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Original Research

Effect of Mifepristone Preconditioning on Stress Response and Sex Hormone Levels after Combined Laparoscopic Treatment for Cesarean Scar Pregnancy: A Prospective Randomized Trial

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Abstract

Background: This study aimed to explore the effect of mifepristone pretreatment on stress response and sex hormone levels after combined laparoscopic treatment for cesarean scar pregnancy. **Methods**: We conducted a prospective, randomized, controlled study from January 2020 to September 2022. A total of 98 pregnant women with cesarean scar pregnancy were included and divided into two groups by the random number table method. The control group received hysteroscopy combined with laparoscopy treatment, and the observation group received mifepristone pretreatment before hysteroscopy, combined with laparoscopy treatment. The surgical efficacy, surgical indices, menstrual recovery time, postoperative residual muscle layer, and scar morphology were observed and evaluated. The ovarian hemodynamic indices, stress indices, and sex hormone levels were measured, and the incidence of complications such as postoperative infection and liver function impairment was calculated. **Results**: There was no significant difference in the surgical success rate between the two groups (97.96% *vs* 95.92%), as well as the thickness and proportion of residual muscle layer, the width, length, and depth of scars, and the incidence of postoperative complications ($p > 0.05$). Combined mifepristone pretreatment reduced intraoperative bleeding, shortened the average time for beta human chorionic gonadotropin (β-hCG) to fall to negative (20.5 days, $p < 0.05$) and vaginal bleeding (19.8 days, $p < 0.05$), lowered Vmax (49.8 cm/s, $p < 0.05$), and elevated resistance index (RI) (0.7, $p < 0.05$) and pulsatility index (PI) (2.5, $p < 0.05$). Moreover, combined mifepristone pretreatment reduced C-reactive protein (CRP: 8.1 mg/L, $p < 0.05$), cortisol (COR: 21.7 mg/L, $p < 0.05$), adrenocorticotropic hormone (ACTH: 40.2 ng/L, $p < 0.05$), as well as progesterone (P: 10.2 mmol/L, $p < 0.05$), luteinizing hormone (LH: 13.2 µg/L, $p < 0.05$), and follicle-stimulating hormone (FSH: 14.8 µg/L, $p < 0.05$). Combined mifepristone pretreatment promoted the recovery of menstruation (25 days, $p < 0.05$). **Conclusion**: Mifepristone pretreatment can promote postoperative recovery, reduce postoperative stress response, improve hemodynamics, regulate sex hormone levels, and promote the early recovery of menstruation in patients with cesarean scar pregnancy. **Clinical Trial Registration**: The study was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn), registration number: ChiCTR1800015514.

Keywords: mifepristone; hysteroscopy; cesarean scar pregnancy; stress response; sex hormone

1. Introduction

Cesarean scar pregnancy is mainly caused by muscle injury at the incision site of the previous cesarean section [1]. If the embryo continues to develop in the scar, it may cause uterine rupture in the early gestation period or complications, such as embryo preconception and late abortion in the middle and late stages, which seriously threaten the life safety of patients [2]. Hysteroscopy combined with laparoscopic debridement can directly observe the intrauterine conditions, determine the size of the gestational sac in the scar and the richness of blood flow in the surrounding tissue, and reduce endometrial damage. It has been reported in the past that Western medicine pretreatment before uterine laparoscopic therapy can effectively improve surgical efficacy and prognosis [3]. Mifepristone is an antiprogesterone drug with antiglucocorticoid activity, which can produce an antagonistic effect on progesterone and block the effect of progesterone, contributing to the shedding of gestational sac and intrauterine induction of fetal death, which is conducive to the implementation of gestational sac removal [4,5]. Mifepristone can effectively inhibit the development of follicles and promote embryo apoptosis, and has a significant curative effect on abnormal uterine bleeding [6]. Based on this, the purpose of this study was to explore the effects of mifepristone preconditioning on stress response and sex hormone levels after hysteroscopy combined with laparoscopy of cesarean scar pregnancy, so as to provide a reference for the clinical treatment of this disease.

2. Data and Methods

2.1 Clinical Data

The number of samples was calculated with Type I errors in hypothesis testing (Unilateral) $\alpha = 0.05$ and Class II error $\beta = 0.2$. By comparing the sample size of two sets of mean noninferiority, the main observation objective is the

Table 1. Clinical data.

Items	Observation group (n = 49)	Control group (n = 49)	*t*	*p*
Age (years)	30.02 ± 3.45	30.27 ± 3.69	0.346	0.73
Gestational age (weeks)	13.17 ± 2.19	13.40 ± 2.43	0.492	0.624
Number of previous cesarean sections	1.34 ± 0.28	1.31 ± 0.25	0.559	0.577
Number of deliveries	1.79 ± 0.27	1.73 ± 0.22	1.206	0.231
Number of pregnancies	2.31 ± 0.52	2.37 ± 0.59	0.534	0.595
Time between cesarean sections (years)	3.09 ± 0.57	3.17 ± 0.52	0.726	0.47
Duration of menstruation (d)	55.85 ± 6.20	55.17 ± 6.34	0.537	0.593
Focal diameter (cm)	5.03 ± 1.14	5.21 ± 1.07	0.806	0.422

time when beta human chorionic gonadotropin (β-hCG) recovers to negative, Margin, $\Delta = -1$. The minimum sample size is 41 cases per group. In our study, the sample size was appropriately expanded to 49 cases per group.

98 parturients with cesarean scar pregnancy from January 2020 to June 2022, and the study was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn), with the Clinical Trial Number: ChiCTR1800015514. The patients were included as research objects and divided into two groups by the random number table method, which is to input all patients' names and other information into Excel and use the Rand function of Excel to randomly generate integers to divide patients into two groups. Clinical data included age, pregnancy age, number of previous cesarean sections, delivery quantity, number of pregnancies, cesarean section interval, duration of menstruation, and focus diameter.

2.2 Inclusion Criteria

① Patients met the diagnostic criteria related to cesarean section scar pregnancy [7]; ② Patients gave informed consent and signed the consent form; ③ Patients received hysteroscopy combined with laparoscopy.

2.3 Exclusion Criteria

① Patients had severe cardiac, liver, and renal dysfunction; ② Patients had reproductive system neoplasms; ③ Patients were at risk of massive bleeding; ④ Patients had contraindications to taking mifepristone (mainly including acute pelvic inflammation, intrauterine device pregnancy, suspected ectopic pregnancy, and allergic constitutions); ⑤ Patients had previous cesarean scar pregnancy surgical treatment history.

2.4 Methods

A prospective randomized controlled trial was performed. The control group was treated with hysteroscopy combined with laparoscopy. The specific operations are as follows: Hysteroscopic surgery (TC200, KARL STORZ Hysteroscopic System, Tuttlingen, Germany) was performed with the patient in a lithotomy position. Hysteroscope was implanted after lumbar epidural anesthesia and pushed into the uterine floor. After comprehensive scanning, the location and size of the lesion were determined, and then the pregnancy sac tissue was removed. The position of the primary gestational sac was observed after removal. At the same time, carbon dioxide pneumoperitoneum was established through umbilical puncture, and 5 mm surgical holes were opened in the upper edge of pubic symphysis and the left and right lower abdominal McBurney's point respectively. A 5 mm 30° laparoscope (TC200, KARL STORZ Laparoscopic System, Tuttlingen, Germany) was introduced through the umbilicus. After determining the location of the lesion through the vagina, hysteroscopy was removed, and instruments were placed to open the uterine bladder and fold the peritoneum, fully exposing the lower uterine segment, and the lower uterine segment was sutured after the lesion was removed by ultrasonic knife (FS-1000-RF, Misonix, Long Island, NY, USA).

The patients in the observation group were treated with mifepristone (H10950004, China Resources Zizhu Pharmaceutical Co., LTD., Beijing, China) and hysteroscopy + laparoscopy (TC200, KARL STORZ, Tuttlingen, Germany). Five days before the operation, 20 mg mifepristone was given orally, twice a day, for consecutive five days. Hysteroscopy combined with laparoscopy was the same as that of the control group.

2.5 Outcome Measures

(1) Criteria related to successful operation: abdominal pain disappeared, vaginal bleeding significantly decreased or disappeared within 2 weeks after the operation, and blood β-hCG level decreased to negative one month after the operation. (2) Operation-related indices: operation time (from the time the anesthesia starts, until the patient leaves the operating room as recorded by the anesthesiologist), intraoperative blood loss (for every 10 d/L decrease in hemoglobin, approximately 400–500 mL of blood is lost), time required for serum β-hCG to fall to negative, vaginal bleeding time, hospital stay, and menstrual recovery time. (3) Hemodynamic indices were measured 7 days before surgery, 1 day after surgery, and 3 days after surgery: the ovarian blood flow indices (Vmax, resistance index (RI) and pulsatility index (PI)) were detected by vaginal three-dimensional energy Doppler ultrasound (LOGIQ-E8, GE company, Boston, MA, USA). (4) Stress

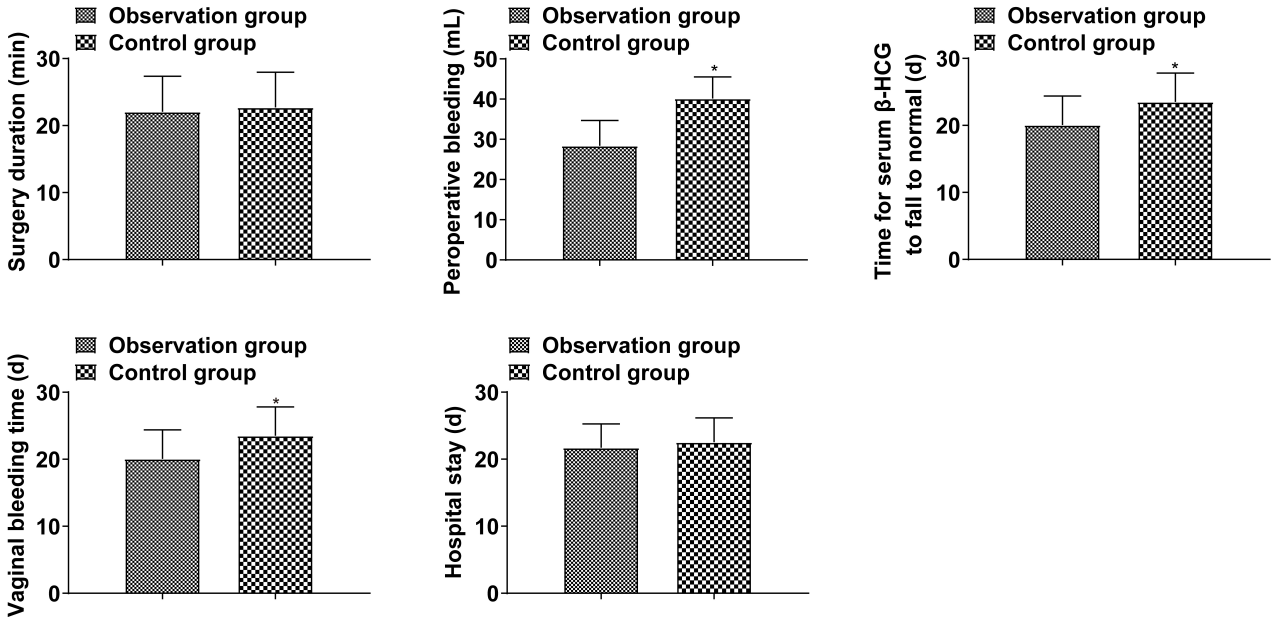

Fig. 1. Operation-related indices. Compared with observation group, * $p < 0.05$.

indices: C-reactive protein (CRP) (KL-H0043c, Shanghai kanglang Biotechnology Co., Ltd, Shanghai, China), Cortisol (COR) (CS10901, Shanghai C-reagent Biotechnology Co., Ltd, Shanghai, China), and adrenocorticotropic hormone (ACTH) (KL-H0130c, Shanghai kanglang Biotechnology Co., Ltd, Shanghai, China) were measured by the chemiluminescence method. (5) Sex hormones: Blood progesterone (P) (FY-EU8931, Wuhan Feiyue Biotechnology Co., LTD, Wuhan, Hubei, China), luteinizing hormone (LH) (FY-EG7417, Wuhan Feiyue Biotechnology Co., LTD, Wuhan, Hubei, China), and follicle-stimulating hormone (FSH) (FY-ER7340, Wuhan Feiyue Biotechnology Co., LTD, Wuhan, Hubei, China) were detected by the electrochemiluminescence method using an electrochemical luminescence instrument (E170, Roche, Basel, Switzerland). (6) Residual muscle layer and scar shape: vaginal three-dimensional energy Doppler ultrasound (LOGIQ-E8, GE company, Boston, MA, USA) was used to detect the thickness and proportion of residual muscle layer and the width, length, and depth of scars in patients 3 months after the operation. (7) Complications: Postoperative infection, liver function impairment, and intrauterine adhesion were evaluated.

2.6 Statistical Analysis

All the data were processed by SPSS 22.0 software (SPSS, Chicago, IL, USA), and the statistical data were expressed as % and compared by χ^2 test. Measurement data were expressed by ($\bar{x} \pm$ s) after the normality test and subjected to *t*-test analysis. $p < 0.05$ meant a statistical difference.

3. Results

3.1 Clinical Data and Operation Success Rates

Table 1 showed no significant difference in clinical data between the two groups ($p > 0.05$). Operation success rates were not significantly different between the two groups (97.96% *vs* 95.92%, $p = 0.558$).

3.2 Operation-Related Indicators

Peroperative blood loss in the observation group was less than that in the control group. The time for serum β-hCG to fall to negative was shorter, and vaginal bleeding time was shorter in the observation group compared with the control group (Fig. 1, $p < 0.05$).

3.3 Hemodynamic Indices

The observation group and control group showed no significant difference in ovarian hemodynamic indices 7 days before the operation and 3 days after the operation ($p > 0.05$). Vmax showed a trend of reducing, and RI and PI were higher in the observation group compared with the control group 1 day before the operation (Fig. 2, $p < 0.05$).

3.4 Stress Indices

The observation group and control group showed no significant difference in CRP, COR, and ACTH before operation ($p > 0.05$). CRP, cortisol (COR), and ACTH in the observation group were lower than those in the control group, 3 days after the operation (Fig. 3, $p < 0.05$).

3.5 Sex Hormone Levels

Preoperative sex hormone levels were not significantly different between the two groups ($p > 0.05$). The

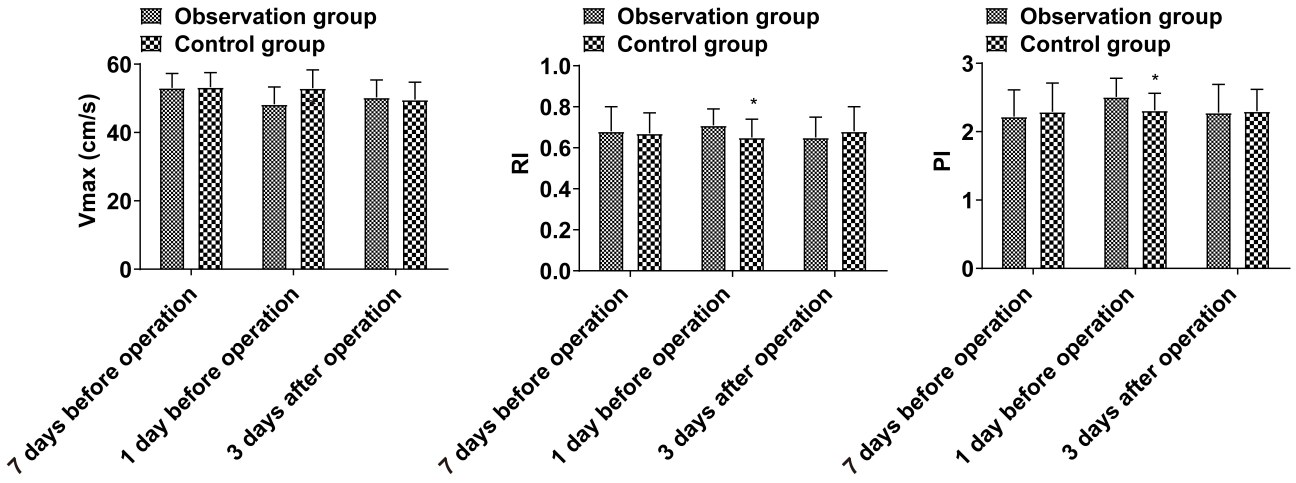

Fig. 2. Hemodynamic indices. Compared with observation group 1 day before the operation, * $p < 0.05$. RI, resistance index; PI, pulsatility index.

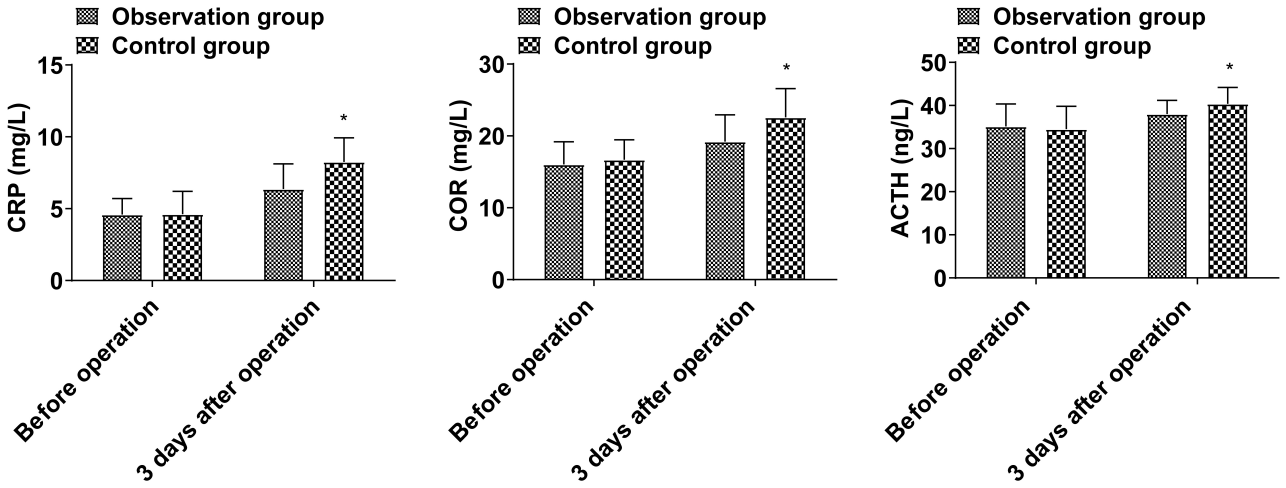

Fig. 3. Stress indices before and after the operation. Compared with observation group, * $p < 0.05$. CRP, C-reactive protein; COR, cortisol; ACTH, adrenocorticotropic hormone.

postoperative levels of P, LH, and FSH in the observation group were lower than those in the control group (Fig. 4, $p < 0.05$).

3.6 Menstrual Recovery

Menstrual recovery time in the observation group was shorter than that in the control group (Fig. 5, $p < 0.05$).

3.7 Postoperative Residual Muscle Layer and Scar Morphology

There were no significant differences in postoperative residual muscle thickness, proportion, and scar morphology (width, length, and depth) between the two groups (Fig. 6, $p > 0.05$).

3.8 Postoperative Complication Rates

Postoperative complication rates demonstrated no difference between the two groups (Table 2, $p > 0.05$).

4. Discussion

At present, laparoscopic-hysteroscopic lesion resection is widely used in the clinical treatment of cesarean scar pregnancy, which has the advantages of less trauma, faster recovery, and fewer complications. Laparoscopic-hysteroscopic lesion resection can effectively remove the lesion and retain the patient's fertility function, but it also has the disadvantage of a large amount of blood loss [8,9]. Clinical therapeutic effects can be improved by Western medicine preconditioning before uterine laparoscopy [10]. Mifepristone treatment can reduce villus activity, reduce local blood supply and intraoperative blood loss, promote embryo apoptosis, and improve uterine bleeding symptoms [11,12]. The results of this study mentioned that there was no significant difference in the success rate of operation between the two groups, suggesting that mifepristone preconditioning had little effect on the surgical efficacy of patients

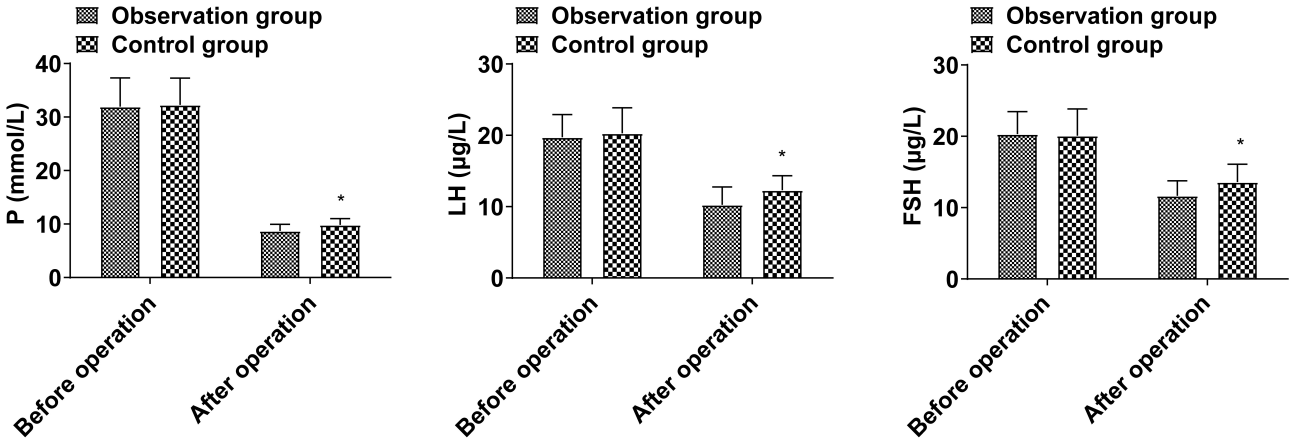

Fig. 4. Sex hormone levels. Compared with observation group, * $p < 0.05$. P, progesterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Table 2. Comparison of postoperative complication rate between the two groups (case, %).

Groups	N	Infection	Liver impairment	Intrauterine adhesion	Total incidence
Observation group	49	1	0	0	2.04
Control group	49	1	1	1	6.12
χ^2					1.043
p					0.307

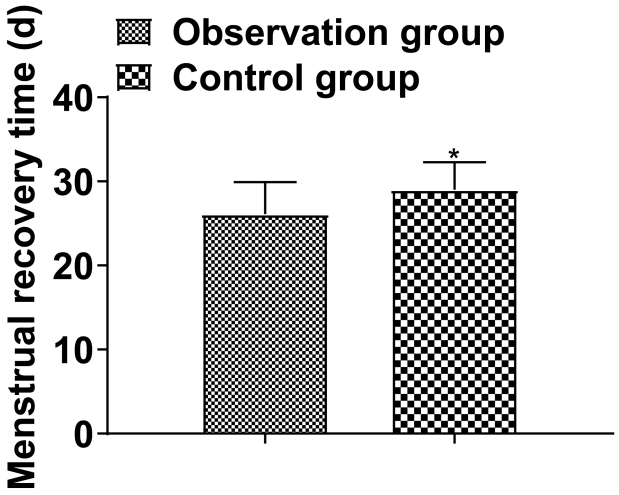

Fig. 5. Menstrual recovery. Compared with observation group, * $p < 0.05$.

treated with uterine laparoscopic therapy. Further analysis in this study showed that the intraoperative blood loss in the observation group was less than that in the control group, the time for serum β-hCG to fall to negative, vaginal bleeding time, and menstrual recovery time were shorter than that in the control group. In other words, mifepristone before surgical treatment could promote postoperative recovery of patients and reduce intraoperative blood loss. This is mainly because mifepristone can play the role of anti-progesterone, preempt the progesterone receptors of patients, reduce the chance of binding with endogenous progesterone, promote luteolysis, and inhibit the normal development of fetal cysts. In this way, blood β-hCG level can be reduced more quickly, while the decrease in intraoperative blood loss results in reduced blood supply to the surrounding tissues due to the shrinkage of the embryo sac [13,14].

Surgery is the main method to treat cesarean scar pregnancy, but intraoperative bleeding may lead to the occurrence of postoperative stress response and affect postoperative recovery [15,16]. This study revealed that the levels of CRP, COR, and ACTH in the observation group were lower than those in the control group 3 days after the operation, indicating that mifepristone can reduce the stress level of the body. The reason is that preoperative application of mifepristone can reduce the volume of pregnant matter in patients and significantly attenuate intraoperative injury, intraoperative blood loss, and the stimulating effect on the hypothalamic-pituitary axis of patients, thus alleviating operation-induced stress response. In this study, the Vmax of the observation group was lower than that of the control group 1 day before the operation, while RI and PI were higher, indicating that mifepristone pretreatment could improve the hemodynamics of the patients, mainly because mifepristone pretreatment could lead to embryo sac atrophy, shrinkage, or even death, resulting in significantly reduced blood supply to the surrounding tissues. This is also an important factor in effectively reducing postoperative stress reactions through this treatment [17]. Mifepristone pretreatment is conducive to smooth operation because it makes the embryo sac smaller [18]. Mifepristone can bind to the progesterone receptor and glucocorticoid receptor,

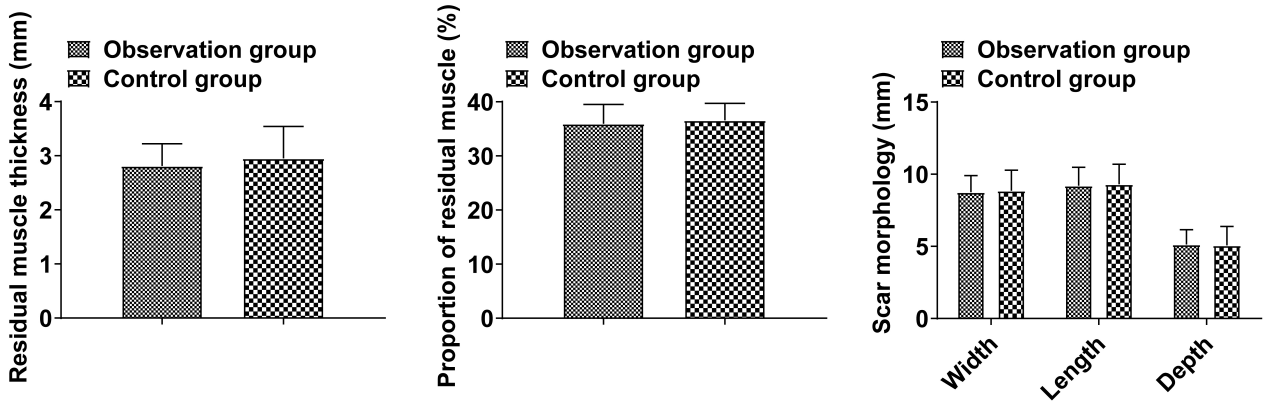

Fig. 6. Postoperative residual muscle layer and scar morphology.

produce a strong anti-progesterone effect, denaturate the villi and decidua tissues of pregnancy, reduce LH hormone and luteolysis, leading to necrosis of embryo sacs dependent on luteal development to produce abortion [19].

Mifepristone can inhibit embryonic development and luteal function, and reduce the activity of ovarian trophoblastic cells [20,21]. In this study, it was found that P, LH, and FSH levels in the observation group were lower than those in the control group after the operation, and mifepristone preconditioning could improve the body's sex hormone levels, mainly because mifepristone could accelerate the apoptosis of scar endometrial cells and inhibit the development of embryos, so as to cause the degeneration, atrophy, and necrosis of pregnancy tissues and reduce the level of progesterone [22,23]. We did not aim to induce cervical maturation, nor did we anticipate that mifepristone might make hysteroscopic surgery easier. In addition, the results mentioned that there were no significant differences in the thickness and proportion of postoperative residual muscle layer and the width, length, and depth of scars between the two groups, indicating that mifepristone pretreatment had little effect on wound healing after scar uterus operation.

5. Conclusion

In conclusion, mifepristone preconditioning can promote postoperative recovery, reduce postoperative stress response, improve hemodynamics, regulate sex hormone levels, and promote the early recovery of menstruation in patients with cesarean scar pregnancy following laparoscopic treatment.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Author Contributions

YC and LP conceived and designed the study. QS and HS analyzed the data. XW contributed to literature review, reviewed and edited the manuscript. YC and LP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The present study was approved by the Ethics Committee of Chenzhou First People's Hospital (No.20190314CZ) and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards. The study was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn), registration number: ChiCTR1800015514.

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Conflict of Interest

The authors declare no conflict of interest.

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