The Effect of Sildenafil Citrate on Poor Endometrium in Patients Undergoing Frozen-Thawed Embryo Transfer following Resection of Intrauterine Adhesions: A Retrospective Study

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Keywords

Clinical pregnancy rate · Frozen-thawed embryo transfer · Implantation rate · Intrauterine adhesions · Sildenafil citrate

Abstract

Background: The recent studies have shown that sildenafil citrate can enhance estrogen-induced proliferation of the endometrium in infertile women. **Objective:** This study was aimed to investigate whether sildenafil citrate could affect pregnancy outcomes in infertile women receiving frozen-thawed embryo transfer (FET) after resection of intrauterine adhesions (IUA). **Materials and Methods:** A total of 310 subjects who met the inclusion criteria were recruited and divided into the control group (group A) and the sildenafil citrate group (or the SC group, group B). The 2 groups were, respectively, divided into 2 subgroups based on the severity of reformed adhesions: (1) group A1 (with mild IUAs) and group A2 (with moderate to severe IUAs) and (2) group B1 (with mild IUAs) and group B2 (with moderate to severe IUAs). Therapeutic effects of sildenafil citrate on the cases were evaluated after resection of IUAs during FET cycles. En-

dometrial thickness, endometrial pattern, and pregnancy outcomes were evaluated and compared between the 2 groups. **Results:** There was no significant difference in the number of embryos transferred between the 2 groups. The endometrial thickness in group B (0.80 [0.68–0.90] cm) was significantly higher than that in group A (0.73 [0.35–0.80] cm). Besides, the biochemical pregnancy rate, clinical pregnancy rate, and live birth rate (LBR) were 71.60, 50.83, and 39.17% in group B, which were significantly higher than those in group A, namely, 57.36, 34.73, and 23.68%, respectively ($p < 0.05$). The univariate analysis and multivariate logistic regression showed that the LBR in either subgroups of group B after vaginal sildenafil treatment was significantly higher than that in the corresponding control group ($p < 0.05$). **Conclusions:** It was observed that the administration of sildenafil citrate during FET could effectively improve the poor endometrial conditions after FET following the resection of IUAs.

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Xin Li and Yan Su contributed equally to this work.

Introduction

Intrauterine adhesions (IUAs), also known as Asherman's syndrome, are caused by damage to the basal layer of the endometrium induced by multiple factors [1, 2]. The common clinical manifestations of this disease are recurrent abdominal pain, menstrual disturbance, amenorrhea infertility, habitual abortion, premature delivery, abnormal placenta implantation, and thin endometrium [3, 4]. IUAs have been listed as one of the leading causes of unsuccessful pregnancy in women receiving in vitro fertilization and embryo transfer (IVF-ET) as it may decrease endometrial receptivity [5]. Sildenafil citrate (Viagra; Pfizer, New York, NY, USA) has been used worldwide as a vasoactive agent for male erectile dysfunction since 1998. The selective phosphodiesterase type 5 (PDE5)-enzyme inhibitor is able to potentiate the downstream effects of nitric oxide (NO) on smooth muscle relaxation and vasodilation by triggering the cyclic guanosine monophosphate (cGMP) pathway in the erectile tissue of the penis [6]. It has been proven that constitutive NO synthase (NOS) and some messenger RNAs are responsible for the same effect of the enzyme in the rat and human endometrium [7, 8]. Some studies show that sildenafil citrate improves uterine blood flow and leads to the estrogen-induced proliferation of the endometrium in conjunction with estrogen [9]. However, there have been no large cohort studies focusing on its effect on endometrial preparation at present, and the efficacy of sildenafil citrate in a poor endometrium induced by multiple causes remains elusive. The purpose of this study was to determine the effect of sildenafil citrate on women receiving frozen-thawed embryo transfer (FET) following hysteroscopic adhesiolysis.

Materials and Methods

Participants

A total of 310 patients who received FET following hysteroscopic adhesiolysis in Nanjing Maternity and Child Health Care Hospital from January 2017 to January 2018 were enrolled. The inclusion criteria were as follows: (1) need for assisted reproduction therapy with IVF or intracytoplasmic sperm injection, (2) the age ≤ 42 years during oocyte retrieval, (3) diagnosed with mild IUAs or moderate to severe IUAs prior to the FET cycle and a normal uterine cavity after hysteroscopic adhesiolysis, (4) endometrial preparation using hormone replacement therapy (HRT) prior to FET regardless of ovulatory status, and (5) one or more high-quality embryos had been transferred on the day of ET. The exclusion criteria were as follows: (1) uterine anomalies, (2) diagnosed with hydrosalpinx by ultrasonography, (3) male factors, (4) pelvic tuberculosis and endometriosis, (5) confirmed chromosomal dis-

eases and genetic diseases in them or their husbands, and (6) severe uterine adhesions not being improved or still obvious on re-examination after TCRA; the characteristics of these patients were as follows: (1) women manifesting as thin endometrium refractory to estrogen treatment, and the endometrium could not grow; (2) patients undergoing failed repeated treatments may need endometrial stem cell transplantation.

Hysteroscopic Surgery for the Removal of IUAs

All patients underwent diagnostic hysteroscopy and treatment within 7 days following the clearance of their menstrual cycles. Physicians performed hysteroscopy to determine the type and extent of IUAs, placed the microshear or vaporization electrode to separate the adhesions, and restored the shape and size of the uterine cavity to the greatest possible extent. Subsequently, an intrauterine device was placed in the uterus. After surgery, the patients were given oral estrogen to promote reparative proliferation of the endometrium [10]. According to the severity of IUAs, some patients received continuous estrogen therapy, namely, estradiol valerate (3–4 mg twice a day) for 3 months plus progesterone capsules (0.2 g per day) in the last 5–6 days. Other patients received estrogen and progesterone cycle therapy, namely, estradiol valerate (2–4 mg twice a day) for 21 days plus progesterone capsules (0.2 g per day) in the last 5–6 days for 3 months. Finally, a hysteroscopic removal of intrauterine device was performed, and if necessary, the IUA removal was repeated.

Classification of IUAs

In the present study, the data were extracted from patients who had been diagnosed as mild (stage I) IUAs or moderate to severe (stage II–III) IUAs by hysteroscopy in accordance with the American Fertility Society (AFS) classification of IUAs [11]. Women who were pregnant or had amenorrhea induced by ovarian and hypothalamus-pituitary lesions were excluded.

Study Population and Design

A retrospective study was conducted at the Department of Reproductive Medicine, The Affiliated Obstetrics and Gynecology Hospital of Nanjing Medical University. A total of 310 patients who accepted FET following hysteroscopic adhesiolysis from January 2017 to January 2018 were enrolled. Depending on whether sildenafil citrate was used or not, 310 patients were divided into 2 groups: group A (the control group, $n = 190$) who underwent FET in HRT cycles and group B (the treatment group or the SC group, $n = 120$) who underwent FET in HRT cycles with vaginal sildenafil citrate (50 mg) before transplantation. For the best results, the blue outer layer of the drug membrane was carefully removed to create vaginal suppositories for all patients in this study. Sildenafil was administered by the patients themselves. Patients in group A were further divided into mild IUAs group (group A1, $n = 96$) and moderate to severe IUAs group (group A2, $n = 94$) and group B into mild IUAs group (group B1, $n = 53$) and moderate to severe IUAs group (group B2, $n = 67$).

In accordance with the principles of the Declaration of Helsinki, this observational study was approved by the Clinical Research Ethics Committee of the Nanjing Maternity and Child Health Care Hospital. Written consent was obtained from all enrolled patients. The study was approved by the Institutional Research Ethics Board of Nanjing Maternity and Child Health Care Hospital, Approval No. 2020KY-020.

Table 1. Basic characteristics of patients of the 2 groups

Characteristics, <i>n</i> = 310	Group A (controls) <i>n</i> = 190)	Group B (cases) (<i>n</i> = 120)	<i>p</i> value
Age, year ^a	33.00 (30.00–37.00)	33.00 (30.00–37.00)	0.652
BMI, kg/m ^{2b}	22.586±3.182	22.072±2.709	0.087
Duration of infertility, year ^a	3.00 (2.00–4.00)	2.00 (1.00–4.00)	0.092
Basal LH, IU/L ^a	4.225 (3.070–6.012)	4.620 (3.270–6.190)	0.338
Basal FSH, IU/L ^a	7.135 (5.870–8.665)	7.590 (6.180–9.030)	0.175
Basal E2, pg/mL ^a	46.00 (32.00–63.25)	46.00 (31.00–61.00)	0.52
Transferred embryos, <i>n</i> ^b	1.91±0.51	1.93±0.50	0.732

E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone. ^a Data are expressed as median (interquartile range) for nonnormally distributed continuous variables. ^b Data are expressed as mean ± SD for normally distributed continuous variables.

Endometrial Preparation and FET

Cryopreserved embryos were used in all FET cycles. All subjects receiving FET were treated with HRT. The E2 regimen was oral administration of estradiol valerate (Progynova; Bayer Schering Pharma, Leverkusen, Germany) twice a day from the second day of menstruation from 3 mg gradually increasing to an appropriate dose according to intimal growth. The course of administration was >11 days. When the endometrial thickness reached 0.7 cm, micronized P (Utrogestan, Besins, Belgium) was taken vaginally at 200 mg twice or 3 times per day. Then, the day 3 embryos were transferred 3 days later, and the blastocysts were transferred on the 5th day. Once pregnancy was achieved, the exogenous estrogen and progesterone supplementation was continued until 10 weeks of gestation.

Midcycle endometrial pattern was assessed and classified into 3 grades A, B, and C according to Zhao et al. [12]. Grade A endometrium has a triple-lined ultrasound pattern, characterized by 3 hyperechogenic lines (a central and 2 outer lines) and separated by 2 hypoechoic areas. Grade C endometrium has a homogenous (nontriple line) hyperechogenic appearance. Grade B endometrium has an intermediate pattern with a poorly defined central echogenic line surrounded by isoechoic or hypoechoic layers.

Measures of Pregnancy Outcome

The primary outcome measure for this study was live birth rate (LBR). The delivery of a viable infant was considered as the live birth. A biochemical pregnancy was defined as a positive human chorionic gonadotropin level without a gestational sac. The presence of a gestational sac with or without fetal heart activity, ectopic pregnancy, and heterotopic pregnancy was regarded as clinical pregnancy and was examined at least 7 weeks after FET. The implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. The miscarriage rate was defined as the proportion of patients with a spontaneous termination of pregnancy.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, 23.0). The normality of continuous variables was tested using the Shapiro-Wilk test. For the normally distributed continuous variables, the data were given as

mean ± standard deviation and compared using the Student *t* test. For the nonnormally distributed continuous variables, the data were given as median (interquartile range) and compared using the Mann-Whitney U test. The χ^2 test was used for categorical variables. Binary logistic regression was performed to quantify the effects of related factors on LBR, clinical pregnancy rate (CPR), biochemical pregnancy rate (BPR), ectopic pregnancy rate (EPR), and early pregnancy loss rate. In the regression analysis, the possible factors in the model include maternal age, infertility duration, BMI, basal follicle-stimulating hormone, basal luteinizing hormone, basal E2, and the number of transferred embryos. The entry method was employed when these factors were introduced into the regression equation. An adjusted odds ratio (OR) and 95% confidence interval (CI) were adopted to reflect the effect of related factors on LBR. A *p* value <0.05 was considered statistically significant.

Results

A total of 310 patients underwent FET during the study period. The baseline clinical characteristics of the 310 participants are shown in Tables 1 and 2. There were no significant differences in the baseline information between the 2 groups and among the 4 subgroups, nor in the number of embryos transferred. However, the endometrial thickness in group B was significantly higher than that in group A (*p* = 0.046, Table 3). No significant differences were found in endometrial patterns between the 2 groups. However, there were significant differences in the endometrial patterns between group B2 and group A2 (*p* = 0.037, Table 3).

The positive pregnancy test was defined as biochemical pregnancy. BPR, CPR, and LBR in group B were 71.67, 50.83, and 39.17%, respectively, which were significantly higher than those in group A, namely, 57.36, 34.73, and

Table 2. Basic characteristics of patients of the 2 subgroups

Characteristics (<i>n</i> = 310)	Mild IUAs group (<i>n</i> = 149)		Moderate to severe IUAs group (<i>n</i> = 161)		<i>p</i> value ^a	<i>p</i> value ^b
	cases <i>n</i> = 53	controls <i>n</i> = 96	cases <i>n</i> = 67	controls <i>n</i> = 94		
Maternal age, year ^c	34.00 (30.00~37.00)	33.00 (29.00~36.75)	32.00 (29.00~38.00)	34.00 (30.00~58.00)	0.374	0.671
BMI, kg/m ^{2d}	22.05±2.36	22.56±3.44	22.09±2.98	22.61±2.91	0.335	0.862
Duration of infertility, year ^c	2.00 (1.00~5.00)	3.00 (2.00~4.00)	2.00 (1.00~4.00)	3.00 (2.00~4.00)	0.154	0.376
Basal LH, IU/L ^d	4.62 (2.83~6.56)	4.21 (3.07~5.97)	4.66 (3.39~5.85)	4.26 (3.06~6.06)	0.422	0.641
Basal FSH, IU/L ^d	7.17 (6.18~9.03)	6.92 (5.85~8.35)	7.68 (6.18~9.02)	7.45 (5.89~9.25)	0.215	0.498
Basal E2, pg/mL ^d	41.00 (31.00~62.50)	46.00 (35.97~55.25)	47.00 (30.59~61.00)	49.00 (31.00~68.50)	0.488	0.656
Transferred embryos, <i>n</i> ^d	1.91±0.45	1.90±0.51	1.94±0.55	1.91±0.50	0.332	0.697

E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone. ^a *p*: group B1 versus group A1. ^b *p*: group B2 versus group A2. ^c Data are expressed as mean ±SD for normally distributed continuous variables. ^d Data are expressed as median (interquartile range) for nonnormally distributed continuous variables.

Table 3. Comparison of endometrial thickness and endometrial patterns in the 2 groups and 2 subgroups

	Case group (group B)			Control group (group A)			Mild IUAs group			<i>p</i> value			Moderate to severe IUAs group			<i>p</i> value		
	A	B	C	A	B	C	cases (group B1)	A	B	C	controls (group A1)		cases (group B2)	A	B	C	controls (group A2)	
<i>N</i>	120			190			53	96			67	94						
Endometrial thickness, cm	0.80 (0.68~0.90)			0.73 (0.35~0.80)			0.046	0.85 (0.80~0.95)	0.80 (0.70~0.90)		0.001	0.70 (0.65~0.80)	0.70 (0.60~0.80)					0.273
Endometrial pattern	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
	3	81	36	3	109	78	2	41	10	3	67	26	1	40	26	0	42	52
Implantation rate, <i>n</i> / <i>N</i> (%)	72/231 (31.16)			79/362 (21.82)			0.011	35/101 (34.65)	50/182 (27.47)		0.207	37/130 (28.46)	29/180 (16.11)					0.009

p < 0.05 (χ² test, *t* test, or Mann-Whitney test as appropriate) is considered to be statistically significant.

Table 4. Pregnancy outcomes of patients in the 2 groups

	Group A (control) (<i>n</i> = 190)	Group B (treatment) (<i>n</i> = 120)	<i>p</i> value
Live birth rate, <i>n/N</i> (%)	45/190 (23.68)	47/120 (39.17)	0.004
Clinical pregnancy rate, <i>n/N</i> (%)	66/190 (34.74)	61/120 (50.83)	0.005
Biochemical pregnancy rate, <i>n/N</i> (%)	109/190 (57.36)	86/120 (71.60)	0.011
Ectopic pregnancy rate, <i>n/N</i> (%)	4/66 (6.06)	2/61 (3.28)	0.681
Early pregnancy loss rate, <i>n/N</i> (%)	17/66 (25.76)	10/61 (16.39)	0.198

p < 0.05 (χ^2 test) is considered to be statistically significant.

Table 5. Binary logistic regression of factors related to the live birth rate, clinical pregnancy rate, biochemical pregnancy rate, ectopic pregnancy rate, and early pregnancy loss rate in the mild IUAs group

Outcome	Mild IUAs group (<i>n</i> = 149)		Univariate analysis		Multivariate analysis	
	group B1 (<i>n</i> = 53)	group A1 (<i>n</i> = 96)	OR	<i>p</i> value	OR	<i>p</i> value
Live birth rate, % (<i>n/N</i>)	49.10 (26/53)	31.30 (30/96)	2.119 (1.062~4.224)	0.033	2.416 (1.155~5.051)	0.019
Clinical pregnancy rate, % (<i>n/N</i>)	58.49 (31/53)	42.70 (41/96)	1.890 (0.985~3.730)	0.066	2.064 (1.000~4.261)	0.049
Biochemical pregnancy rate, % (<i>n/N</i>)	77.40 (41/53)	64.60 (62/96)	1.874 (0.870~4.036)	0.109	1.738 (0.769~3.929)	0.184
Ectopic pregnancy rate, % (<i>n/N</i>)	3.20 (1/31)	2.40 (1/41)	1.333 (0.080~22.190)	0.841	1.642 (0.080~33.770)	0.748
Early pregnancy loss rate, % (<i>n/N</i>)	12.90 (4/31)	24.40 (10/41)	0.459 (0.129~1.634)	0.229	0.368 (0.094~1.440)	0.151

All values are OR (95% CIs). Values were determined by using logistic regression. *p* value shows significance of entrance in the logistic regression model. OR, odds ratio; IUAs, intrauterine adhesions. *p* values in bold indicate statistical significance.

23.68%, respectively ($p < 0.05$). Patients in group B presented a significantly higher implantation rate of 31.16% compared with group A, namely, 21.82%. No significant differences were found in miscarriage rate and EPR ($p > 0.05$) between the 2 groups (Tables 2, 4).

Table 5 shows the results of binary logistic regression analyses of related factors including LBR, CPR, BPR, EPR, and early pregnancy loss rate. The dependent variables include maternal age, infertility duration, BMI, basal luteinizing hormone, basal follicle-stimulating hormone, and basal E2, which were analyzed using the entry method. The LBR (OR = 2.119, 95% CI: 1.062–4.224, $p = 0.033$) significantly increased after the vaginal administration of sildenafil citrate in group B1 compared with group A1. Then, a multivariate analysis performed to adjust for confounding factors showed that the LBR (OR = 2.416, 95% CI: 1.155–5.051, $p = 0.019$) and CPR (OR = 2.064, 95% CI: 1.000–4.261, $p = 0.049$) significantly increased after the vaginal administration in the SC group (group B) compared with the control group (group A).

Table 6 presents the results of binary logistic regression analyses of the moderate to severe IUAs groups. The univariate analysis showed that the LBR (OR = 2.404, 95% CI: 1.129–5.119, $p = 0.023$), CPR (OR = 2.238, 95% CI: 1.152–4.348, $p = 0.017$), and BPR (OR = 2.045, 95% CI: 1.067–3.921, $p = 0.031$) significantly improved after sildenafil citrate treatment in group B2 compared with group A2. The multivariate analysis adjusting for confounding factors shows that the LBR (OR = 2.139, 95% CI: 1.004–4.791, $p = 0.049$) significantly increased after sildenafil citrate treatment in group B2 compared with group A2.

Discussion

Recently, assisted reproductive technology is increasingly used as a useful procedure in women suffering from infertility. However, implantation is a complex initial step in the establishment of a successful pregnancy. The 3 prerequisite factors for successful implantation are the em-

Table 6. Binary logistic regression of factors related to the live birth rate, clinical pregnancy rate, biochemical pregnancy rate, ectopic pregnancy rate, and early pregnancy loss rate in the moderate to severe IUAs group

Outcome	Moderate to severe group (<i>n</i> = 161)		Univariate analysis		Multivariate analysis	
	group B2 (<i>n</i> = 67)	group A2 (<i>n</i> = 94)	OR	<i>p</i> value	OR	<i>p</i> value
Live birth rate, % (<i>n</i> / <i>N</i>)	31.30 (21/67)	16.00 (15/94)	2.404 (1.129~5.119)	0.023	2.193 (1.004~4.791)	0.049
Clinical pregnancy rate, % (<i>n</i> / <i>N</i>)	44.80 (30/67)	26.60 (25/94)	2.238 (1.152~4.348)	0.017	2.165 (1.066~4.398)	0.330
Biochemical pregnancy rate, % (<i>n</i> / <i>N</i>)	67.20 (45/67)	50.00 (47/94)	2.045 (1.067~3.921)	0.031	1.801 (0.905~3.857)	0.094
Ectopic pregnancy rate, % (<i>n</i> / <i>N</i>)	3.30 (1/30)	12.00 (3/25)	0.253 (0.025~2.599)	0.247	0.100 (0.002~5.248)	0.255
Early pregnancy loss rate, % (<i>n</i> / <i>N</i>)	20.00 (6/30)	28.00 (7/25)	0.643 (0.184~2.244)	0.488	0.988 (0.213~4.590)	0.988

All values are OR (95% CIs). Values were determined by using logistic regression. *p* value shows significance of entrance in the logistic regression model. OR, odds ratio; IUAs, intrauterine adhesions. *p* values in bold indicate statistical significance.

bryo with implantation competency, the endometrium in receptive state, and the synchronized development of both the embryo and the endometrium [13]. It is generally accepted that endometrial receptivity is critical to successful pregnancy [14], it is a multifactorial process [15], and secondary infertility is a common initial symptom of IUAs [2]. The present study has revealed that vaginal administration of sildenafil citrate during FET in patients receiving resection of IUAs evidently improves their pregnancy outcomes, which can be viewed as a promising treatment for infertile women with endometrial insufficiency after FET.

Any trauma to the basal layer of the endometrium caused by surgical instruments (sharp, blunt, or suction curettage) or infection with tuberculosis leads to the formation of IUAs and cervical adhesions. The reported prevalence of IUAs varies from 0.3 to 21.5% [16]. Adhesions are described as any abnormal fibrous connection containing vascular channels joining tissue surfaces in abnormal sites with varied etiology [17]. The adhesions can cause partial or complete obliteration of the uterine cavity, narrow down the space for implantation, and even diminish the receptive endometrium by impairing the blood supply. As these irregular and high-dense fibrous adhesions develop, women may experience menstrual disorders, cyclic pelvic pain, recurrent pregnancy losses, and subfertility. Diminished endometrial blood flow may hamper effective implantation. Patients with moderate to severe IUAs or adhesions in the uterine horn have high incidence of adhesion reformation after hysteroscopic adhesiolysis, which is difficult to tackle with. Moreover, evidence shows that repeated surgery also causes thin endometrium and low implantation rate. Our results indi-

cate that patients with IUAs receiving sildenafil citrate treatment present significantly higher CPR, BPR, and LBR than those without sildenafil citrate treatment. And, in the moderate to severe IUAs group, sildenafil citrate significantly increased implantation rates compared with the control group in patients with IUAs. In the moderate and severe IUAs group, it may damage endometrial receptivity, and it could result in damage to the basal layer of the endometrium. The main effect of sildenafil is to improve endometrial blood flow and receptivity, thereby improving endometrial proliferation, rather than directly increasing endometrium thickness. Therefore, we considered that for the same endometrial thickness, the improvement in blood flow was greater with sildenafil, hence more significant improvement in implantation rate.

Since the approval from the US Food and Drug Administration in March of 1998, sildenafil citrate (Viagra®) has been used by millions of men for the treatment of erectile dysfunction [18]. Sildenafil citrate is a specific PDE5 inhibitor that augments the vasodilatory effects of NO on the vascular smooth muscle by preventing the degradation of cGMP. The animal research has shown that NO relaxes the vascular smooth muscle through a cGMP-mediated pathway [19]. Isoforms of endothelial NOS and inducible NOS have been identified in both the vascular endothelium of the human endometrium and the myometrium [7]. Estrogen-induced endometrial proliferation is largely dependent on blood flow to the basal endometrium. Therefore, it has been speculated that sildenafil citrate may exert therapeutic effects on the damaged endometrium after FET.

PDE is a family of isoenzymes that hydrolyze cyclic nucleotides like cGMP. Inhibitors of specific PDE subtypes have been identified, which are able to augment the effects of cyclic nucleotides on target tissues, for instance, human spermatozoa [20]. Healthy blood perfusion of the uterus and ovaries for the success of assisted reproduction therapy alongside sildenafil citrate's effects on the uterine artery smooth muscle makes the agent prominent in enhancing the uterine artery flow and ameliorating the endometrial receptivity. Several studies have demonstrated the efficacy of vaginal sildenafil in improving endometrial growth, endometrial blood flow, and pregnancy rates in women with failed IVF/intracytoplasmic sperm injection cycle associated with thin endometrium [9, 21, 22]. Previous studies have demonstrated the ability of sildenafil in modulating uterine artery blood flow and ameliorating endometrial pattern and thickness, as well as implantation rate and pregnancy rate [23]. It is also effective for patients undergoing resection of IUAs. Consistently, in our study, there is a significant increase in CPR, LBR, and implantation rate in the SC group.

The term "endometrial receptivity" refers to the ability of the uterine lining to accept and accommodate a nascent embryo, resulting in a successful pregnancy [24]. An adequate endometrial thickness is indispensable for a successful pregnancy [25, 26]. Meanwhile, a triple-line pattern also seems to be favorable for pregnancy [11]. In patients after the resection of IUAs, the thin and damaged endometrium has lost its receptivity, which may hamper the implantation process. Moreover, an imbalanced immune response to endometrial response may occur after the resection of IUAs. Clinically, endometrial thickness on the human chorionic gonadotropin "trigger day" (or progesterone conversion "trigger day") is regarded as an appropriate evaluation of the embryo reception of the endometrium [17]. Clinical studies have shown that if the endometrial thickness is ≤ 0.7 cm, the clinical pregnancy probability will be significantly reduced [27]. In this study, we found that the severity of adhesion could affect the BPR, CPR, and LBR.

Our results have demonstrated the effect of sildenafil citrate on the poor endometrium in infertile women receiving FET after resection of IUAs. However, there were several limitations such as small sample size and single-center design assessing a Chinese population. Thus, multicenter investigations with larger sample size should be conducted further. Second, the study collected the data of the patients during the first trimester of pregnancy, and the conclusions are limited to this trimester. Third, this

study was retrospective and nonrandomized. Thus, we are looking forward to the well-designed clinical trial, which might give us more conclusive results in the future. In conclusion, transvaginal sildenafil citrate effectively improves the endometrial thickness and endometrial receptivity in female patients undergoing FET after the resection of IUAs. The results allow us to propose an effective and convenient protocol for patients with a poor endometrium after FET cycles. As this is a retrospective study, a large-sample clinical trial using vaginal sildenafil is recommended for this group.

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Statement of Ethics

In accordance with the principles of the Declaration of Helsinki, this observational study was approved by the Clinical Research Ethics Committee of the Nanjing Maternity and Child Health Care Hospital. Written consent was obtained from all enrolled patients. The study was approved by the Institutional Research Ethics Board of Nanjing Maternity and Child Health Care Hospital, Approval No. 2020KY-020.

Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

X.L. (the principal investigator) designed the study, performed the statistical evaluations, assisted in writing the manuscript, and edited it in all its revisions. Y.S. participated in designing the study, assisted in writing the manuscript and edited it, proofread the manuscript, and took part in discussions regarding the results. Q.X. retrieved the data, assisted in writing the manuscript and edited it, proofread the manuscript, and took part in discussions re-

garding the results. T.L. participated in designing the study, assisted in writing the manuscript and edited it, proofread the manuscript, and took part in discussions regarding the results. M.Z. participated in designing the study. X.J. assisted in writing the manuscript and edited it. Y.L. proofread the manuscript. C.Z. took

part in discussions regarding the results. X.L. participated in designing the study, retrieved the data, assisted in writing the manuscript, and edited it in all its revisions. All authors read and approved the final manuscript.

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