

# High-intensity Focused Ultrasound is a Better Choice for Women with Fertility Desire: A Systematic Review and Meta-analysis of the Comparison between High-intensity Focused Ultrasound and Laparoscopic Treatment of Uterine Fibroids

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## Abstract

High-intensity focused ultrasound (HIFU) is commonly used to treat uterine fibroids and adenomyosis, but there is no evidence using metadata to compare fertility outcomes between conventional laparoscopic procedures and HIFU. The purpose of this study analysis is that evidence-based fertility outcomes may provide better treatment options for clinicians and patients considering fertility. The literature on fertility data for HIFU surgery versus laparoscopic myomectomy was searched in seven English language databases from January 1, 2010, to November 23, 2022. A total of 1375 articles were received in the literature, 14 of which were selected. We found that women who underwent HIFU surgery had higher rates of spontaneous pregnancy, higher rates of spontaneous delivery, and higher rates of full-term delivery but may have higher rates of miscarriage or postpartum complications than women who underwent laparoscopic myomectomy. Looking forward to future studies, it is hoped that the literature will examine endometrial differences in women who undergo HIFU and laparoscopic myomectomy to demonstrate the ability of endometrial repair. The location of fibroids in the sample should also be counted to allow for attribution statistics on the cause of miscarriage.

**Keywords:** Adenomyosis, fertility outcome, high-intensity focused ultrasound ablation, laparoscopic myomectomy, leiomyoma, uterine fibroids

## INTRODUCTION

Uterine fibroids (leiomyomas or fibroids) are the most common benign pelvic tumors in women of childbearing age.<sup>[1]</sup> The lifetime prevalence of fibroids exceeds 80% in upfront women and approaches 70% in European descent women.<sup>[2]</sup> The main manifestations of uterine fibroids are bleeding, pressure, pain, and decreased fertility.<sup>[3]</sup> In contrast, the prevalence of adenomyosis ranges from 5% to 70% in

women of childbearing age (depending on the definition) over 35 years.<sup>[4]</sup> Adenomyosis usually presents debilitating symptoms, including irregular menstruation, chronic pelvic pain, dysmenorrhea, and infertility.<sup>[5]</sup>

To protect the fertility of young women, minimally invasive procedures are being considered for the treatment of

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uterine fibroids or adenomyosis, including laparoscopic and robot-assisted laparoscopic procedures, as well as high-intensity focused ultrasound (HIFU) ablation.<sup>[3,6]</sup> As a nonsurgical treatment option, HIFU uses ultrasound waves to cause coagulative necrosis and cell death of the diseased tissue.<sup>[7]</sup>

Although there have been some systematic evaluations of high-intensity ultrasound focusing, none have used metadata evidence to compare fertility outcomes between conventional laparoscopy and HIFU.<sup>[6,8,9]</sup> We hope such evidence-based fertility outcomes will improve treatment options for clinicians and patients considering fertility.

### MATERIALS AND METHODS

We performed a systematic evaluation and meta-analysis of all trials according to the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis guidelines.<sup>[10]</sup> The review is available at <https://www.crd.york.ac.uk/PROSPERO/> with under the identification number CRD42022383030.

A systematic and comprehensive literature search was completed using PubMed/Embase/Cochrane Library/Proquest/Clinical Trials/Scopus/Web of Science databases between January 1, 2010 and November 23, 2022. Two authors conducted separate searches for English language articles. Keyword, free text, and medical subject heading terms were also used to enhance further and expand the investigation [Appendix 1].

- Women who want to conceive are undergoing HIFU or laparoscopic treatment for fibroids or adenomyomas
- Target populations containing >30 patients

- Follow-up time >12 months
- The primary outcome is the fertility outcome of the target population, spontaneous pregnancy, assisted pregnancy, miscarriage or ectopic pregnancy, preterm birth, postpartum complications, and the interval between pregnancies.

Robotic-assisted laparoscopic procedures were excluded from the study. Exceptions are reviews, abstracts, studies with incomplete experimental data, repeat publications, trial registries, and case reports.

### Data extraction

Two of us independently classified the interventions, with differences resolved by a third reviewer. When further information needs to determine eligibility, we contacted the trial authors. The literature screening process is shown in Figure 1, and maternal characteristics are shown in Table 1.

### Outcomes

The primary outcomes are fertility outcomes for the target population, which include spontaneous pregnancy, assisted pregnancy, miscarriage or ectopic pregnancy, preterm birth and postpartum complications, and the interval between pregnancies.

### Assessment of risk of bias

The critical review was done independently by two reviewers. Retrospective studies without a comparison group were assessed using the Joanna Briggs Institute for Evidence Based Nursing and Midwifery (JBI) Critical Assessment Checklist for Quasi-Experimental Studies (nonrandomized experimental studies).<sup>[11]</sup> This form was used to determine

**Table 1: Study characteristics**

| First author                  | Year | Country     | Center        | Type | Follow-up time (mean) months | Interventions (n) | Surgical procedures (n) | Pregnant outcome |
|-------------------------------|------|-------------|---------------|------|------------------------------|-------------------|-------------------------|------------------|
| Jiang <sup>[12]</sup>         | 2021 | China       | Single center | ROS  | 16–81 (42)                   | USgHIFU (152)     | LM (194)                | ①②③④⑤⑥⑦⑧⑩        |
| Wu <sup>[13]</sup>            | 2020 | China       | Multi-center  | ROS  | 12–96 (60)                   | USgHIFU (336)     | LM (340)                | ①②③④⑤⑥⑦⑧⑨⑩       |
| Huang <sup>[14]</sup>         | 2020 | China       | Single center | ROS  | 60 (NS)                      | USgHIFU (50)      | LM (43)                 | ①②③④⑤⑥⑧          |
| Rodríguez <sup>[15]</sup>     | 2021 | Spain       | Single center | ROS  | 3–120 (48)                   | USgHIFU (160)     |                         | ①②⑤⑥⑦⑧⑨          |
| Liu <sup>[16]</sup>           | 2018 | China       | Single center | ROS  | 1–76                         | USgHIFU (174)     |                         | ①②④⑤⑥            |
| Ji <sup>[17]</sup>            | 2022 | China       | Single center | ROS  | >12 (NS)                     | USgHIFU (80)      |                         | ①④⑤⑥             |
| Lu <sup>[18]</sup>            | 2022 | China       | Single center | ROS  | 1–72 (NS)                    |                   | LM (156)                | ①③④⑤⑥⑧⑨⑩         |
| Fagherazzi <sup>[19]</sup>    | 2014 | Italy       | Single center | ROS  | 14 years (NS)                |                   | LM (185)                | ①③④⑤⑥            |
| Hong <sup>[20]</sup>          | 2021 | South Korea | Single center | ROS  | >12 (NS)                     |                   | SPLM (56)               | ①②③④⑤⑥⑧⑨⑩        |
| Bernardi <sup>[21]</sup>      | 2014 | Germany     | Single center | ROS  | 1–72 (NS)                    |                   | LM (59)                 | ①②④⑤⑥            |
| Tian <sup>[22]</sup>          | 2015 | China       | Single center | ROS  | 1–60 (NS)                    |                   | LM (179)                | ①②④⑤⑥⑧           |
| Kim <sup>[23]</sup>           | 2014 | Korea       | Single center | ROS  | 23.2–24.4                    |                   | LM (38)                 | ①②④⑤⑥⑧⑨          |
| Zhang and Hua <sup>[24]</sup> | 2014 | China       | Single center | ROS  | 1–53 (NS)                    |                   | LM (280)                | ①③⑤              |
| Arena <sup>[25]</sup>         | 2021 | Italy       | Single center | ROS  | 45±11                        |                   | LM (164)                | ①②④⑤⑥⑧⑩          |

①: Pregnancy, ②: Natural pregnancy/assisted pregnancy, ③: Pregnancy interval (m) average time to pregnancy, ④: Miscarriage, ⑤: Delivery, ⑥: Cesarean delivery or spontaneous vaginal delivery or forceps delivery, ⑦: Pregnancy complication, ⑧: Labor complication, ⑨: Ended delivery, ⑩: Preterm birth. ROS: Retrospective study, USgHIFU: Ultrasound-guided high-intensity focused ultrasound, LM: Laparoscopic myomectomy, SPLM: Single-port LM, NS: Not stated

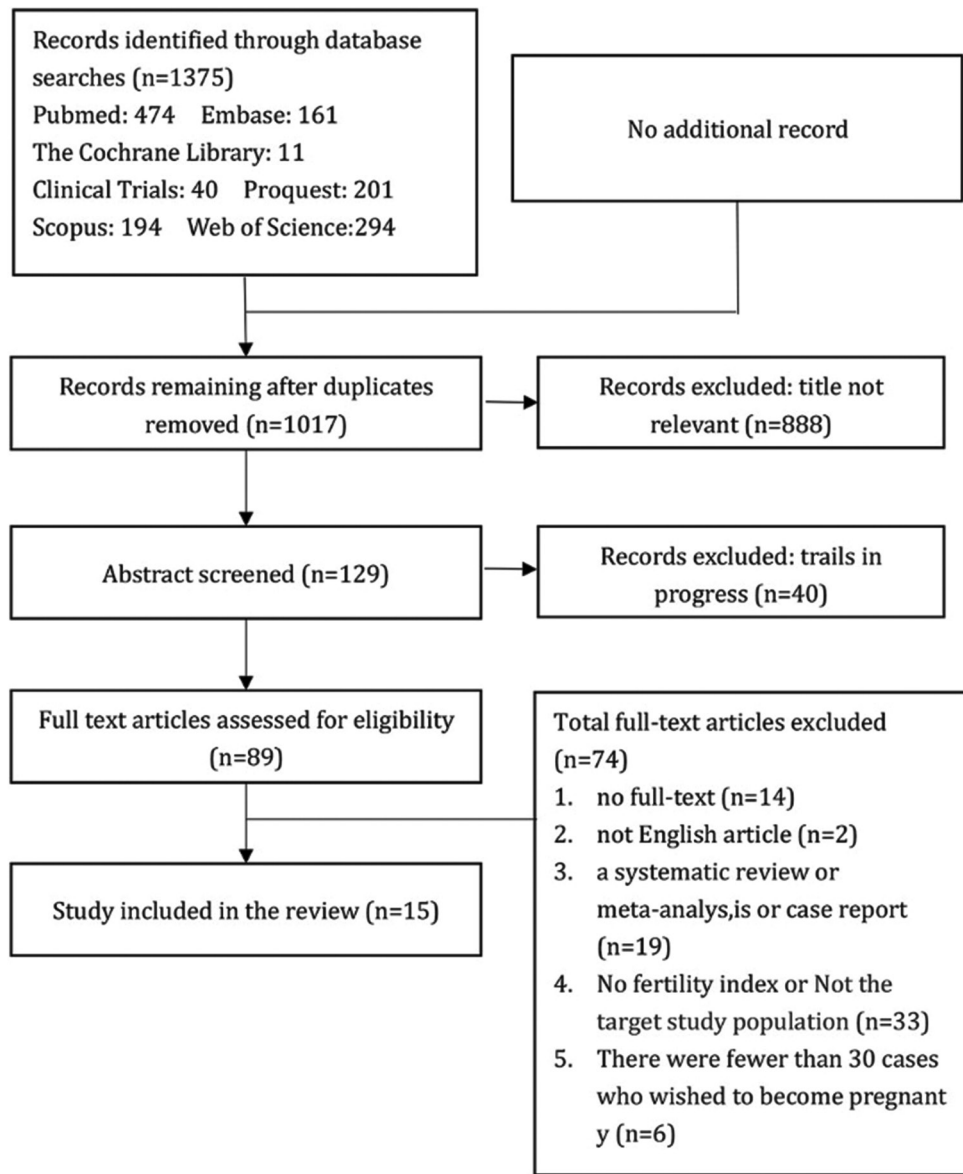


Figure 1: Flow diagram of literature search process

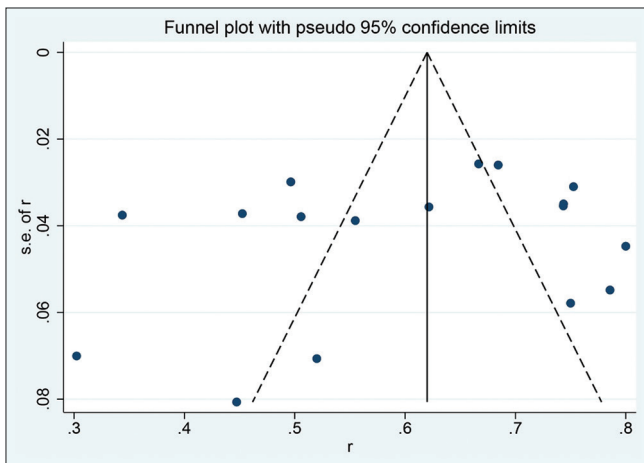


Figure 2: The publication bias

the quality of cohort and case-control studies. Scores of 7–9 were defined as “good,” 4–6 as “fair,” and <4 as “poor.”

**Data synthesis and statistical analysis**

Stata 16.0 software (Stata Corp, Texas, USA) was used for this meta-analysis. All studies underwent a meta-analysis of pooled proportions. These data and single ratios were calculated as overall proportions with 95% confidence intervals (CIs) to summarize the postoperative data and outcomes for each study. A combination of fixed and random effects models was used to analyze and calculate pooled Merge effect quantity (ES) and 95% CIs. For high heterogeneity ( $I^2 > 50\%$ ), a random effects model was used, while for low heterogeneity ( $I^2 < 50\%$ ), a fixed effects model was used. Publication bias was assessed by analysis of the

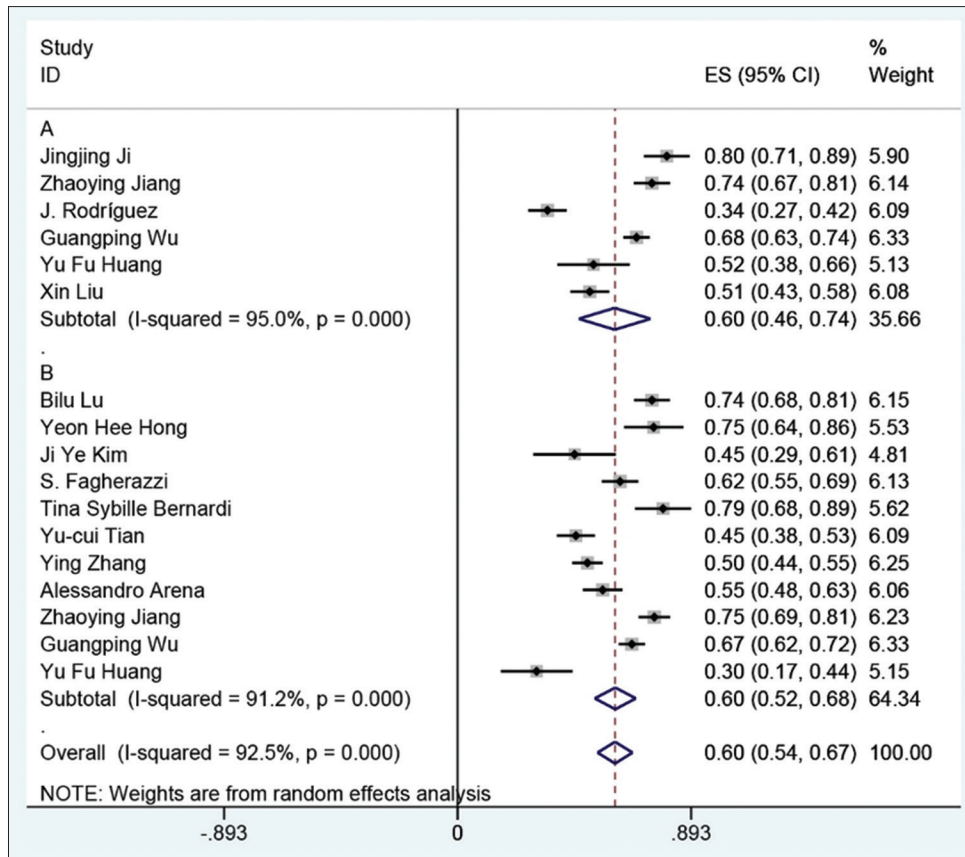


Figure 3: Pregnancy rates

output of the fixed effects versus random effects models Funnel plots and analysis of Egger regression tests.

## RESULTS

### Study selection

A total of 1375 articles were generated from the database search; reports were retained after removing duplicates and filtering based on title and abstract. A total of 89 full-text articles were assessed as eligible, and 74 articles were ultimately removed compared to the inclusion and exclusion criteria. Fifteen full-text articles were included in the analysis [Figure 1].

### Study, patient, and treatment characteristics

These sample trials involved 2646 women. Of these, 952 women were treated with HIFU, and 1694 underwent laparoscopic myomectomy. These studies were retrospective.<sup>[12-25]</sup> It was a comparative study between the HIFU and laparoscopic myomectomy groups.<sup>[12-14]</sup> The only data for the HIFU group were from these studies,<sup>[15-17]</sup> whereas data for the laparoscopic myomectomy group were from these studies only.<sup>[18-25]</sup> Risk of bias assessment scores ranged from a maximum of 9 to a minimum of 5 (one of the four items<sup>[26]</sup> was removed). The current meta-analysis used funnel plots to check for publication bias in the

included literature. It retested them for publication bias using the Egger test ( $P = 0.405$ ), both of which were free of publication bias [Figure 2].

### Fertility outcomes for high-intensity focused ultrasound and laparoscopic treatment of uterine fibroids

#### Pregnancy rate

A total of 14 articles were included in this meta-analysis. Pregnancy rates of 60% [Figure 3] were achieved in women who underwent both HIFU and laparoscopic myomectomy. Regarding spontaneous pregnancy rates, women who underwent HIFU achieved 82%, while women who underwent laparoscopic myomectomy also achieved 80%. However, the success rate of assisted pregnancy was 9% for women who underwent HIFU compared to 13% for women who underwent laparoscopic myomectomy. The meta-analysis results are shown in Table 2. A logistic regression analysis of the results in one study<sup>[12]</sup> also showed that age, history of infertility, number, and type of fibroids were not significantly different between the two groups.

#### Delivery rate

The results in terms of birth rate were analyzed in four areas: vaginal delivery rate, cesarean delivery rate, full-term delivery rate, and preterm delivery rate. The vaginal delivery rate was 43% in women treated with HIFU compared to 33% in women

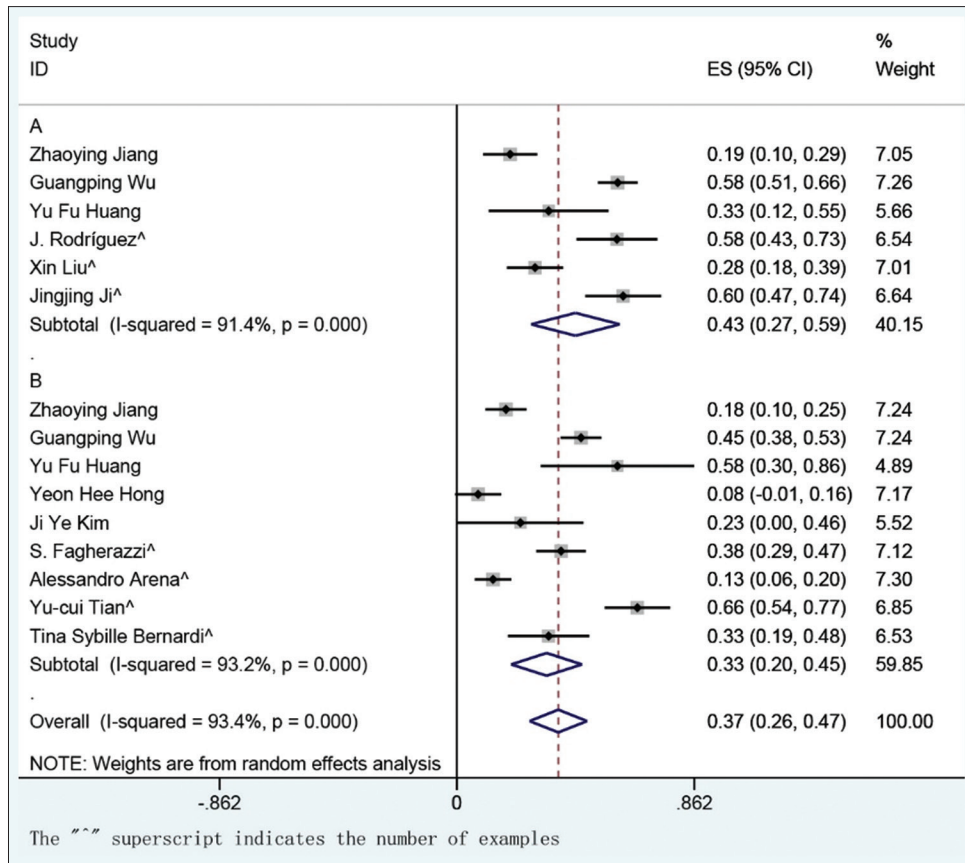


Figure 4: The vaginal delivery rate

who underwent laparoscopic myomectomy, with a significant difference of 10% [Figure 4]. Regarding the cesarean delivery rate, 58% of women received HIFU compared to 64% of women who received laparoscopic myomectomy. Women who underwent HIFU had a 95% chance of delivering at term compared to 93% of women who underwent laparoscopic myomectomy. There was no statistically significant difference in the incidence of premature birth between the two groups. The specific data results are shown in Table 2 (This evidence supports sources and Appendix 2 ).

**Miscarriage rate and labor complications**

The incidence of miscarriage and ectopic pregnancy was 22% in women who received HIFU and 17% in women who underwent laparoscopic myomectomy. The incidence of intrapartum complications was 8% in women receiving HIFU and 10% in women undergoing laparoscopic myomectomy. These obstetric complications included uterine rupture, amniotic fluid embolism, postpartum infection, and postpartum hemorrhage. These results are also presented in Table 2.

**DISCUSSION**

This meta-analysis only analyzed fertility data in women with fertility intentions after HIFU and laparoscopic myomectomy.

However, to our knowledge, this is the first single-group rate meta-analysis comparing fertility outcomes in women after HIFU with women after laparoscopic myomectomy.

The current study compared the number of successful pregnancies to the total number of women with the same chance of pregnancy with laparoscopic myomectomy using HIFU. This is a side effect of the magnitude of the effect of both procedures on fertility. However, it is also influenced by the age of the sample, number, size, location of fibroids, history of miscarriage, ovarian function, etc., which may also be reflected in the higher heterogeneity of the data.

Regarding natural pregnancy rates, ignoring factors such as age, size, and location of the fibroids, women treated with HIFU were slightly more likely than those who underwent laparoscopic myomectomy, possibly, because HIFU ablates only the lesion and caused less damage to the surrounding tissue and endometrium. This seems to be supported by the fact that in some studies,<sup>[11-13]</sup> women after HIFU had shorter pregnancy cycles than women who underwent laparoscopic myomectomy. However, no studies are comparing endometrial differences between women who underwent HIFU and those who underwent laparoscopic myomectomy to prove this point. However, regarding assisted pregnancy rates, women who underwent HIFU



**Table 2. The analysis of outcomes reveals a comparison between high-intensity focused ultrasound and laparoscopic myomectomy**

| Outcome  | Number of articles (n)         | Analysis model | I <sup>2</sup> (%) | Total, ES (95% CI) | HIFU, ES (95% CI) | LM, ES (95% CI)  | P     |
|--|--------------------------------|----------------|--------------------|--------------------|-------------------|------------------|-------|
| Spontaneous pregnancy rates                        | 11 (12-16, 19-23, 25)          | REM            | 94.3               | 0.81 (0.75-0.88)   | 0.82 (0.72-0.92)  | 0.80 (0.71-0.90) | 0.000 |
| The success rate of assisted pregnancy             | 11 (12-16, 19-23, 25)          | REM            | 72.8               | 0.11 (0.08-0.15)   | 0.09 (0.06-0.13)  | 0.13 (0.08-0.18) | 0.000 |
| Vaginal delivery rate                              | 12 (12-17, 19-23, 25)          | REM            | 93.4               | 0.37 (0.26-0.47)   | 0.43 (0.27-0.59)  | 0.33 (0.20-0.45) | 0.000 |
| Cesarean delivery                                  | 12 (12-17, 19-23, 25)          | REM            | 91.6               | 0.61 (0.52-0.71)   | 0.58 (0.42-0.73)  | 0.64 (0.51-0.76) | 0.000 |
| Full-term delivery rate                            | 11 (12, 13, 15, 16, 18-23, 25) | REM            | 55.4               | 0.94 (0.92-0.96)   | 0.95 (0.91-0.99)  | 0.93 (0.91-0.96) | 0.010 |
| Preterm delivery rate                              | 11 (12, 13, 15, 16, 18-23, 25) | REM            | 18.2               | 0.05 (0.04-0.07)   | 0.05 (0.01-0.09)  | 0.06 (0.04-0.08) | 0.265 |
| The incidence of miscarriage and ectopic pregnancy | 12 (12-23)                     | REM            | 89.1               | 0.19 (0.13-0.24)   | 0.22 (0.13-0.31)  | 0.17 (0.10-0.24) | 0.000 |
| The incidence of intrapartum complications         | 5 (12-15, 18)                  | REM            | 54.6               | 0.09 (0.06-0.12)   | 0.08 (0.05-0.11)  | 0.10 (0.03-0.16) | 0.040 |

REM: Random effect model, CI: Confidence interval, LM: Laparoscopic myomectomy, HIFU: High-intensity focused ultrasound, ES: Merge effect quantity

had lower pregnancy success than those who underwent laparoscopic myomectomy. This may be related to many factors, such as the direct damage to the endometrium caused by thermal ablation during the treatment, which is often from the basal to the endometrial layer of the uterus. There is also edema and inflammation of the endometrium after uterine thermal ablation. According to reproductive endocrinologists, a preimplantation vaginal ultrasound view to observe the degree of inflammation of the endometrium is associated with the implantation success rate. That is, the whiter the echogenicity of the endometrium in the preimplantation ultrasound view, the more pronounced the inflammation of the endometrium and the lower the success rate of assisted implantation pregnancy.

However, there is no evidence of changes in the echogenic intensity of the endometrium after HIFU treatment. Therefore, future studies should look for changes in the endometrium after HIFU treatment and laparoscopic treatment, such as changes in color Doppler ultrasound and changes in endometrial sampling at hysteroscopy. Moreover, other factors influence the success of assisted pregnancy. A study<sup>[27]</sup> showed that maternal age, controlled ovarian stimulation protocol, cycle type, and serum human chorionic gonadotropin level at 14 days posttransplantation had an independent effect on miscarriage, mainly before 12 weeks of gestational age. A systematic review<sup>[9]</sup> involving HIFU surgery and other modalities for treating uterine fibroids counted the number of successful pregnancies and the total number of pregnancies in women after HIFU surgery rather than the number of planned pregnancies. Furthermore, it supported that women who underwent HIFU had higher pregnancy rates.

Women who have undergone HIFU surgery have higher rates of vaginal delivery, lower rates of cesarean section, higher rates of full-term delivery, and lower rates of preterm delivery. Although there is no valid evidence that a history of previous surgery for uterine fibroids carries an absolute risk of uterine rupture, such patients are generally conservatively advised to undergo cesarean section before delivery.<sup>[28]</sup> It has also been shown<sup>[29]</sup> that uterine scarring is one of the six independent factors influencing preterm delivery. This will explain the lower rate of full-term deliveries and a higher rate of preterm deliveries in women who underwent laparoscopic myomectomy.

The current study suggests that women treated with HIFU have a higher rate of miscarriage. Although ectopic pregnancy rates are included in the miscarriage rate statistics, there may be limitations in simply entering that miscarriage rate due to the lack of attribution statistics for the uterine fibroid factors in the sample in some miscarriage rate

statistics. This is because there is evidence that the location of adenomyosis and the type of adenomyosis significantly impact birth outcomes.<sup>[14]</sup> However, the incidence of delivery complications may be higher. It has been suggested<sup>[16]</sup> that HIFU ablation effectively relieves symptoms. Still, thermal damage to the endometrium may be irreversible in treating submucosal fibroids but does not affect vaginal delivery. Even HIFU treatment has a relatively lower risk of bleeding and postpartum complications. However, it cannot be ignored that women who experience uterine cavity rupture during laparoscopic myomectomy are more likely to implant the placenta, which indirectly increases the likelihood of undergoing a hysterectomy during childbirth.<sup>[30]</sup> Therefore, gynecologists should pay special attention to the preoperative magnetic resonance imaging results of these women, especially the uterine fibroids near the muscle layer, between the muscle walls, or in the sessile serosa or submucosa. These studies only include statistical data on delivery complications. The complications of laparoscopic myomectomy include intraoperative bleeding, postoperative adhesions, as well as small intestinal obstruction, and chronic pelvic pain caused by adhesions or impaired fertility.<sup>[31-34]</sup> There is even data showing that the incidence of adhesions after laparoscopic myomectomy can reach one-fifth.<sup>[31]</sup> There are also literature reports that the complications of uterine fibroid after surgery are as high as 10%.<sup>[35]</sup> For women with reproductive needs, it is recommended to consider HIFU treatment as a better option.

These studies only partially counted the age, size, number, and location of fibroids in the sample, but did not count pregnancy rates or miscarriage rates by category, the inclusion of which may have led to some limitations in the results of this study. Because there were not enough controlled studies, single-group rates were counted in this study, subgroup analysis was used, and no comparisons were made between the two groups. No ratio data could be generated, leading to an absolute inability to discuss the sources of heterogeneity using regression analysis.

Therefore, it would be helpful to have more retrospective studies with control groups and independent statistics on pregnancy or miscarriage rates among women undergoing HIFU and laparoscopic myomectomy regarding age, size, number, location of fibroids, and other factors affecting pregnancy.

## CONCLUSIONS

The results of the current meta-analysis show that HIFU is not worse than laparoscopic myomectomy in terms of fertility and is even better regarding spontaneous pregnancy rates, spontaneous labor, and full-term delivery. HIFU is a better option for women with fibroids with fertility requirements.

## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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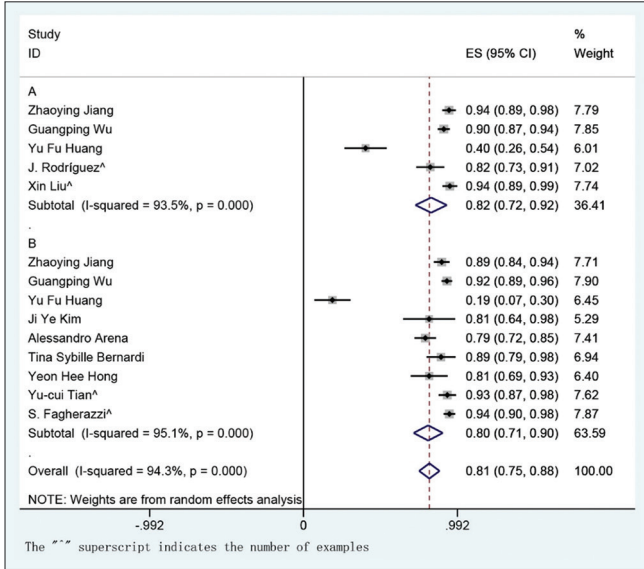
## APPENDICES

### Appendix 1

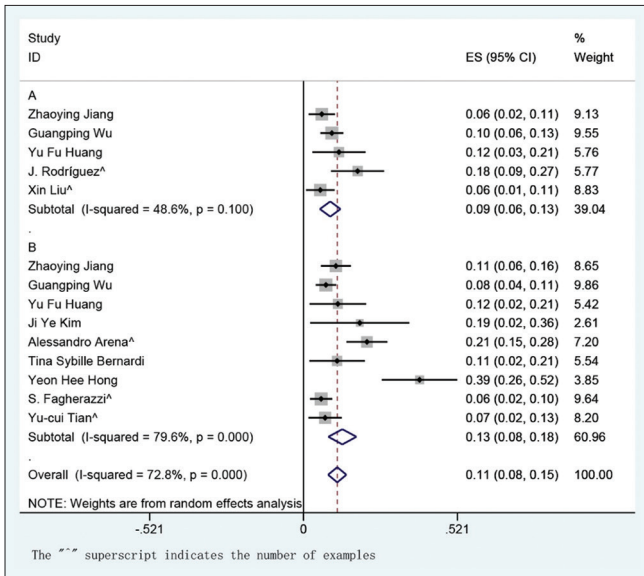
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### Appendix 2

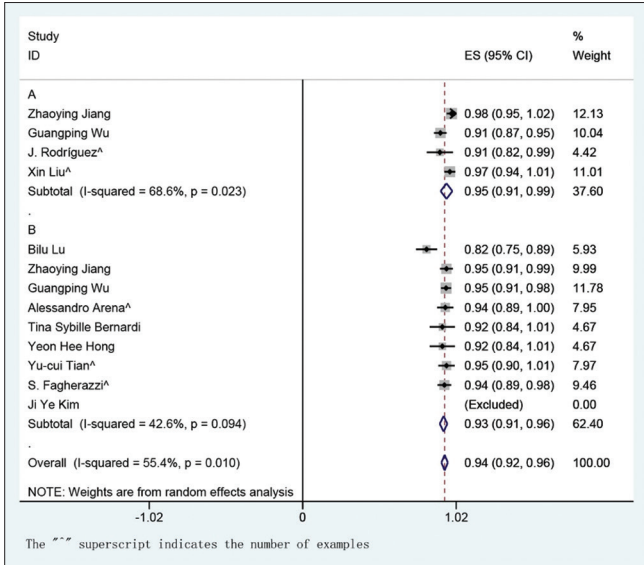
The spontaneous pregnancy rates



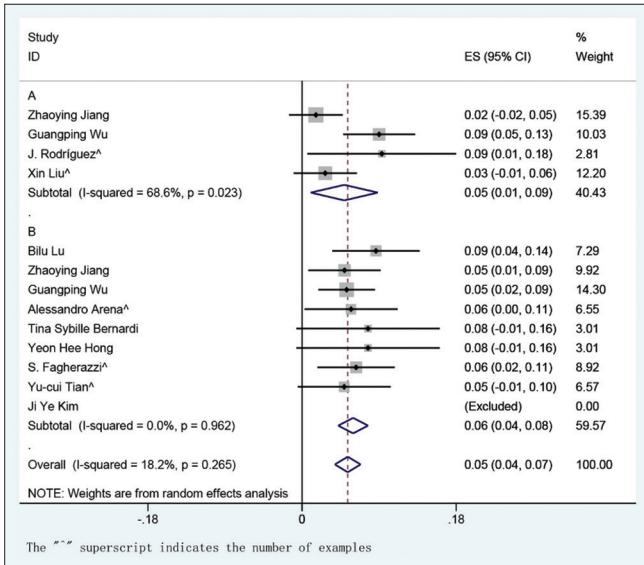
The success rate of assisted pregnancy



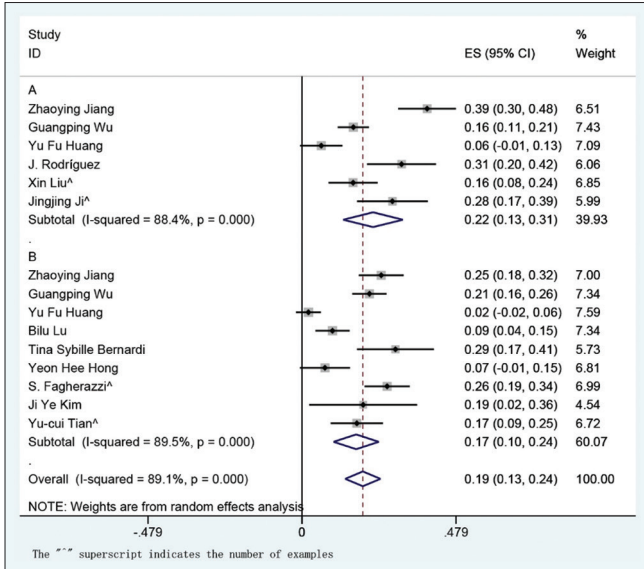
The chance of delivering at term rate



The preterm delivery rate



The incidence of miscarriage and ectopic pregnancy



The incidence of intrapartum complications

