

A large-scale, prospective cohort study on the association between treatment management models and the prognosis of intrauterine adhesions.

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Research Proposal Summary

Trial Title: A Large-Scale, Prospective Cohort Study on the Association Between Treatment Management Models and Prognostic Factors of Intrauterine Adhesions

Research Objective: This project aims to explore the efficacy of the new IUA treatment model through a multi-center real-world study and demonstrate its high-quality medical service model, laying the foundation for its future promotion.

Experimental Design: Based on previous research, our team proposed a "new model for the whole-course management and treatment of IUA": preoperative four-dimensional color ultrasound diagnosis and assessment, intraoperative "immediate diagnosis and treatment" cold knife plowing- style adhesion separation using an integrated hysteroscope, postoperative application of a patented intrauterine stent to prevent re-adhesion, postoperative adjuvant therapy with renowned doctors and prescriptions to promote endometrial repair, postoperative four-dimensional color ultrasound assessment and follow-up to replace multiple hysteroscopy examinations, and combined with intraoperative hysteroscopic AI counting of endometrial gland openings and gland density, multimodal data fusion to predict and assess pregnancy prognosis after IUA treatment.

Experimental Procedure: Prospective, Observational Real- Event Study

Selection criteria:

Patients with intrauterine adhesions diagnosed and treated at our hospital and the branch centers of this project: aged 18-45 years; collection began after ethical review was approved, with a total of 5,000 cases collected, of which 2,000 cases were collected by our center.

Exclusion criteria:

Patients with abnormal ovarian function, male infertility, and inability to cooperate with diagnosis, treatment, and follow-up.

Statistical methods: A super-resolution IUA ultrasound image enhancement algorithm based on transfer learning was used. Lesions in the reproductive terminal chain (ovary, follicle, uterus, endometrium, myometrium- mesenchymal junction, and fallopian tubes) were annotated on the enhanced 3D ultrasound images. Based on the enhanced 3D ultrasound image features of the IUA reproductive terminal chain from the second part of the study, and the multimodal large dataset from the first part

of the study, multimodal data feature extraction and fusion were achieved using deep learning and natural language processing techniques to realize automatic detection of IUA clinical subtyping, thereby constructing an AI-based IUA classification and grading algorithm.

Research Text

1. Research Background

1.1 Preoperative diagnosis of intrauterine adhesions

There is currently a consensus on the diagnosis and assessment of intrauterine adhesions. The gold standard is hysteroscopy ^[4]. The existing IUA severity scoring standards are all based on hysteroscopic findings. Commonly used scoring standards include the American Fertility Society (AFS) (1988) score ^[5]. The European Society of Gynecological Endoscopy (ESGE) (1998) score ^[6], the March (1978) score ^[7] and the Chinese expert consensus on the clinical diagnosis and treatment of intrauterine adhesions published in 2015 ^[8]. However, hysteroscopy is an invasive examination that depends on the surgeon's skill and subjective impression ^[6]. When the cervical canal, the lower segment of the uterine cavity, or even the uterine cavity is completely closed, hysteroscopy may fail, and the condition of the uterine cavity cannot be fully assessed. It may even cause uterine perforation. In IUA patients with reproductive tract malformations such as unicornuate uterus, it is difficult to determine the correct shape of the uterine cavity under hysteroscopy. Hysteroscopic distension fluid may cause water intoxication. Furthermore, the above limitations, such as the need for anesthesia and high cost, limit its use as a routine screening for intrauterine adhesions. Currently, a large number of studies have demonstrated that four-dimensional ultrasound has a high accuracy in diagnosing intrauterine adhesions. Correlation analysis with hysteroscopy results shows that four-dimensional ultrasound diagnosis of intrauterine adhesions is consistent with hysteroscopy results ^[6]. Studies have also confirmed that multiple ultrasound parameters can accurately screen for intrauterine adhesions ^[7]. Menstrual status, number of intrauterine procedures, uterine cavity morphology, endometrial continuity, endometrial homogeneity, endometrial-myolipin boundary, endometrial blood flow, peristaltic waves, etc. can all be used as evaluation criteria for diagnosing intrauterine adhesions ^[7-8].

1.2 Surgical treatment of intrauterine adhesions

Since the advent of hysteroscopy, the surgical approach for IUA has gradually

shifted from traditional open surgery, blind curettage, and cervical dilation to... TCRA has become the preferred treatment for IUA . At present, there is still controversy in the clinical practice regarding whether to use energy devices in TCRA. Scholars who support the application of energy devices in TCRA believe that its advantages are simple operation, short operation time, and obvious effects on tissue cutting and hemostasis of bleeding points during operation. However, when energy devices cut the surgical area, the heat released by them can damage the surrounding normal endometrial tissue ^[24] . Non-energy devices mainly use various types of micro forceps and micro scissors to separate and loosen the adhesions in the uterine cavity through blunt and sharp separation, so as to restore the shape of the uterine cavity. This method does not release heat and there is no possibility of thermal damage to the remaining endometrium in the uterine cavity. In order to try to improve the efficacy of traditional cold knife method for TCRA, cold knife plowing- style intrauterine adhesion separation was proposed and gradually began to be used in clinical practice ^[23] . The cold-blade plowing technique , similar to plowing a field, longitudinally severs adhesions and scar tissue within the uterine cavity, exposing the underlying myometrium and any remaining endometrial tissue. Under postoperative medication stimulation, the endometrium has room to grow, and the blood supply from the myometrium can extend upwards to the endometrial layer, improving endometrial blood flow. This is consistent with the approach used by Sun Kun et al. ^[32] This aligns with the view that endometrial volume is related to blood flow parameters. Furthermore, the longitudinal plowing method reduces surgical trauma, which may decrease the likelihood of bleeding and TURP syndrome. Relieving uterine contractions after scar plowing can increase uterine cavity volume, creating more space for endometrial growth .

1.3 Research on Anti-Adhesion Barriers

Since intrauterine adhesions may cause obstruction of menstrual flow, leading to abdominal pain, amenorrhea, and decreased fertility in women of childbearing age, surgical treatment is usually required for patients with intrauterine adhesions who have obstructed menstrual flow and desire to have children. However, after surgery, the wounds separated in the uterine cavity are exposed, and they may still adhere again

after contact, leading to recurrence of adhesions. Therefore, some barriers are needed after surgery to separate the wounds and prevent recurrence of adhesions 错误!未找到引用源。, 错误!未找到引用源。. Over the years, scholars have conducted studies on intrauterine anti-adhesion barriers for intrauterine adhesions, either individually or in different combinations. The most commonly used are intrauterine devices (IUDs), hyaluronic acid gel, Foley catheters, intrauterine balloons, and amniotic membrane transplantation 错误!未找到引用源。, 错误!未找到引用源。. Although efforts have been made to prevent recurrence after surgery, most current research results show that the adjuvant treatment after intrauterine adhesion separation is not effective. In view of this, a new medical silicone rubber material was processed into a uterine cavity-shaped stent, which is specifically used for the postoperative adjuvant treatment of intrauterine adhesions. After nearly 10 years of effort, we have successfully designed and developed a new type of silicone device (called an intrauterine stent) that can theoretically prevent the recurrence of intrauterine adhesions through the physical barrier effect, and applied for patent protection 错误!未找到引用源。. It is made of medical silicone rubber, which is non-irritating to human tissues, has no toxic side effects, is non-carcinogenic, has good biocompatibility, is corrosion resistant, will not swell, soften, or deteriorate due to water absorption, is easy to process and manufacture, is convenient to use, and has good thermal stability. The uterine support mainly consists of a reinforcing ring, a membrane, a tail-shaped structure, and a placement device. The placement device comprises a placement cannula, a positioning block, and a push rod. It is made of medical-grade silicone rubber. The reinforcing ring is elastic, and its shape and size conform to the periphery of the uterine wall. Three drainage grooves are located at the lower end of the reinforcing ring, which facilitates the drainage of intrauterine fluid and reduces the chance of intrauterine infection due to poor drainage. The membrane completely separates the anterior and posterior walls of the uterine cavity, physically preventing adhesions between them. Furthermore, because the membrane is very thin, it exerts almost no pressure on the endometrium it contacts. The tail-shaped structure is primarily responsible for preventing adhesion recurrence. This longitudinal, solid structure connects to the midpoint of the lower segment of the ring and communicates

with the uterine cavity. Its length can be trimmed according to the patient's specific situation, effectively preventing adhesions in the lower segment of the uterine cavity and the internal cervical os, while maximizing material savings, reducing manufacturing costs, and providing better drainage of intrauterine fluid.

1.4 Famous doctors and prescriptions as adjunctive treatment for intrauterine adhesions

Endometrial damage is the main cause of uterine secondary infertility, and how to repair the damaged endometrium has always been a research bottleneck. Intrauterine adhesions can lead to sparse endometrium, low cell proliferation, insufficient response to estrogen, and inability to fully proliferate and repair ^[26]. An immunohistochemical study to detect the expression of estrogen receptors in the endometrium found that the expression of estrogen receptors in the proliferative and secretory phase thin endometrial stromal cells was significantly lower than that in normal endometrium ^[27-29]. Therefore, high doses of estrogen have limited effect on promoting endometrial growth ^[30]. From the perspective of traditional Chinese medicine, the proliferation of endometrium in intrauterine adhesions is closely related to the strength and weakness of kidney essence and kidney qi. Modern research has confirmed that kidney-tonifying Chinese medicine can significantly increase uterine blood supply by promoting blood circulation in the internal reproductive organs, thereby improving the receptivity of the endometrium, increasing the affinity of target tissue estrogen receptors, promoting endometrial proliferation, and improving secretory function ^[31]. In addition, kidney-tonifying Chinese medicine increases the weight of the uterus in experimental animals, significantly thickens the endometrium, increases the number of endometrial gland openings, shows a secretory tendency, and increases the content of estrogen and progesterone receptors in the endometrium. Kidney-tonifying Chinese medicine has an endocrine hormone-like effect, which can improve the low estrogen environment in the uterine cavity ^[32,33]. Professor You Zhaoling believes that kidney deficiency and blood stasis are the main causes, and uses kidney-tonifying and blood-activating Chinese medicine to nourish the endometrium, thereby improving the overall environment of the endometrium ^[57]. Modern medical research

shows that the application of Chinese medicine to tonify the kidney can promote blood circulation in the internal reproductive organs, increase blood supply to the uterus, significantly improve endometrial receptivity, and increase the affinity of target tissue estrogen receptors, causing endometrial proliferation and transformation to the secretory phase ^[60].

1.5 Post-IUA infertility seriously affects my country's fertility rate

A study published in **The Lancet** indicates a continued decline in global fertility rates, with an average infertility rate of 10%-16%, reaching as high as 18% in China. In China, intrauterine adhesions (IUA) account for 22.0% of female infertility cases, making it a "characteristic disease" of the country. IUA involves endometrial damage and fibrosis. Even after adhesion separation surgery, endometrial repair remains poor, and re-adhesion is common. The lack of early detection and prevention leads to an infertility rate as high as 40%-60% (including infertility and miscarriage treated with Western medicine). Given the national commitment to improving fertility, preventing infertility after IUA surgery is of great significance. Therefore, it is urgent to develop accurate risk prediction models to identify high-risk groups and provide prevention and control guidance. Our team has achieved near-adhesion-free uterine cavity after the last IUA surgery through surgical technique innovation and the clinical application of a patented intrauterine stent. However, postoperative estrogen therapy to promote endometrial recovery is ineffective, resulting in poor endometrial receptivity and a high rate of re-adhesion, leading to a high infertility rate. Currently, scoring criteria for predicting pregnancy outcomes after intrauterine adhesions (IUA) are based on indicators such as the morphology, extent, and type of adhesions observed under hysteroscopy, resulting in poor predictive efficacy. Furthermore, there is a lack of research on predicting post-IUA infertility risk using Traditional Chinese Medicine (TCM). Professor You Zhaoling, a nationally renowned TCM practitioner, guided a research group to use transvaginal three-dimensional ultrasound to analyze endometrial receptivity after IUA and developed a TCM-based treatment plan for IUA and a post-operative TCM management system, which can effectively improve the success rate of conceiving after IUA and provide insights for the prediction and prevention of post-IUA infertility.

However, the characteristics of post-IUA three-dimensional ultrasound images are highly variable and easily affected by machine noise and physician diagnostic experience; how to accurately extract image features is a bottleneck in its application. The information from the four diagnostic methods of TCM is complex, and how to simplify complex information is a challenge for its use in prediction. The integration and enhancement of multidimensional TCM and Western medicine risk factors is a key challenge in establishing a post- IUA infertility risk prediction model. Machine learning technology holds promise for solving these bottlenecks.

2. Research Objectives

2.1 To reveal the intrinsic relationship between three-dimensional ultrasound image characteristics and diagnosis and prognosis in the IUA population;

2.2 Multicenter clinical studies have confirmed the clinical efficacy of the cold knife plowing technique and uterine stent in preventing adhesions;

2.3 Standardize treatment plans for renowned doctors and prescriptions to promote endometrial growth and maintain pregnancy and assist in conception, and confirm their clinical efficacy;

2.4 Construct and validate a multidimensional infertility risk factor prediction model based on integrated traditional Chinese and Western medicine after IUA, and visualize it for easy application;

3. Research Design

3.1 Establish four-dimensional ultrasound diagnostic evaluation standards

A super-resolution model for enhancing 3D ultrasound images was trained using transfer learning across multiple tasks, and its parameters were fine-tuned to obtain a super-resolution model capable of enhancing IUA 3D ultrasound image features. Lesions in the reproductive terminal chain (ovary, follicle, uterus, endometrium, myometrium-mesenchymal junction, and fallopian tubes) were annotated on the enhanced 3D ultrasound images , resulting in a large-scale, precisely annotated IUA 3D ultrasound image dataset. Using this dataset and object detection algorithms in artificial

intelligence, automatic and accurate detection of lesions in the reproductive terminal chain can be achieved, thus enabling accurate diagnosis of IUA 3D ultrasound. Furthermore, a scoring standard was constructed based on the characteristic indicators of endometrial receptivity assessed by 4D ultrasound.

3.2 Standardize IUA diagnosis and treatment data and build a large database and data queue

To strengthen the standardization and normalization of integrated traditional Chinese and Western medicine (TCM) diagnosis and treatment, and addressing the current lack of unified standards for IUA (Intrauterine Adnexation) medical data , this project pioneered the development of the "Expert Consensus on Integrated TCM and Western Medicine Diagnosis and Treatment of IUA." This consensus standardizes preoperative diagnosis, preoperative TCM conditioning, surgical procedures, postoperative TCM treatment, and pregnancy guidance for IUA, and has been disseminated and promoted nationwide. A national-level big data platform has been established, relying on TCM clinical research bases and national regional obstetrics and gynecology medical centers. The database is constructed in two parts: based on established multi-dimensional data standards , previous IUA data (including images) is collected and cleaned, and clinical information data extraction and storage methods are improved to establish a systematic, structured, and standardized integrated TCM and Western medicine IUA big data database across multiple centers ; simultaneously, regional medical centers connect the information systems of hospitals within the network region to the medical center through the data platform, providing real-time monitoring and follow-up , and contributing to the establishment of an IUA cohort dataset.

3.3 Evaluate the clinical efficacy of the new integrated traditional Chinese and Western medicine treatment model for IUA through real-world research.

This project conducts prospective and retrospective studies by systematically collecting real-world data and utilizing practical clinical trials. Based on a large database of integrated traditional Chinese and Western medicine treatments for IUA (Intrauterine Adhesion) patients, it compares the clinical efficacy of the new treatment

model with the traditional model. The "New Model for IUA Whole-Process Management and Treatment" includes: preoperative 4D ultrasound diagnosis and assessment; intraoperative "immediate diagnosis and treatment " cold-knife plowing-style adhesion separation using an integrated hysteroscope; postoperative application of a patented uterine stent to prevent re-adhesion; postoperative adjuvant therapy with renowned doctors and prescriptions to promote endometrial repair; postoperative follow-up using 4D ultrasound assessment instead of multiple hysteroscopy examinations; and combining intraoperative hysteroscopic AI counting of endometrial gland openings and gland density, multimodal data fusion to predict and assess pregnancy prognosis after IUA treatment.

3.4 Constructing a Predictive Model for Post-IUA Infertility Risk Based on Machine Learning Integration and Enhancement of Multidimensional Risk Factors from Traditional Chinese and Western Medicine

Potential risk factors were extracted from the post-IUA cohort in the second part of the study and standardized. A predictive factor system was constructed by combining four-dimensional image feature variables and TCM syndrome element variables, and pregnancy outcomes were analyzed after two years of follow-up following IUA . Two machine learning algorithms, Logistic Regression and XGBoost , were used to establish the predictive model . The Logistic Regression model used stepwise regression to select variables, and the final predictive factors were determined by comprehensively considering the minimum Akaike information criterion, Bayesian information criterion, and clinical significance. The XGBoost model used the Boruta algorithm to select the final predictive factors. After model establishment, internal and external validations were performed. The predictive performance of the models was compared and evaluated in terms of discrimination and calibration. Finally, the models were visualized and applied using nomograms, an app, or a webpage.

4. Research Content

4.1 Collect IUA diagnosis and treatment data and build a large database and data queue

Under the leadership of Professors Xu Dabao and You Zhaoling , a consensus among experts in both traditional Chinese medicine and Western medicine with extensive experience in the diagnosis and treatment of IUA (Intrauterine Adnexation) was jointly developed , outlining the "Expert Consensus on the Integrated Traditional Chinese and Western Medicine Treatment of IUA." This consensus standardizes IUA diagnostic methods and criteria, surgical procedures , traditional Chinese medicine treatment plans, and pregnancy guidance protocols , and is being promoted through clinical training demonstration bases and academic conferences . Relying on the platform of the Traditional Chinese Medicine Clinical Research Base and the National Regional Medical Center for Obstetrics and Gynecology , a big data platform for integrated traditional Chinese and Western medicine diagnosis and treatment has been established. This platform collects IUA diagnosis and treatment data (including imaging data) from IUA-specific alliance units, with Xiangya Third Hospital of Central South University as the chair unit . The data is then recorded and stored in a standardized and structured manner , serving as modeling indicators for the integrated traditional Chinese and Western medicine diagnosis and treatment decision- making system for IUA . By collecting image data from examinations, textual data from Western medicine surgeries and TCM treatment cases, and numerical data from laboratory tests in IUA's integrated traditional Chinese and Western medicine treatments through a big data platform , we first retrospectively collected treatment data from each alliance unit from 2017 to 2022, performed structured storage and cleaning, and completed follow-up to establish a training dataset. Then, we continuously completed high-quality prospective data collection, established the IUA Integrated Traditional Chinese and Western Medicine Treatment Center's official WeChat account, and enabled patient follow-up, real-time storage, export and analysis , real-time efficacy assessment and fertility measurement and evaluation, and established a test dataset for the decision-making model. We continuously expand the sample size to collect treatment data more comprehensively.

The big data platform of the Traditional Chinese Medicine Clinical Research Base and the National Regional Medical Center for Obstetrics and Gynecology encompasses health data from over 50 gynecological specialty alliance units nationwide,

including Xiangya Third Hospital of Central South University, the First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, Xiangya Hospital of Central South University, Xiangya Second Hospital of Central South University, Hunan Provincial Maternal and Child Health Hospital, and Hunan Provincial People's Hospital. Based on the existing IUA case database, IUA patients from the past two years were retrospectively screened. Most of these patients underwent transvaginal 3D ultrasound follow-up on days 20-24 of their menstrual cycle one month after surgery. More than 5,000 IUA patients with relatively complete information were identified, sufficient for subsequent machine learning modeling needs. Furthermore, patients within the past two years could clearly recall their disease, making the retrospective investigation and supplementary data reliable. Data was collected on individual patient information, family history, lifestyle, past medical history, marital and reproductive history, clinical symptoms, clinical diagnosis, laboratory test results, treatment methods, postoperative 3D ultrasound images, male partner fertility-related information, and TCM syndromes. (This project involves the collection and analysis of clinical medical records of IUA patients, **which has been approved by the Ethics Committee of the chair unit, Xiangya Third Hospital of Central South University, and filed with the alliance units** .) Data underwent standardization, cleaning, and outlier/ missing value handling . Simultaneously, unified follow-up standards and evaluation mechanisms were established to strengthen follow-up examinations and monitoring of the cohort population, forming a comprehensive monitoring and follow-up system. Follow-up efforts were intensified, with reproductive follow-ups conducted every 3 months, utilizing multiple channels such as WeChat, telephone, and Douyin (TikTok) to improve timeliness. Pregnancy outcomes were followed up two years after the start of conception . Multi-center clinical diagnosis and prognostic information collection was completed, constructing a multi-center IUA cohort for Chinese women.

4.2 Evaluate the clinical efficacy of the new integrated traditional Chinese and Western medicine treatment model for IUA through real-world research.

Real-world research involves systematically collecting real-world data and employing appropriate design and analytical methods to conduct prospective or

retrospective studies. This project, based on the IUA's integrated traditional Chinese and Western medicine treatment database, compares the clinical efficacy of new and traditional treatment models through practical clinical trials (PCTs). PCTs, also known as practical clinical trials or efficacy clinical trials, are clinical trials that closely resemble real-world clinical practice. They are a type of research between traditional randomized controlled trials (RCTs) and observational studies, and fall under the category of interventional research.

IUA (Intrauterine Adhesion) treatment model utilizes the CTM platform , where nine teams sequentially manage six key stages: pre - TCRA (Transcervical Resection of Adhesion) procedures, TCRA procedures, post- TCRA procedures, pre - pregnancy period , pregnancy , and perinatal period, achieving integrated traditional Chinese and Western medicine management of intrauterine adhesions throughout the entire course of the disease. **Pre-TCRA :** For examination, the ultrasound imaging department uses the American GE-E10 4D color Doppler ultrasound to assess the uterus, ensuring clear and intuitive visualization while minimizing intrauterine manipulation and damage. For treatment, the gynecology department, based on a detailed assessment and prediction of the disease and complications, decides on the treatment / surgical plan. For conditioning, pre-operatively, patients take Professor You Zhaoling's exclusive traditional Chinese medicine formula " Gongzhan No. 1 " to promote blood circulation, remove blood stasis, and condition the endometrium, creating favorable conditions for intrauterine adhesion separation. **TCRA Procedure :** The first surgery for intrauterine adhesions is particularly important. Because during the first surgery, the patient's uterine anatomy is natural; if the surgical anatomical layers are incorrect, even by only a few millimeters, it is very difficult to correct in later surgeries. Professor Xu Dabao, the project leader, performed a " cold knife " precision adhesiolysis procedure to separate intrauterine adhesions, avoiding damage to the endometrium while separating them. Post - operatively, a patented uterine stent was placed in the uterine cavity to reduce the incidence of re-adhesion, achieving both treatment and protection. **Post- TCRA surgery :** During the golden recovery period, a combination of traditional Chinese and

Western medicine treatments continued. The gynecology department provided precise medication based on the cause and individual differences; the traditional Chinese medicine department used the You family's secret formula " Gongzhan No. 1 " to promote endometrial repair, reduce scar fibrosis, lower the re-adhesion rate , and provide sufficient nutrition for uterine repair. **During the pre-conception period:** The genetics and laboratory departments conducted necessary medical genetic testing and prenatal diagnosis to improve pregnancy and birth rates, ensuring the embryo " grows well " after conception ; the andrology department screened for male diseases that might be caused by embryonic factors leading to miscarriage or infertility, addressing conditions such as asthenospermia, teratospermia , oligospermia, and delayed or non-liquefied semen; the infertility department provided precise intervention and scientific guidance for infertility, helping patients achieve pregnancy as soon as possible . **Pregnancy and perinatal period:** Integrating personalized treatment based on syndrome differentiation, we conduct scientific and precise full-course management of pregnancy maintenance . The team proposes a differentiated and step-by-step approach, followed by a two-step approach to pregnancy maintenance, which effectively improves embryo implantation rate and clinical pregnancy success rate. Through meticulous and comprehensive diagnosis and treatment, we address the underlying causes of maternal problems, regulate maternal hormone levels, improve maternal physical condition, and help the fetus develop healthily.

4.3 Based on machine learning, a multidimensional risk factor prediction model for post-IUA infertility was constructed and validated by integrating traditional Chinese and Western medicine.

By reviewing domestic and international literature on risk factors for infertility after intrauterine device (IUA) surgery, and combining the characteristics of traditional Chinese medicine (TCM) and Western medicine clinical risk factors for IUA infertility in Chinese patients, this study, based on the IUA integrated TCM and Western medicine cohort data constructed in Part I, standardized the data and established a multi-dimensional candidate variable dataset that may be related to IUA infertility. This dataset included multi-dimensional TCM and Western medicine diagnostic and

treatment data such as age, lifestyle, family history, laboratory tests, surgical details, male partner's semen and sexual activity, 3D ultrasound image feature combinations, and TCM syndrome combination variables. Follow-up results for the corresponding population, i.e., pregnancy outcomes two years after surgery, were also collected. This study used two machine learning methods to construct IUA infertility risk prediction models: traditional logistic regression and XGBoost. The logistic regression model used stepwise regression to screen variables, combining the least Akaike information criterion, Bayesian information criterion, and clinical significance to determine the final predictive factors included in the model. After determining the predictive factors, a logistic regression equation was used to establish a predictive model to predict the probability of IUA infertility. The effect of the predictive factors was reflected by the regression coefficient or OR value and its 95% CI. After model establishment, multicollinearity tests were performed. Multicollinearity is assessed using the correlation coefficient method/variance inflation variable. Strong collinearity among variables can severely impact the model's generalization ability. XGBoost, short for "Extreme Gradient Ascent," is an ensemble machine learning algorithm based on decision trees and using a gradient boosting framework. It employs the Boruta algorithm to select the final predictive factors for inclusion in the model. The importance of predictive factors is reflected by the SHAP (Shapley Additive Explanation) value; a higher SHAP value indicates a more important predictive factor. The resulting model combines a Logistic Regression model and an XGBoost model to predict infertility risk after IUA (Intrauterine Access) surgery.

5. Key Evaluation Indicators

This study employed both internal and external validation methods for model evaluation. Internal validation used a validation set derived from the same source as the training set to assess model reproducibility. This study used a random split validation approach, randomly dividing the dataset into training and validation sets in a 7:3 ratio. The training set data was used to build the model, and the validation set data was used to evaluate model performance. External validation used a prospective dataset collected based on the IUA data platform. The predictive performance of both the Logistic Regression and XGBoost models for predicting post-IUA infertility risk was compared

and evaluated in terms of discriminability and calibration. The Area Under the Receiver Operating Characteristic (AUC) was used for evaluation; a higher AUC value indicates higher discriminability. The DeLong 's test was used to compare the AUC values of the two models to determine statistical significance. The Brier score was used to plot the calibration curve, and the Hosmer- Lemeshow goodness-of-fit test was used to assess model calibration and plot the calibration curve. Finally, to promote the application of predictive models, the Logistic regression model for predicting infertility risk after IUA is visualized using a nomogram, and the Youden index is calculated using the ROC curve method. The optimal cutoff value for the total score of the nomogram is then derived based on the Youden index. The XGBoost model for predicting infertility risk after IUA is presented in an app/webpage format. Two different predictive models are provided for selection in both traditional Chinese medicine and Western medicine clinical practice.

6. Safety considerations

Surgical risks, anesthesia risks, etc.

7. Statistical Analysis Plan (SAP)

A super-resolution IUA ultrasound image enhancement algorithm based on transfer learning was developed. Lesions in the reproductive terminal chain (ovary, follicle, uterus, endometrium, myometrium- mesenchymal junction, and fallopian tubes) were annotated on the enhanced 3D ultrasound images. Based on the enhanced 3D ultrasound image features of the IUA reproductive terminal chain from the second part of the study, and the multimodal large dataset from the first part of the study, deep learning and natural language processing technologies were combined to achieve multimodal data feature extraction and fusion, enabling automatic detection of IUA clinical subtyping, thus constructing an AI-based IUA classification and grading algorithm. Two machine learning methods were used to construct a predictive model for post-IUA infertility risk: traditional logistic regression and XGBoost . The logistic regression model used stepwise regression to screen variables, combining the minimum Akaike information criterion, Bayesian information criterion, and clinical significance to determine the final

predictive factors included in the model. After determining the predictive factors, a predictive model was established using the logistic regression equation to predict the probability of post-IUA infertility. The effect of the predictive factors was reflected by the regression coefficient or OR value and its 95% CI. After model establishment, multicollinearity tests were performed. Multicollinearity is assessed using the correlation coefficient method/variance inflation variable. Strong collinearity among variables can severely impact the model's generalization ability. XGBoost, short for "Extreme Gradient Ascent," is an ensemble machine learning algorithm based on decision trees and using a gradient boosting framework. It employs the Boruta algorithm to select the final predictive factors for inclusion in the model. The importance of predictive factors is reflected by the SHAP (Shapley Additive Explanation) value; a higher SHAP value indicates a more important predictive factor. The resulting model combines a Logistic Regression model and an XGBoost model to predict infertility risk after IUA (Intrauterine Access) surgery.

8. Data integrity and quality assurance

Researchers should ensure that data is authentic, accurate, complete, and traceable, and should ensure the integrity of basic clinical research documents during retention, avoiding intentional or unintentional alteration or loss.

9. Ethical Statement

The clinical research will adhere to the relevant regulations of the World Medical Association's Declaration of Helsinki and the Ethical Review Guidelines for Biomedical Research Involving Human Subjects. The research protocol will be approved by the ethics committee before the clinical research can commence. The privacy of research participants and the confidentiality of data will be protected throughout the research process.

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