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HIFU babies: Dose the high-intensity focused ultrasound (HIFU) treatment of adenomyosis improve pregnancy?

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 September 2023 and was last updated on 28 September 2023.

INTRODUCTION

Review question / Objective The aim of this systematic review is to evaluate the impact of high-intensity focused ultrasound (HIFU) treatment on pregnancy outcomes in patients with adenomyosis.

Condition being studied Based on Lynn's concept of using High-Intensity Focused Ultrasound (HIFU) for non-invasive surgeries in 1942, China successfully developed the world's first "High-Intensity Focused Ultrasound Tumor Treatment System" in 1996, marking the beginning of clinical applications of HIFU. HIFU employs brief yet intense ultrasound waves, typically raising temperatures above 55°C momentarily, causing irreversible thermal damage to crucial and sensitive proteins within cells, severely impacting cellular physiological functions, and even leading to cell death. Combining thermal effects with various mechanisms such as acoustic cavitation, radiation force, shear force, and microstreaming, HIFU can coagulate and ablate lesions within the body from outside, achieving a "surgical strike" effect. Its non-invasive nature significantly reduces recovery time, alleviates patient suffering, and delivers better cosmetic results, opening up exciting new dimensions in treatment and demonstrating effectiveness in a range of diseases.

Adenomyosis, as a common and challenging gynecological condition, poses the urgent question of how to effectively alleviate symptoms, prevent recurrence, particularly improve pregnancy rates, and enhance pregnancy outcomes. A series of review articles on HIFU treatment for uterine adenomyosis, with follow-up periods ranging from 3 to 40 months (mostly within 12-18 months), suggest the effectiveness of HIFU in improving symptoms. It is promoted as the 'preferred' treatment method for adenomyosis patients seeking fertility, due to its short-term uterine repair after surgery, catering to patients with urgent fertility desires. However, there is a lack of long-term follow-up data and information on fertility

outcomes after HIFU treatment. There is a concern that residual or incompletely absorbed lesions may regrow under the influence of estrogen. Additionally, there are worries that lesions close to the endometrial or serosal surface may lead to excessive damage to adjacent endometrial or serosal tissue. Furthermore, there is a risk of excessive energy accumulation or prolonged treatment duration, regardless of the lesion's proximity to the endometrial or serosal surface. Therefore, it is crucial to offer careful recommendations to patients.
This article conducts a systematic review of post-treatment fertility outcomes in uterine adenomyosis patients who have undergone High-Intensity Focused Ultrasound (HIFU) therapy. It also evaluates the effect of HIFU treatment of patients with adenomyosis on the pregnancy outcome.

METHODS

Search strategy We will search the following databases: PubMed, Web of Science, The Cochrane Library, EMBASE, CNKI, and Wanfang. Our search terms will include 'Adenomyosis,' 'Adenomyoma,' 'High-intensity focused ultrasound,' 'Pregnancy,' and 'Gestation.' Articles published in both English and Chinese will be considered. Our goal is to identify all relevant studies published up to the date of the initial search. The search will be re-run just before the final analysis, and further studies meeting our criteria will be included.

Participant or population This article conducts a systematic review of post-treatment pregnancy outcomes in uterine adenomyosis patients who have undergone High-Intensity Focused Ultrasound (HIFU) therapy.

Intervention HIFU treatment in patients with adenomyosis.

Comparator Adenomyosis patients.

Study designs to be included We will search the following databases: PubMed, Web of Science, The Cochrane Library, EMBASE, CNKI, and Wanfang. Our search terms will include 'Adenomyosis,' 'Adenomyoma,' 'High-intensity focused ultrasound,' 'Pregnancy,' and 'Gestation.' Articles published in both English and Chinese will be considered. Our goal is to identify all relevant studies published up to the date of the initial search. The search will be re-run just before the final analysis, and further studies meeting our criteria will be included.

Eligibility criteria The exclusion criteria: (1) Reviews, animal experiments, case reports, conference abstracts, conference proceedings, editorial letters, guidance or comments; (2) repeated studies; (3) studies where full text is not available.

Information sources We will search the following databases: PubMed, Web of Science, The Cochrane Library, EMBASE, CNKI, and Wafang. Our search terms will include 'Adenomyosis,' 'Adenomyoma,' 'High-intensity focused ultrasound,' 'Pregnancy,' and 'Gestation.'

Main outcome(s) A total of 26 studies involving 4,299 patients were retrieved and evaluated. All articles were conducted in Asian, including China (18/26, 69.2%), South Korea (19.2%), India (7.7%), and Japan (3.8%). The authors of three articles were affiliated with HIFU research institutions or medical companies as shareholders or employees. And only 1 article actively disclosed conflicts of interest, while the Chinese articles did not mention whether conflicts of interest existed.
Among these studies, 10 reported the number of planned pregnancies. The overall pregnancy rate among patients who underwent HIFU treatment was 22.7% (95%CI 13.9%, 32.7%), while the pregnancy rate among those with planned pregnancies was 53.7% (95%CI 39.5%, 67.5%). Among these, there were 168 natural pregnancies, with a natural pregnancy rate of 21.9% (95%CI 8.2%, 39.4%). There were 41 pregnancies through assisted reproduction, and 243 cases did not mention the method of pregnancy. The average time from treatment to pregnancy was 11.6±6.3 months. The miscarriage rate was 13.7% (95%CI 6.3%, 22.7%). The live birth rate was 61.9% (95%CI 46.4%, 76.6%), and the full-term pregnancy rate was 50.1% (95%CI 40.1%, 60.1%). Among the 214 patients who had live births, 118 underwent cesarean birth, resulting in a cesarean birth rate of 56.3% (95%CI 42.9%, 69.3%), while 86 had vaginal deliveries, and 10 cases did not report delivery outcomes. There were 21 cases of complications during pregnancy or delivery (21/214, 9.8%), including 9 cases of postpartum hemorrhage (4.2%), 8 cases of placental abnormalities (3.7%), 3 cases of preterm premature rupture of membranes, and 1 case of hypertensive disorders of pregnancy. No cases of uterine rupture were reported.

Quality assessment / Risk of bias analysis Two investigators screened titles and abstracts for eligibility as well as the full text of each eligible study, to confirm the inclusion criteria. The quality evaluation criteria of individual studies were

assessed using the Newcastle-Ottawa Scale (NOS) of Cohort studies, MINORS of single-arm clinical trials, and Cochrane of RCT.

Strategy of data synthesis State 17.0 (Stata Corp. LLC, College Station, TX, USA) was used for the data analysis by two review authors (YSC and SWG). The heterogeneity of included studies was assessed using the Q test (I2 value). If $P > 0.1$ and $I2 \leq 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used. For single-arm studies, the effect sizes were directly combined, while for two-arm studies, the effect sizes were combined as standardized mean differences (SMD) or weighted mean differences (WMD), and their 95% confidence intervals were calculated. Publication bias was assessed using a funnel plot, which visually represents the potential bias in the publication of studies. Sensitivity analysis was conducted to evaluate the stability of the study results. A significance level of $P < 0.05$ was considered statistically significant for all studies.

Subgroup analysis According to the sub-group analysis based on patient age (≤40 years or ≥40 years), treatment modality (HIFU alone or HIFU combined with GnRH-a and/or LNG-IUS), NPV% (≤70% 0r≥70%), uterine volume (<10weeks gestation or ≥10weeks gestation), and lesion size (diameter ≤6cm or 26cm), the pregnancy rates were evaluated.

Sensitivity analysis Publication bias was assessed using a funnel plot, which visually represents the potential bias in the publication of studies. Sensitivity analysis was conducted to evaluate the stability of the study results. A significance level of $P < 0.05$ was considered statistically significant for all studies.

Country(ies) involved China.

Keywords HIFU, Adenomyosis, Pregnancy.

Contributions of each author

Author 1 - Yishan Chen - The author provided statistical expertise and drafted the manuscript.
Email: ys.chen@outlook.com
Author 2 - Zhenhong Wang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 3 - Xi Xie - The author read and provided feedback.
Author 4 - Jingsong YI - The author read and provided feedback.
Author 5 - Shunhe Lin - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 6 - Sun-Wei Guo - The author provided statistical expertise and approved the final manuscript.
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