HIFU treatment

Total of 160 women met the inclusion criteria:

- 85 previously pregnant, 64 of which ended with miscarriages.
- 154 opted for natural methods of conception and 6 ART

- 54 women fell pregnant, resulting in 59 pregnancies, this is inclusive of 1 set of twins.
- Pregnancy rate: 54/160
- 44 livebirths and 13 miscarriages
- Out of the 44 pregnancies: 8 preterm and 2.3% NND (early and late)

The analysis included 160 women who expressed a desire to conceive after undergoing HIFU treatment (Table 1). Consent was obtained telephonically and documented on RedCap. Their average age was 34.9 (5.4) years (range, 22 – 45 years) at the time of treatment, with 83 (51.9%) being 35 years of age or older. Approximately half of women were diagnosed with nulligravidae. Of the 85 women who had previously been pregnant, 64 (75.3%) had a history of miscarriages. Forty-one patients (25.6%) had a history of uterine surgery and 42 (26.3%) had a history of chronic illness. Of the 41 patients with a history of uterine surgery, 13 (31.7%) and nine (22.0%) had a history of caesarean section and myomectomy, respectively. Among the 42 patients who reported a history of chronic illness, 29 (69%) had HIV infection and seven (16.6%) had hypertension.

Pregnancy, birth, and neonatal outcomes post HIFU treatment

The pregnancy rate among 160 women was 33.8% (54/160) post HIFU treatment (Table 2). Data of time between HIFU treatment and delivery was not collected. Of the 54 women who conceived, 50 (92.6%) had one pregnancy, 3 (5.5%) had two pregnancies each, and 1 (1.9%) had three pregnancies, resulting in a total of 59 pregnancies. Of these 59 pregnancies, 58 (98.3%) were singleton and one (1.7%) was a twin, yielding 60 expected infants at delivery. Of the 60 expected infants, 13 (21.7%) had miscarriages and 3 (5.0%) were pregnant (at the time of data collection). Among the 44 live births, eight (18.2%) were preterm. At the time of data collection, 42 (94.4%) live-born infants were still alive, while two (4.6%) resulted in early and late neonatal death, of which one was a preterm birth.

Table 1:Patient's characteristics (N=160)

Variables	N (%)
Age, years (mean sd, range)	34.9 (5.4), (22 – 45)
Obstetric History	
Nulligravida (Gravidity = 0)	75 (46.9)
Gravida ≥ 1	85 (53.1)
History of miscarriage before (n=85)	
No	21 (24.7)
Yes	64 (75.3)
Diagnosis	
Fibroids	158 (98.7)
Fibroids & Adenomyosis	2 (1.3)
HIFU treatment cycles	
1	151 (94.4)
2	9 (5.6)
History of uterine surgery	
No	119 (74.4)
Yes	41 (25.6)
History of Chronic Illness	
No	118 (73.7)
Yes	42 (26.3)
Pregnancy approach	
Spontaneous conception method (natural)	154 (96.3)
Assisted reproductive therapy (ART)	6 (3.7)

HIV: Human immunodeficiency virus. HIFU: high-intensity focused ultrasound. Sd: Standard deviation from the mean.

Table 2: Pregnancy, birth, and neonatal outcomes post HIFU treatment

Variables	N (%)
Pregnancy status (n =160)	
No	106 (66.3)
Yes	54 (33.7)
Gravidity post HIFU‡ (n =54)	
Gravida 1	50 (92.6)
Gravida 2	3 (5.5)
Gravida 3	1 (1.9)
Pregnancies (n=59)	
Singletons	58 (98.3)
Twins	1 (1.7)
Birth outcomes (n =60)	
Miscarriages	13 (21.7)
Live births	44 (73.3)
Current pregnancies	3 (5.0)

Live births (n=44)	
Preterm	8 (18.2)
Full term	36 (81.8)
Live births (n=44)	
Alive	42 (94.4)
Early neonatal death	1(2.3)
Late neonatal death	1 (2.3)

‡Number of pregnancies post HIFU did not include the number of pregnancies before HIFU.

Pregnancy rate post HIFU treatment

Of the 54 women who conceived, 5.6% (3.0) were 40 years and older and 40.7% (22.0) were previously nulliparous (Table 3). Of the 64 women with a history of miscarriages, 35.9% (n = 23) conceived. Among the pregnancies, 72.2% (39.0) had no history of uterine surgery, 14.8% (8.0) had a history of "other uterine surgeries," 7.4% (4.0) had a history of caesarean section, and 3.7% (2.0) had a history of myomectomy. Regarding the history of illness, 16.7% (9.0) of those who conceived had a history of chronic illness. Of these pregnancies, 94.4% (n = 51) were achieved through spontaneous conception.

Comparative analysis of pregnancy outcomes post-HIFU

The average age of the 54 pregnant women was 32.3 (4.9) years (range: 22–42 years) at the time of treatment initiation vs 36.2 (5.1) years (range: 23 – 45 years) of 106 women who did not get pregnant. The differences in the average age between the two groups were statistically significant ($P < 0.01$, $P = 0.000$, respectively) **(Table 4).** Moreover, when using age groups, the rate of pregnancy differed significantly across age groups, with a higher number of women aged < 30 years in the pregnant group than in the non-pregnant group (18.0, 58.1% vs. 13.0, 41.9%), whereas among those aged ≥ 35 years (n= 83), 18 (21.7%) conceived. The pregnancy rate was significantly higher among women without a history of chronic illness than among those with a history of chronic illness (38.1%, 45/118 vs. 21.4%, 9/42, $P <0.05$, $P =0.049$).

Pregnancy rate did not differ significantly according to obstetric history, history of miscarriage, history of uterine surgery, or pregnancy approach. Although not statistically significant, the results showed a higher pregnancy rate among those who reported a history of pregnancy before HIFU treatment than among their counterparts (nulligravida) (37.4%, 32/85 vs. 29.3%, 22/75, $P>0.05$, $P= 0.267$). Those with a history of miscarriage had a lower pregnancy rate than those without history of miscarriage (35.9%, 23/64 vs. 42.9%, 9/21, $P>0.05$, $P= 0.570$). Lastly,

the pregnancy rate was higher in those with a history of uterine surgery than in those without a history of uterine surgery (66.7%, 8/12 vs. 32.8%, 39/119).

Table 3: Rate of pregnancy across characteristics of women who fell pregnant Post HIFU (N=54)

Variables	N (%)
Age, years	
<30	18 (33.3)
30 - 34	18 (33.3)
35 - 39	15 (28.3)
>=40	3 (5.6)
Obstetric History	
Nulligravida (Gravidity = 0)	22 (40.7)
Gravida ≥ 1	32 (59.3)
History of miscarriage before (n=32)	
No	9(28.1)
Yes	23 (71.9)
Diagnosis	
Fibroids	54 (100)
Fibroids & Adenomyosis	0 (0.0)
HIFU treatment cycles	
1	50 (92.6)
2	4 (7.4)
History of uterine surgery	
None	39 (72.2)
Myomectomy	2 (3.7)
Caesarean Section	4 (7.4)
Laparotomy in ectopic pregnancy	1 (1.9)
Other Uterine Surgeries	8 (14.8)
History of Chronic Illness	
No	45 (83.3)
Yes	9 (16.7)
Pregnancy approach	
Spontaneous conceptive method (natural)	51 (94.4)
Assisted reproductive therapy (ART)	3 (5.6)

Caesarean Section	**4 (7.4)**
Laparotomy in ectopic pregnancy	1 (1.9)
Other Uterine Surgeries	8 (14.8)
History of Chronic Illness	
No	45 (83.3)
Yes	9 (16.7)
Pregnancy approach	
Spontaneous conceptive method (natural)	51 (94.4)
Assisted reproductive therapy (ART)	3 (5.6)

Table 4: Comparative analysis of pregnancies outcome post HIFU (N=160)

Variables	N	Pregnant After HIFU (N=160)		P. value
		NO (N= 106)	YES (N=54)	
Age (mean, sd, range)	34.9 (5.4)	36.2 (5.1), (23 – 45)	32.3 (4.9), (22 – 42)	<0.001
Age, years				
<30	31	13 (41.9	18 (58.1)	<0.001
30 - 34	46	28 (60.9)	18 (39.1	
35 - 39	48	33 (68.7)	15 (31.3)	
>=40	35	32 (91.4)	3 (8.6)	
Obstetric History				
Nulligravida (Gravidity = 0)	75	53 (70.7)	22 (29.3)	0.267
Gravidity ≥1	85	53 (62.4)	32 (37.4)	
History of miscarriage (n=85)				
No	21	12 (57.1)	9(42.9)	0.570
Yes	64	41 (64.1)	23 (35.9)	
Diagnosis				
Fibroids	158	104 (65.8)	54 (34.2)	0.310
Fibroids & Adenomyosis	2	2 (100.0)	0 (0.0)	
HIFU treatment cycles				
1	151	101 (66.9)	50 (33.1)	0.485
2	9	5 (55.6)	4 (44.4)	
History of uterine surgery				
None	119	80 (67.2)	39 (32.8%)	0.171
Myomectomy	9	7 (77.8)	2 (22.2)	
Caesarean Section	13	9 (69.2)	4 (30.8)	
Laparotomy in ectopic pregnancy	6	5 (83.3)	1 (16.7)	
Laparoscopy in ectopic pregnancy	1	1 (100.0)	0 (0.0)	
Other Uterine Surgeries	12	4 (33.3)	8 (66.7)	
History of Chronic Illness				
No	118	73 (61.9)	45 (38.1)	0.049
Yes	42	33 (78.6)	9 (21.4)	
Pregnancy Approach				
Spontaneous conception	154	103 (66.9)	51 (33.1)	0.391
Assisted Reproductive Therapy	6	3 (50.0)	3 (50.0)	

**Statistically significant (p<0.05)

DISCUSSION

This study describes pregnancy outcomes amongst women with fibroids and associated factors in women of reproductive age at CHBAH. The results demonstrated that women with uterine fibroids who aspire to have children can successfully achieve full-term pregnancies via natural

conception following HIFU treatment. However, the possibility of conception decreases with age, with women above 40 years less likely to conceive than younger women.

In this study, the pregnancy rate was 33.8%, recorded as 59 pregnancies among 54 women. This result is consistent with previous studies, which report rates ranging from 19.2% to 74.3% (14,23–27), supporting the use of HIFU as a fertility-preserving treatment. The observed rate was higher than the 19.2% noted by Zou et al. [24], and lower than that reported by Liu et al. (46.6%), Li et al. (69%), and Wu et al. (74.3%) [23,25,26]. Nonetheless, it aligns closely with the findings of Rodriguez et al. (34%) and Li et al. (35%) [14,27]. Compared to myomectomy studies, the pregnancy rate after HIFU (33.8%) is notably lower than the 62.2% to 80.0% seen in those studies [25–28]. Notably, most pregnancies (94.4%) in this research occurred spontaneously, which is in line with the results of other HIFU studies (82.0% to 95.4%) [12,23,25–29]. Despite some variation in pregnancy rates, consistency across studies suggests that HIFU has a minimal impact on fertility outcomes, potentially preserving or even improving reproductive capabilities in treated patients.

This study observed a delivery rate of 73.3% alongside a spontaneous abortion rate of 21.7% after HIFU treatment, with 18.2% of deliveries being preterm. The higher delivery rate indicates that HIFU may facilitate live births, as 94.4% of the 44 live births remained alive during the data collection period. These results are consistent with the findings of other HIFU studies, although some variations exist. For instance, Rodriguez et al. noted a lower delivery rate of 61% [27], while Li et al. reported a rate of 70% [23]. Some studies indicated even higher delivery rates, ranging from 84% to 95% [12,25,27].

While the results were generally positive, two significant concerns were noted: the higher spontaneous abortion rate (21.7%) compared to other studies (8% to 19%) [23,25,26,29,32] and the elevated preterm delivery rate (18.2%), surpassing the range reported in other HIFU studies (2% to 9%) [23,25–28]. However, the rates of spontaneous abortion and preterm delivery in our study closely resemble those seen in myomectomy studies (21.0% to 29.0% and 5.0% to 8.0%, respectively) [12,26,28,30,31]. Although these rates align more closely with myomectomy outcomes, it is essential to further explore whether the higher incidence of both spontaneous abortion and pre-term births are directly linked to HIFU treatment or affected by other factors, such as maternal age or fibroid location. Notably, there is an association between a history of pregnancy loss and spontaneous abortion following HIFU in this study, where 53.8% of women who experienced miscarriage had a prior history of miscarriages. Li et al. found a similar trend, with 76.5% of post-HIFU miscarriages occurring in women with a history of spontaneous abortions [23]. Thus, the increased risk of spontaneous abortion and

preterm delivery highlights the importance of considering a patient's obstetric history when advising on pregnancy outcomes post and close monitoring during pregnancy post-HIFU treatment.

The variability in reported outcomes across studies, such as delivery rates (61%–95%), spontaneous abortion rates (8%–39%), and preterm birth rates (2%–18%), may reflect differences in patient characteristics, comorbidities, HIFU treatment parameters, study design, and follow-up periods in these studies [12,14,23,25–29,32]. Despite some variations in outcomes, HIFU treatment appears to offer a balance between preserving fertility and managing uterine fibroids, with relatively high delivery and manageable spontaneous abortion rates [12,23,25,26,29,32]. Moreover, while HIFU may improve fertility and manage uterine fibroids, the increased risk of spontaneous abortion and preterm delivery requires careful monitoring and follow-up care to optimize the outcomes.

The findings from this descriptive study suggested a potential association between age and the presence of chronic illnesses with pregnancy rates. Meanwhile, factors such as obstetric history, miscarriage history, prior uterine surgeries, diagnosis, the timing of HIFU treatment, number of HIFU treatment cycles, and the method of pregnancy did not show a significant impact on pregnancy rates within this research.

The study showed that younger women and those free from chronic conditions experienced significantly higher pregnancy rates following HIFU compared to their counterparts. Age emerged as a crucial element, with younger women demonstrating better odds of conception than their older counterparts. The average age for women who achieved pregnancy was 32.3 years, contrasting with 36.2 years for those who did not conceive. Significantly, more than half (58%) of the women under 30 successfully became pregnant after undergoing HIFU, whereas pregnancy rates for older groups fell below 50%. Previous studies also support these findings, emphasizing age's impact on pregnancy outcomes [23,27]. For example, Rodriguez et al. found a lower pregnancy rate (34%) in women with a mean age of 37 years [27], whereas Li et al. reported a higher pregnancy rate (69%) in younger women with a mean age of 31 years [23]. These differences emphasize the significant role of age in fertility and pregnancy outcomes after HIFU treatment.

Moreover, the study showed that older women, particularly those over 35 years, experienced reduced pregnancy rates, suggesting a decline in fertility with age. This aligns with Rodriguez et al.'s observation that fertility declines after age 32 years [23,27]. The results suggest that younger women seeking fertility preservation may benefit most from HIFU treatment, whereas older women, especially those aged > 35 years, may have lower success rates. Early diagnosis

and treatment of uterine fibroids in women under 30 years of age could increase their chances of conception, and healthcare providers should prioritize fertility education and interventions for women in their late 20s and early 30s.

On the other hand, the potential benefits of HIFU for fertility preservation prompt questions regarding its effects on pregnancy rates, especially in women with preexisting conditions. Women with a history of chronic illnesses had lower pregnancy rates, highlighting the importance of thorough pre-treatment assessments to predict treatment outcomes. Moreover, the finding highlights the need for tailored post-treatment care and monitoring of women with comorbidities to improve conception and pregnancy success rates. Further research is needed to explore the impact of chronic illnesses on fertility outcomes after HIFU, and the long-term effectiveness of HIFU in women with various comorbidities.

STRENGTHS AND LIMITATIONS OF THE STUDY

This study was the first to evaluate the effects of HIFU treatment on pregnancy, birth, and neonatal outcomes in South African women with uterine fibroids. However, the retrospective design and small sample size of the study limit the generalizability of the results. Future research should adopt a prospective design with a larger participant pool to improve the reliability. Additionally, factors such as fibroid characteristics (size, number, and location), time to pregnancy post-treatment, infertility history, and prior uterine surgeries, which are crucial for understanding reproductive outcomes, were not considered. To strengthen the evidence, future studies should incorporate these variables, standardize HIFU techniques, and include more comprehensive data collection. Despite these limitations, this study highlighted the potential of HIFU as a fertility-preserving treatment for fibroids.

CONCLUSION

This study indicates that women with uterine fibroids may achieve successful pregnancies through spontaneous conception following HIFU treatment. However, when counselling women on pregnancy outcomes post-HIFU, it is essential to consider age and the history of chronic illnesses. Additionally, to enhance the chances of conception after HIFU treatment, uterine fibroid screening programs should target women at a younger age. Nonetheless, more comprehensive studies are necessary to identify and analyse the various factors that may influence pregnancy outcomes after HIFU treatment, including comorbidities.

Declaration. This study was performed as part of the partial fulfilment of the requirements for Master of Medicine (Obstetrics and Gynaecology) degree completion for KMM at the University of the Witwatersrand.

Acknowledgements. The authors thank the CHBAH, obstetrics and gynaecology department, special thanks to HIFU unit staff for availing the data and their eagerness to help in any way possible to see this research done. We further thank Jane Scotch for her technical support in data analysis. Finally, we thank the participants of this study for being transparent and co-operative.

Author contributions. KMM contributed to conceptualization, design, data analysis, interpretation, and manuscript writing. CM and RS, as supervisors and mentors, contributed to the conceptualization, design, analysis, interpretation of data, manuscript revision, and approved the final version of the manuscript for publication.

Ethical Compliance: All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees.

Data Access Statement: Research data supporting this publication are available from the corresponding author KMM upon request.

Funding Statement: None

Conflicts of interest: None

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Appendix A: Data Sheets

Demographics

Record ID	_____
Age at recieving HIFU	_____
Date of HIFU treatment	_____
Gravidity before HIFU	_____
Parity before HIFU	_____
Diagnosis (Fibroids=1 Adenomyosis=2)	◯ 1. Fibroids ◯ 2. Adenomyosis ◯ 3. Fibroids and Adenomyosis
HIFU treatment indication	☐ AUB-L ☐ Chronic pain/Dysmenorrhea ☐ Pressure Symptoms ☐ Aesthetic Mass ☐ Infertility ☐ Recurrent Miscarriages
Cycles of HIFU	_____
Previous uterine surgeries	☐ None ☐ Myomectomy ☐ Caesarean Section ☐ Laparoscopy for ectopic pregnancy ☐ Laparotomy for ectopic pregnancy ☐ Others
Chronic illnesses	☐ None ☐ HIV ☐ Diabetes mellitus ☐ Hypertension ☐ Other
Tubal Patency	◯ Both patent ◯ One tube blocked ◯ Both tubes blocked ◯ Not tested

Pregnancy Outcomes post HIFU

Record ID	_____
Did you fall pregnant after HIFU	◯ Yes ◯ No
If No, were you on birth control	◯ Yes ◯ No
Did you want to fall pregnant	◯ Yes ◯ No
Did you use any form of assisted reproduction for you to fall pregnant e.g IVF?	◯ Yes ◯ No

If yes, type of assistance

	IVF	Artificial insermination	Donor egg	Embryo transfer	Other
Assistance type	◯	◯	◯	◯	◯

Did you have a miscarriage?	◯ Yes ◯ No

If yes, how many weeks were you?

	Less than 13 weeks (1-3 months)	14 to 24 weeks (4-6 months)
Gestational age	◯	◯

Gestational age at delivery beyond 24 weeks

	24-28 weeks (6-7 months)	28-32 weeks (7-8 months)	32-36 weeks (8-9 months)	36-40 weeks (9-10 months)	40 weeks plus (More than 10 months)
How many weeks/months were you at delivery	◯	◯	◯	◯	◯

Pregnancy outcomes

	Live baby	Still born	Early neonatal death	Late neonatal death
Pregnancy beyond 24 weeks	◯	◯	◯	◯

Are you currently Pregnant	◯ Yes ◯ No

Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Makhatheng Khanya July-Montsho

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230142 MED22-10-113

NAME: (Principal Investigator)	Dr Makhatheng Khanya July-Montsho
DEPARTMENT:	Health Sciences Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	*Pregancy outcomes post high intensity focused ultrasound (HIFU) at Chris Hani Baragwanath Academic Hospital*
DATE CONSIDERED:	27/01/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr C Mpehle and Dr R Setzen
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/07/2023 **EXPIRY DATE:** 07/07/2028

UNIVERSITY OF THE WITWATERSRAND OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH 10 JUL 2023 RESEARCH OFFICE JOHANNESBURG

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 Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Makhatheng Khanya July-Montsho
Principal Investigator Signature

10/07/2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Turnitin report

SAJOG FINAL KMM -12-3.docx

ORIGINALITY REPORT

8%	7%	7%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.nature.com Internet Source	1%
2	Min Zhao, Dan Wang, Yong Zhang, Ligang Wang. "Evaluating pregnancy outcomes in women with uterine fibroids treated with high-intensity focused ultrasound: insights from a single-institution study", Reproductive Health, 2024 Publication	1%
3	Reppe, S.. "Gene expression profiles give insight into the molecular pathology of bone in primary hyperparathyroidism", Bone, 200607 Publication	<1%
4	www.researchgate.net Internet Source	<1%
5	qspace.qu.edu.qa Internet Source	<1%
6	www.utupub.fi Internet Source	<1%
7	Submitted to Aspen University Student Paper	<1%
8	onlinelibrary.wiley.com Internet Source	<1%
9	A.-M. N. Andersen. "Maternal age and fetal loss: population based register linkage study",	<1%

	BMJ, 2000 Publication	
10	Min He, Hayley Jacobson, Cai Zhang, Raymond Setzen, Lian Zhang. "A retrospective study of ultrasound-guided high intensity focussed ultrasound ablation for multiple uterine fibroids in South Africa", International Journal of Hyperthermia, 2018 Publication	<1 %
11	Submitted to University of Witwatersrand Student Paper	<1 %
12	eurjther.com Internet Source	<1 %
13	jtultrasound.biomedcentral.com Internet Source	<1 %
14	link.springer.com Internet Source	<1 %
15	doi.org Internet Source	<1 %
16	www.dovepress.com Internet Source	<1 %
17	www.frontiersin.org Internet Source	<1 %
18	bmcnutr.biomedcentral.com Internet Source	<1 %
19	medilib.ir Internet Source	<1 %
20	wiredspace.wits.ac.za Internet Source	<1 %
21	www.femisa.org.uk Internet Source	<1 %

Exclude quotes	On	Exclude matches	< 10 words
Exclude bibliography	On		

Appendix D: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Khanya Makhatheng Montsho (Student number: 2527440) am a student registered for the degree of Master of Medicine in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 01 Febrruary 2025

1

Appendix E: Acknowledgement of research submission

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

ACKNOWLEDGEMENT OF RESEARCH SUBMISSION FOR ADMINISTRATION OF EXAMINATION

STUDENT FULL NAME: KHANYA MAKHATHENG MONTSHO

STUDENT NUMBER: 2527440

QUALIFICATION: MASTER OF MEDICINE

FIELD OF STUDY: OBSTETRICS AND GYNAECOLOGY

	YES	NO
SUBMISSION DATE	X	
EXAMINERS NOMINATED & APPROVED	X	
ETHICAL CLEARANCE / WAIVER	X	
CERTIFICATE OF SUBMISSION FORM - SUPERVISOR	X	
CERTIFICATE OF SUBMISSION FORM - STUDENT	X	
1 (ELECTRONIC COPY) (PHD & MASTERS)	X	
DECLARATION **(SIGNED)**	X	
TURN-IT-IN (PLAGIARISM) REPORT – *acknowledged by supervisor(s)*	X	
SIGNED SUPERVISOR REPORT	X	

ACKNOWLEDGEMENT OF DOCUMENTS will be via email due to current situation with Covid-19

Appendix F: Certificate of submission for examination

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

CERTIFICATE OF SUBMISSION FOR EXAMINATION OF MASTERS RESEARCH REPORT / DISSERTATION OR PHD THESIS SIGNED BY HIGHER DEGREES CANDIDATES

Full name	Khanya Makhatheng Montsho		
Student number	2527440		
Title of submitted Research Project: Pregnancy outcomes post high intensity frequency ultrasound (HIFU) at Chris Hani Baragwanath Academic Hospital *NB: If this title is different to your previously approved title, no further action can be taken by the Faculty Office until a change of title has been approved.*			
Contact no	0825470009	E-mail	makhatheng@gmail.com

1. If you are likely to move in the next 6-12 months, please give the anticipated date of move: 28 February 2025
2. I hereby submit my **Masters (dissertation)** for examination
3. I have checked all copies of my research report / dissertation / thesis and declare that no pages are missing or poorly reproduced.

4. **I confirm that I have:**
   a) A signed declaration indicating my understanding of the concept of plagiarism and a denial of plagiarism in my research document.
   b) A report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document included as an appendix.

5. **I confirm that I have:**
   a) Not used either human or animal tissue or records **Yes**
   b) If yes: I have included the ethics waiver letter pertinent to my research as an appendix **Yes**
   c) Done research using animals **No**
      If yes: I have included a copy of the animal ethics committee clearance certificate as an appendix in this document **Yes/No**
   d) Done research using human subjects, human tissue or patient records **Yes**
      If yes: I have included a copy of the human ethics clearance certificate as an appendix to the research document **Yes**

6. I understand that I may not graduate unless my University fees have been paid in full.
7. My Supervisor(s) names, departments, telephone numbers and email addresses are as follows:

Name	Chileshe Mpehle		
Department	Obstetrics and Gynaecology		
Telephone	0727238827	E-mail	chileshempehle@yahoo.com
Name	Raymond Setzen		
Department	Obstetrics and Gynaecology		
Telephone		E-mail	rsetzen@gmai.com
Name			
Department			
Telephone		E-mail	

List all publications, which you have published in peer-reviewed journals from your postgraduate research report/dissertation/thesis during the course of your studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

1

None

Signature of candidate:  Date: 01 February 2025

Appendix G: Certificate of submission signed by supervisors



CERTIFICATE OF SUBMISSION FOR EXAMINATION SIGNED BY SUPERVISORS OF HIGHER DEGREES CANDIDATES

Full name	Khanya Makhatheng Montsho		
Student number	2527440		
Candidate for the degree of: Master of Medicine in Obstetrics and Gynaecology *has submitted his/her thesis/dissertation/research report* Entitled: Pregnancy outcomes post high intensity frequency ultrasound (HIFU) at Chis Hani Baragwanath Academic Hospital			
Contact no	0825470009	E-mail	makhatheng@gmail.com

Mark with an X on appropriate box	Yes	No
Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?	√	
To the best of your knowledge are you able to verify that this is the candidate's work, except as otherwise stated by the candidate?	√	
The substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university?	√	
The candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions?	√	
Have examiners been nominated and approved?	√	

I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee / Committee for Research on Human Subjects and the Number of the Certificate of Approval is:

M230142-10-113

List all publications, which your student has published in peer-reviewed journals from his/her postgraduate research report/dissertation/thesis during the course of his/her studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

This work has been submitted to the South African Journal of Obstetrics and Gynaecology for publication.

Pending a response.

_____

_____

_____

_____

_____

Name of Supervisor 1: Dr Chileshe R. Mpehle

Telephone: 0727238827 Email: chileshempehle@yahoo.com

Signature:  Date: 25/02/2025

Name of Supervisor 2: DR. RAYMOND SETZEN

Telephone: 082-4431577 Email: rsetzen@gmail.com.

Signature:  Date: 25/2/2025.

==========

IMPORTANT NOTICE WITH REGARD TO THE SENATE STANDING ORDERS:

A.22 Submission against advice of Supervisor

If the Supervisor is not prepared to agree to the submission of a thesis, the candidate shall still be entitled, if he or she wishes, to submit it for examination. When a thesis is submitted against the advice of the Supervisor, this should be recorded in the minutes of the Faculty Graduate Studies Committee. In such a case, no internal examiners are appointed but a Supervisor's report will still be required. After the examination process, the external examiner(s) will be advised by the Chairperson of the Faculty Graduate Studies Committee that the thesis was submitted against the advice of the Supervisor.

A.24 *Nomination of Examiners*:

Nomination of examiners should take place at least six weeks before submission of the thesis or dissertation. *(The Postgraduate Office will not accept any submission for examination without the confirmed appointment of the nominated examiners.*)

A.25 Confidentiality of names of examiners (both external and internal)

The names of the examiners should be confidential during the examination process and may only be revealed to the candidate with the acquiescence of the examiner once the final version of the thesis has been submitted to the Faculty and the process has been completed.

Appendix H: Supervisor Report

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

SUPERVISOR REPORT on submission of a dissertation, thesis or research report for examination

Senate Standing Orders on higher degrees require that all dissertations, theses and research reports that are submitted must be accompanied by a supervisor's report (see A.20). This report will not be seen by the examiners, but it will be given to the student along with the examiners' reports, once the examination process is complete. It is the responsibility of the principal or main supervisor to complete the form below to report on the supervision process. In the case of more than one supervisor, the completion of the form by the second or third supervisor is optional.

Name of Supervisor: Dr Chileshe R Mpehle **Contact email:** chileshempehle@yahoo.com

School: School of Medicine **Department:** Obstetrics and Gynaecology

Signature:  **Date:** 24/02/2025

Student Name: Khanya Makhatheng Montsho **Student number:** 2527440

Degree registered for: MMED (Obstetrics and Gynaecology)

Title of submitted dissertation/thesis/research report:

Pregnancy outcomes post High Intensity Focused Ultrasound at Chris Hani Baragwanath Academic Hospital

1. **Please Comment on the Supervision Process:**

   Frequency of meetings: Every 2-3 Months

   Number of drafts reviewed for protocol: 8 drafts reviewed

   Extent of assistance with data collection/analysis: Overseen and incorporated Wits statistical department assistance

   Number of drafts reviewed for final submission: 4 drafts reviewed

   Have you requested progress reports from the student? If yes, how often? Yes, frequently via telephone, roughly with every 6-month rotation change.

   Any difficulties in the relationship: No difficulties

   Other comments: .....

   .....

2. **Please comment on the student's ability to work independently during supervision process:**

   Selection of topic: Topic negotiated between candidate and supervisors. Candidate expressed interest in topic and supervisors worked in the HIFU department at CHBAH.

   Protocol development: Initial drafts well written by candidate. Multiple sessions done to adjust protocol.

   Data collection/experimental procedures: Candidate collected all data independently and diligently.

   Data analysis: Independent statistician was used to assist and guide analysis, done by the candidate.

Dissertation/thesis/research report write up: Drafts chiefly done by the candidate with supervisor input, only for revision and corrections

Ability to meet deadlines: Encountered pressures at time but worked quickly to meet deadlines. Often work at very late and early hours to ensure work was done

Other comments: .....

3. **Please comment on the quality of the submitted dissertation, thesis or research report:**

Language and presentation: Good and grammar checked

Contribution the research makes to knowledge in the field: Very informative as data emanates from the singular HIFU unit in South Africa, at the time of submission.

Standard of work: Very well put together thesis

4. **Please list conferences attended by student:**

O&G Update 2023

Navigating the Menopause Journey 2025

.....

.....

5. **Please list publications emanating from student's work (include each authors role in the case of joint publications).**

None.....

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.....

6. **Confidential Report:** (Should the supervisor wish to add any comments which will not be provided to the student, these can be added here).

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Appendix I: Guidelines for South African Journal of Obstetrics and Gynaecology

11.9. South African Journal of Obstetrics and Gynaecology submission guidelines

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:
• An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
• Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
• Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:
• Manuscripts must be written in UK English (this includes spelling).
• The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
• Please make your article concise, even if it is below the word limit.
• Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
• Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
• Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
• Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
• Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the only exception. Please DO NOT use fill, format lines and so on.

SAJOG is a general specialist obstetrics and gynaecology journal, therefore for articles involving genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
o Human Gene Mapping Workshop (HGMW): genetic notations and symbols
o HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
o OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
o Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the

recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Illustrations/photos/scans

• If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
• Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
• Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
• All images must be of high enough resolution/quality for print.
• All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
• Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
• Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

• Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
• Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
• Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
• Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
• Ensure each table has a concise title and column headings, and include units where necessary.
• Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..
• Authors must verify references from original sources.
• Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
• All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
• Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
• Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
• Volume and issue numbers should be given.
• First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
• Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
o On the Crossref homepage, paste the article title into the ‘Metadata search’ box.
o Look for the correct, matching article in the list of results.
o Click Actions > Cite
o Alongside 'url =' copy the URL between { }.
o Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Submission Preparation Checklist

All submissions must meet the following requirements.

- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- Where available, URLs for the references have been provided.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
- The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
- he submission file is in Microsoft Word format.
- Disclosure of whether any artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) has been used in the production of submitted work.
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Material submitted for publication in the *SAJOG* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

Appendix J: Protocol

PREGNANCY OUTCOMES POST HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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LIST OF ABBREVIATIONS

CHBAH: Chris Hani Baragwanath Academic Hospital

Fibroids: Uterine Fibroids

HIFU: High intensity focused ultrasound

HSG: Hysterosalpingogram

IQR: Inter-quartile range

MRgFUS: Magnetic Resonance guided focused ultrasound

MRgHIFU: Magnetic Resonance Imaging guided High intensity focused ultrasound

UAE: Uterine artery embolization

USgHIFU: Ultrasound-guided high intensity focused ultrasound

WHO: World Health Organization

INTRODUCTION

High intensity focused ultrasound (HIFU) is a non-invasive mode of management for tumours and is relatively new. The principle was introduced in 1942(1). It uses focused ultrasound energy to induce coagulative necrosis in the target tissue while sparing adjacent vital structures (1). In gynaecology, it has been adopted as a non-surgical and uterine protective option for women looking for options other than hysterectomy and myomectomy, for leiomyomas and adenomyosis(1). To-date it has been used to treat symptomatic fibroids, such as abnormal uterine bleeding and dysmenorrhoea, however the question remains as to how effective HIFU is as a treatment for infertility and if there are adverse pregnancy outcomes.

There are about 48 million couples and 186 million people affected by infertility in the world. (2). Infertility is defined by the failure to become pregnant after a period of one year or more of regular unprotected sexual intercourse (2). WHO classifies infertility into two categories; when a couple has never gotten pregnant is termed as primary infertility and when pregnancy had been achieved before despite the outcome of the pregnancy as secondary infertility (2)

Infertility in women may be caused by structural and non-structural causes. The structural causes may include disorders of the fallopian tubes, which are the most common reasons for infertility, occurring in about 35–40% of cases, uterine fibroids and adenomyosis are also commonly implicated as causes of infertility, as well as structural abnormalities of the cervix(3). Ovarian causes are another significant contributory factor (3). Genital tract

infections which are sexually transmitted are the most common cause of infertility, which affects both men and women (4,5).

Leiomyomata, known commonly as fibroids, are benign monoclonal tumours arising from smooth muscle cells of the uterus. They constitute of collagen and fibrous tissues. Fibroids are the most common tumours, occurring in women of reproductive age and they are found frequently in patients with infertility (6). Fibroids are categorized by their anatomical location as no classification includes other parameters such as their size and number (6). According to Doherty (2014), the fibroids' location within the uterus has an important role on their fertility effects (7).

Some women in reproductive age also suffer adenomyosis which is characterized by the presence endometrial glands and stroma within the myometrium, thus enlargement of the uterus. It can present with no symptoms or be symptomatic giving rise to frequently menorrhagia, dysmenorrhea, and infertility (8).

This study aims to assess the pregnancy outcomes in patients who received HIFU at CHBAH from 01 October 2015 until 30 June 2022 with an indication of fibroids and adenomyosis. We believe that it may show a trend towards increased pregnancy rates in such patients and thus may contribute to the knowledge pool, regarding HIFU uses in South Africa.

LITERATURE ANALYSIS

The prevalence of fibroids varies from 5.4% to 77% in different races. Independently they are associated with infertility and cause 1–2.4% of cases of infertility and 7% of recurrent miscarriages(9). It is also noted that, miscarriage rate in women with fibroids is 20–30% higher than those without fibroids (5).

Fibroids have a negative effect on fertility as they distort the endometrial cavity by obstructing the cervical canal, or obstruction of the tubal ostia. Doherty 2014 goes on to state that in vitro fertilization (IVF) pregnancy rates in women with endometrial cavities distorted by myomas are lower than those not affected. In studies comparing infertile women without myomas, and those with submucosal myomas it was found that those with fibroids have very low pregnancy rates, and poor pregnancy outcomes(7).

Other changes brought about by fibroids in the uterus may include increased contractility of uterus, impairment of supply of blood to the endometrium, and chronic inflammation of the endometrium (6). Glandular atrophy and ulceration are the commonest histological changes attributed to fibroids affecting the endometrium. Zepiridis 2016 says that fibroids may cause paracrine molecular effects on the adjacent endometrium, this is to say, secretion of vasoactive amines and local inflammatory substances capable of negative effect on fertility(10).

As already discussed above adenomyosis causes enlargement of uterus which microscopically reveal ectopic, non-cancerous, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium (8). Adenomyosis has adverse effect on a woman's quality of life and on fertility of women of childbearing age, but the treatment for this disorder still poses a challenge for the gynaecologist.

Shue et al, (11)suggest that women with more than six fibroids removed had less chances to become pregnant, more likely to require fertility treatment, and had reduced chances of having a term birth when compared with women with six or less removed fibroids. Even though the literature suggests the improvement of fertility with myomectomy (11), Shue et al believes that this is not necessarily true for women who have myomectomy for more than 6 fibroids. An increased number of fibroids excised is associated with increased blood loss during

myomectomy (11), thus increased risk of surgical complications from myomectomy. Cases with high fibroid numbers, may outweigh the fertility benefit.

Uterine artery embolization (UAE) can reduce the fibroid symptoms by significantly reducing the fibroid volume, but the risk of ovarian failure should be considered carefully in women who wish to maintain fertility (12).

HIFU started receiving significance in the 1980's and of recent, it is used in the management of uterine fibroids and adenomyosis (1). The safety, effectiveness, and high acceptability of patients to HIFU has been shown by various research groups (1).

HIFU constitute of numerous ultrasound beams produced by piezoelectric or piezoceramic transducers directed into a three-dimensional focal points small volume of 5mm in diameter and 10 mm in length. The intension is to increase and maintain temperature of more than 60°C for more than 1 second or longer at the target tissue thus causing, coagulative necrosis and cell death. "Synergistically, mechanical effect mostly by cavitation (intracellular water expands and contracts under the influence of acoustic pressure and develops microbubbles, which collapse and produce shock waves), and damaging effect to tumour blood vessels, also contribute to tissue destruction"(13). In the process of ablation, the HIFU beam must be targeted and monitored under image guidance either by ultrasound or magnetic resonance (13).

Ultrasound-guided HIFU is different from MRI-guided HIFU MRgFUS/MRgHIFU in that it is silent and does not require the patient to be closed in a confined space(1). During the procedure, the patient lies prone, with their abdomen submerged in a reservoir of cold, temperature regulated, degassed water, which allows for an enhanced acoustic window and at the same time reducing the risk of skin burns (1)(14).

A nurse and an anaesthetist sit close to the patient, throughout the procedure. The patient can comfortably communicate with the health care workers. Compared to MRgFUS/MRgHIFU, USgHIFU is less costly (14).

The current agreement amongst HIFU doctors suggests that HIFU treatment for fibroids and adenomyosis could be a safe alternative to surgical intervention or UAE for females who wish to conceive, but there is limited evidence to support this (15). It also noted that this non-invasive HIFU treatment shortens the treatment to pregnancy interval after HIFU ablation(16). In a study conducted in 2016, by Zepiridis patients who had adenomyosis and wished to conceive showed high pregnancy and live birth rates post HIFU treatment.

IN OUR SETTING

HIFU is offered to women up to 45years old with a uterine size of less than or equal to 18 weeks. There should be a sonar confirmation of fibroids, a recent Papanicolaou smear (pap smear) and a Z-sample for abnormal uterine bleeding patients, 40 years or more.

Contraindications to HIFU in our setting include haemoglobin of less than 8, any abnormal pap smear, clinically unstable patients, large fibroids with a height of fundus of more than 18weeks, central obesity (subcutaneous fat) more than 6-7 cm.

Symptoms included in our HIFU pre-treatment chart include, heavy menstrual bleeding, dysmenorrhea, pelvic pressure (bladder symptoms, constipation) and lastly infertility. About 500 women went through HIFU in CHBAH between 01 October 2015 and 30 June 2022.

Fibroids have conventionally been treated by medical treatment, uterine artery embolization, myomectomy, and or hysterectomy.

STUDY AIM

To assess pregnancy rates and outcomes post treatment with HIFU in patients treated for fibroids and adenomyosis from 01 October 2015 to 30 June 2022.

OBJECTIVES

(i) To describe the sociodemographic and clinical characteristics of patients, treated with HIFU at CHBAH

(ii) To describe the incidence of pregnancy and the pregnancy outcomes, in all patients who underwent HIFU for uterine fibroids in CHBAH.

(iii) To determine the incidence of pregnancy amongst patients who received HIFU, whilst having an infertility indication.

METHODS

STUDY SITE

The study will be conducted in CHBAH, Johannesburg, South Africa. The hospital is the largest in the Wits circuit and the only one with a HIFU unit, in that regard, patients are transferred from the other hospitals to CHBAH for HIFU. Data from 01 October 2015 and 30 June 2022 will be analysed in this study. Currently, 572 patients have gone through this procedure for different conditions.

STUDY DESIGN

Retrospective study that will involve reviewing patient files and data base maintained at the HIFU unit from the selected study period that is between 01 October 2015 and 30 June 2022.

STUDY GROUPS

Women of childbearing age with infertility indication who have been treated with HIFU will be selected from the data base. The data will then be analysed to select patients had uterine fibroids and or adenomyosis with either primary or secondary infertility.

RECRUITMENT STRATEGY

Patients will be selected from the HIFU database at CHBAH. The database has recorded all treatments from 01 October 2015 to date. Patient files will be assessed for suitability

for inclusion in the study, after which the patients will be contacted telephonically and informed consent obtained, with an offer to participate in the study.

INCLUSION CRITERIA

1) All patients of childbearing age who received HIFU up to 45yrs of age
2) Patients who conceived naturally
3) Patients who had Invitro fertilization (IVF)

EXCLUSION CRITERIA

1) Patients who were sterilized prior to treatment.
2) Patients who are unable to fill the questionnaire our in English, Tswana or Zulu.

DATA COLLECTION

The data in the RedCap database will be exported and uploaded into a Stata 15.0® data analysis file. Data will be cleaned by running frequencies and tabulations in order to check for errors and, if present, correct any using the source data.

DATA ANALYSIS AND STATISTICS

(i) *Sociodemographic and clinical characteristic of patients treated with HIFU at CHBAH*: Simple descriptive analysis will be conducted. Categorical variables will be described using frequencies and percentages, whilst continuous variables will be described using means (with standard deviations) for parametric data and medians (with inter-quartile range [IQR]) for non-parametric data.

(ii) Describe the incidence of pregnancy among the patients who underwent HIFU treatment at CHBAH: Incidence will be computed by dividing the number of new pregnancies by the total number of women who agreed to participate in the study.

(iii) Determine the incidence of pregnancy among patients who underwent HIFU treatment for infertility reasons: Incidence will be computed by dividing the

number of new pregnancies by the total number of women who underwent HIFU treatment for infertility indication and have agreed to participate in the study.

All data analyses will be conducted in Stata 15.0® (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

ETHICS

a) Ethics clearance for the study will be applied for with the University of the Witwatersrand Health Research Ethics Committee.

b) The study will be conducted with patient identification data being completely confidential, known only to the researcher.

c) Patient identifiers such as names or hospital and file numbers will be kept separate from the data sheet.

d) A study number will be allocated to patients used in the study.

The study will be registered in the National Health Research Database.

Permission from the head of the HIFU unit, the HOD of obstetrics and gynaecology and CEO of CHBAH to use data base will be acquired.

TIMING

2022	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol development		x	x	x	x	x						
Submission							x					
Correction								x	x			
Ethics										x	x	x
2023	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
Data Collection	x	x	x									
Analysis				x	x							
Write up						x	x	x				
Marking									x	x		
Corrections											x	x

FUNDING

The study will be funded solely by the researcher to cover costs of printing materials, stationery, and basic miscellaneous goods. Upon completion for publication funding will be applied for at Wits university.

ITEM	COST
Printing data sheet	R500 (R1 per sheet)
Printing dissertation	R500 (R1 per sheet)
Airtime for calling patients	R504: (5min pre patient x 500n=2500min) 2500min/60min=42hours of calling patients Vodacom R12/hrx24hrs=R504
Statistical Analysis Aid	R4000

Publication	R7000 (according to SAMJ)
Total	R12,504-00

POTENTIAL BIAS AND LIMITATIONS

There may be difficulties retrieving all the required files due to loss or misplacement.

Patients may not be contactable on numbers provided on the file.

CONCLUSION

My proposed study is one that has not been done before in the Wits circuit. I feel it carries relevance in that it will provide new insight into the use of HIFU and pregnancy outcomes, while appreciating the non-invasiveness of this procedure. This new knowledge will contribute towards modalities of treatment of patients with fibroids and poor pregnancy outcomes and infertility.

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