

Clinical Outcomes of Sildenafil Application in Patients of Poor Endometrial Development

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Research

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Abstract

Problem: Does sildenafil have an effect on pregnancy outcomes in patients with poor endometrial development?

Methods: This study included 472 infertility patients who underwent in vitro fertilization/intracytoplasmic sperm injection and frozen-thawed embryo transfer (IVF/ICSI-FET) and suffered from poor endometrial development in the hormone replacement cycle (HRC) from April 2017 to July 2019. The patients were divided into two groups: the sildenafil group(n=88) and the control group(n=384). Endometrial thicknesses and types on endometrial transformation day, as well as pregnancy outcomes after FET (biochemical pregnancy, clinical pregnancy, early abortion, late abortion, and live birth rates) between two groups were analyzed.

Results: No significant differences were observed in endometrial thicknesses and types on endometrial transformation day between the sildenafil group and the control group. There were also no statistically significant differences in pregnancy outcomes between the two groups. After adjusting for confounding factors, the application of sildenafil could not improve endometrial thickness and type of the day of endometrial transformation and the growth of endometrial thickness. Moreover, the sildenafil was not closely related to clinical pregnancy outcomes.

Conclusions: Sildenafil could not better endometrial development and pregnancy outcomes in patients with poor endometrial development.

Introduction

In recent years, with the rapid development of assisted reproductive technology (ART), the pregnancy rate of infertility patients has been greatly increased. It is generally accepted that frozen-thawed embryo transfer (FET) has higher clinical pregnancy and live birth rates than fresh embryo transfer[1, 2]. FET is a better choice for patients with high risk of ovarian hyperstimulation syndrome(OHSS)[3],for patients whose endometrium(EM) is out of sync with embryo development[4], and for patients who plan to undergo pre-implantation genetic testing (PGT)[5]. The success of pregnancy depends on high-quality embryos, synchronized uterine environment and a harmonious dialogue between the two. The preparation of the endometrium is required in order to coordinate the development of the endometrium and the embryo during embryo transfer cycles. For patients with poor endometrial development during their previous controlled ovarian hyperstimulation (COH) or FET cycles, hormone replacement appears to be more appropriate. During the hormone replacement cycle (HRC), estrogen and progesterone are continuously administered to simulate the hormone secretion of a normal menstrual cycle. Estrogen is firstly offered to promote endometrial proliferation, and then progesterone is supplemented when the endometrium grows to an appropriate thickness, so that the proliferated endometrium turns into a secretory period and waits for embryo transfer. The timing of estrogen supplementation is inconclusive[6–8]. In our center, patients are usually given estrogen from the 2nd-4th days of the menstruation, and then progesterone is added to transform the endometrium when the endometrium reaches the transfer standard (commonly at least 8mm).

As its name denotes, poor endometrial development is a general description based on endometrial thickness and receptivity. Clinically, it is defined as the EM less than 8mm after 10 days of estrogen application in the HRC. Accumulating evidence has demonstrated that thinner endometrium is associated with lower clinical pregnancy rates. It is generally accepted that EM < 7mm or 8mm hampers clinical pregnancy and live birth[9, 10]. The underlying mechanisms of poor endometrial development are complex, and there is no specific remedial method for prevention and treatment. Abnormal endometrial blood flow is thought to be an important cause of poor endometrial development. A number of drugs reported to advance endometrial blood flow, such as aspirin, low-molecular heparin, sildenafil and others, have been recommended for these patients [11].

Sildenafil citrate is a type 5 specific phosphodiesterase inhibitor, which can prevent the damage of cyclic guanosine monophosphate(cGMP)and enhance the relaxation effect of nitric oxide (NO) on vascular smooth muscle, thus achieving the effect of increasing uterine blood perfusion and improving pregnancy outcome. However, its application in patients with poor endometrial development is still controversial[12–14].

Therefore, the purpose of this study was to explore the application value of sildenafil in patients with poor endometrial development in the IVF/ICSI-FET cycles, and to provide a new clinical basis for improving pregnancy outcomes of patients with poor endometrial development.

Materials And Methods

Study population

A total of 472 infertility female patients who were treated with IVF/ICSI-CET and had poor endometrial development in HRC were recruited in the Center for Reproductive Medicine of Shandong University from April 2017 to July 2019. The women characterized by the following issues were included: patients with age < 35 years old; EM less than 8mm after 10 days with estradiol valerate application in HRC and high-quality

blastocysts. Women were excluded from this study if they had abnormal karyotypes; previous or untreated uterine pathologies (i.e., uterine malformation, endometriosis, submucosal leiomyoma, endometrial polyps, intrauterine adhesions); and known systemic disorders correlated with abnormal pregnancy outcomes. These patients were divided into two groups depending on whether they used sildenafil citrate (sildenafil group, n = 88) or not (control group, n = 384).

Study Procedures

All patients were treated with oral estradiol valerate 4 mg/d from the 2nd -4th day of menstruation for 5 days continuously, and 6 mg/d for the subsequent 5 days. Patients whose EM were less than 8mm after 10 days of estradiol valerate application measured by transvaginal ultrasound were included in this study. Then, the oral dose of estradiol valerate was increased to 8 mg/d, or estradiol gel 2 calipers/d (equivalent to 3 mg estradiol) was added to the original oral dose of estradiol valerate via the skin. At the same time, some patients who were given vaginal sildenafil citrate (50 mg/d) were included in the sildenafil group (n = 88), while other patients without using sildenafil citrate were included in the control group (n = 384). Sildenafil citrate was stopped and endometrial transformation was initiated when $EM \geq 8mm$ or the optimal thickness of the patient's previous treatment cycle has been reached or has been approached. Two primary protocols were used for endometrial transformation and subsequent luteal phase support after FET. One was taken oral dydrogesterone (40 mg/d) combined with progesterone capsules (200 mg/d) for each patient. The other was supplied with both oral dydrogesterone (10 mg/ d) and vaginal progesterone gel (90 mg/ d). The frozen-thawed blastocysts were transferred on the 5th day after endometrial transformation. Serum human chorionic gonadotropin (hCG) levels measured 12 days after FET and transvaginal ultrasound taken among 7–12 weeks of gestation were used to assess pregnancy conditions. To further explore the role of sildenafil citrate in improving poor endometrial development, subgroup analysis was performed among three groups: group one ($7 \leq EM < 8mm$), group two ($6 \leq EM < 7mm$), and group three ($EM < 6mm$).

Outcome Measures

The primary observation indicators were the thickness and type of EM on the day of endometrial transformation and the growth of EM. The measurement methods by transvaginal ultrasound were as follows:(1) The thickness of EM was the thickest distance measured from the uterine sagittal plane/long axial section, within 1 cm from the bottom of the uterus, and vertically across the uterine cavity line from one side of the basement membrane to the other side; (2) Endometrial types were divided into A, B or C type[15]. Type A meant three lines types with strong echo line in the outer and middle and low echo in the inner. Type B showed unobvious midline echo. Type C indicated the endometrium was a homogeneous strong echo area without sub echoic area. (3) The growth of EM was namely the differences of EM thicknesses measured between the day after 10 days of estradiol valerate application and endometrial transformation. The secondary observation indexes were pregnancy outcomes of each FET cycle, including biochemical pregnancy, clinical pregnancy, early abortion, late abortion, and live birth rates. Biochemical pregnancy was defined as serum hCG levels ≥ 25 IU/L measured 12 days after FET. Clinical pregnancy was diagnosed by ultrasonographic visualization of a discernible heartbeat in the intrauterine gestational sac during 7–8 weeks of gestation. Abortions were referred to the termination of clinical pregnancy and classified into early abortion at less than 12 weeks and late abortion between 12 and 28 weeks. Live birth was registered as one delivery of a viable infant at ≥ 28 weeks of gestation.

Statistical Analysis

SPSS software (version 26.0) was applied for statistical analysis. Continuous variables were expressed as mean \pm standard deviation ($\bar{x} \pm s$). Based on distribution of variables, two-tailed student's *t*-test was appointed for normally distributed data, and Mann-Whitney U test was used for non-normal data. Categorical variables were expressed as percentages, and the Chi-square test (including Fisher's exact test) was used for inter-group comparison. Two-sided *P*-value < 0.05 were considered statistically significant differences. Multiple linear regression and binary logistic regression were given to adjust the differences between groups.

Results

The baseline characteristics of the study population were shown in Table 1. The clinical features between the sildenafil and control group were not statistically different except the thickness of EM after 10 days of estradiol valerate application (0.65 ± 0.08 vs. 0.68 ± 0.08 , *P* = 0.003).

Table 1
The baseline characteristics of all patients($\bar{x} \pm s, \%$)

variable	Sildenafil group	Control group	P value
Age(year)	28.92 ± 3.19	28.80 ± 2.91	0.670
Body mass index(kg/m ²)	24.43 ± 4.26	23.79 ± 3.71	0.370
Basal FSH(IU/L)	6.56 ± 2.67	6.29 ± 3.09	0.261
Basal LH (IU/L)	6.38 ± 3.71	6.81 ± 4.48	0.603
Basal E2 (pg./ml)	40.76 ± 24.93	40.30 ± 25.20	0.966
PRL (ng/mL)	17.57 ± 7.11	17.56 ± 8.70	0.492
To (ng/dL)	27.17 ± 14.45	30.62 ± 16.20	0.084
TSH (uIU/mL)	2.36 ± 1.17	2.21 ± 1.09	0.330
AMH (ng/L)	5.28 ± 3.71	6.10 ± 3.71	0.053
No. of previous abortions	0.75 ± 0.89	0.62 ± 0.95	0.066
No. of high-quality embryos	4.93 ± 3.27	5.48 ± 3.28	0.153
No. of embryo transferred	1.05 ± 0.21	1.05 ± 0.21	0.955
EM after 10 days of estradiol valerate application(cm)	0.65 ± 0.08	0.68 ± 0.08	0.003
Type A endometrium after 10 days of estradiol valerate application	90.91% (80/88)	88.80% (341/384)	0.566
Notes: FSH indicates follicle stimulating hormone, LH indicates luteinizing hormone, E2 indicates estradiol, PRL indicates prolactin, TO indicates androgen, TSH indicates thyroid stimulating hormone, AMH indicates Anti-Mullerian Hormone, EM indicates endometrium.			

The thickness and type of EM on the day of endometrial transformation and the growth of EM were compared in Table 2. The thickness of EM on endometrial transformation day was thinner in the sildenafil than that of the control group (0.79 ± 0.08 vs. 0.81 ± 0.09, P = 0.035). No differences were observed in the endometrial type on endometrial transformation day and the growth of EM between the two groups (P > 0.05). After adjusting for confounding variables, the application of sildenafil was not associated with either the thickness and the type of EM on the day of endometrial transformation or the growth of EM.

Table 2
Endometrial conditions and Pregnancy outcomes of all patients($\bar{x} \pm s, \%$)

Variable	Sildenafil group	Control group	P value	P-adjust [§]
EM on endometrial transformation day(cm)	0.79 ± 0.08	0.81 ± 0.09	0.035	0.144*
Type A endometrium on endometrial transformation day	79.76% (67/84)	83.87% (312/372)	0.364	0.402 [#]
The growth of EM (cm)	0.14 ± 0.10	0.13 ± 0.10	0.706	0.144*
Biochemical pregnancy rate	75.0% (66/88)	76.8%(295/384)	0.716	0.892 [#]
Clinical pregnancy rate	59.09% (52/88)	69.53%(267/384)	0.059	0.087 [#]
Early abortion rate	17.31% (9/52)	14.61%(39/267)	0.618	0.557 [#]
Late abortion rate	3.85% (2/52)	4.49%(12/267)	1.000	0.859 [#]
Live birth rate	45.45% (40/88)	55.47%(213/384)	0.089	0.101 [#]
Notes: EM indicates endometrium. [§] Adjusted by the thickness of EM after 10 days of estradiol valerate application. *Adjusted with Multiple linear regression. [#] Adjusted with binary logistic regression.				

Table 2 showed that there were no significant differences in biochemical pregnancy, clinical pregnancy, early abortion, late abortion and live birth rates between the sildenafil and control group (P > 0.05). After adjusting for confounding variables, the employment of sildenafil could not improve pregnancy outcomes in patients with poor endometrial development.

In order to further explore the role of sildenafil citrate in bettering poor endometrial development and pregnancy outcomes, the patients were divided into three groups: group one (7 ≤ EM < 8mm), group two (6 ≤ EM < 7mm), and group three (EM < 6mm). Table 3 exhibited the baseline

characteristics of patients in the subgroups. In group one, the sildenafil group had a higher BMI level than the control group (25.67 ± 4.36 vs. 24.04 ± 3.81 , $P < 0.05$), while other baseline characteristics were not significantly different between the two groups. In group two, there were statistical differences in basic FSH level (7.27 ± 3.62 vs. 5.90 ± 1.56 , $P < 0.05$), number of previous abortions (0.88 ± 0.88 vs. 0.56 ± 0.95 , $P < 0.05$) and the thickness of EM after 10 days of estradiol valerate application (0.62 ± 0.02 vs. 0.63 ± 0.02 , $P < 0.05$) between the sildenafil and control groups. In group three, all clinical characteristics displayed no statistically significant differences between the sildenafil and control groups. As shown in Table 4, no differences were observed in both endometrial indicators and pregnancy outcomes between the sildenafil and the control groups among the three subgroups. After adjusting the confounding variables of group one and two, the application of sildenafil could not provide prominent benefits for patients with poor endometrial development.

Table 3
baseline characteristics of every group($\bar{x} \pm s, \%$)

Variable	Group one($7 \leq EM < 8mm$)			Group two($6 \leq EM < 7mm$)			Group three($6mm < EM$)		
	Sildenafil group (n = 42)	Control group (n = 235)	P value	Sildenafil group (n = 34)	Control group (n = 111)	P value	Sildenafil group (n = 12)	Control group (n = 38)	P value
Age(year)	28.98 ± 3.50	29.03 ± 2.79	NS	28.68 ± 3.07	28.61 ± 3.21	NS	29.42 ± 2.47	27.92 ± 2.61	NS
Body mass index(kg/m ²)	25.67 ± 4.36	24.04 ± 3.81	<0.05	23.56 ± 4.27	23.66 ± 3.53	NS	22.58 ± 2.45	22.57 ± 3.37	NS
AMH (ng/L)	5.27 ± 3.94	6.00 ± 3.57	NS	6.01 ± 3.75	6.21 ± 3.76	NS	3.43 ± 1.87	6.42 ± 4.52	NS
Basal FSH(IU/L)	5.85 ± 1.54	6.40 ± 3.66	NS	7.27 ± 3.62	5.90 ± 1.56	<0.05	6.99 ± 2.14	6.75 ± 2.43	NS
Basal LH (IU/L)	6.07 ± 3.33	6.66 ± 4.12	NS	7.22 ± 4.34	7.00 ± 5.15	NS	5.09 ± 2.55	7.20 ± 4.55	NS
Basal E2 (pg./ml)	41.43 ± 26.98	38.87 ± 24.75	NS	42.86 ± 25.50	42.09 ± 27.47	NS	32.48 ± 12.68	43.98 ± 20.49	NS
PRL (ng/mL)	17.03 ± 5.51	17.93 ± 9.52	NS	17.98 ± 8.74	16.47 ± 6.61	NS	18.29 ± 7.43	18.45 ± 8.66	NS
To (ng/dL)	27.50 ± 14.75	30.97 ± 16.77	NS	28.13 ± 12.91	30.82 ± 15.99	NS	23.25 ± 17.90	27.84 ± 13.06	NS
TSH (uIU/mL)	2.17 ± 1.01	2.23 ± 1.06	NS	2.59 ± 1.41	2.04 ± 1.04	NS	2.35 ± 0.82	2.53 ± 1.33	NS
No. of previous abortions	0.76 ± 0.93	0.62 ± 0.98	NS	0.88 ± 0.88	0.56 ± 0.95	<0.05	0.33 ± 0.65	0.76 ± 1.00	NS
No. of high-quality embryos	4.69 ± 2.79	5.49 ± 3.26	NS	5.62 ± 3.74	5.53 ± 3.26	NS	3.83 ± 3.24	5.26 ± 3.55	NS
No. of embryo transferred	1.02 ± 0.15	1.05 ± 0.22	NS	1.06 ± 0.24	1.03 ± 0.16	NS	1.08 ± 0.29	1.08 ± 0.27	NS
EM after 10 days of estradiol valerate application(cm)	0.72 ± 0.03	0.73 ± 0.02	NS	0.62 ± 0.02	0.63 ± 0.02	<0.05	0.52 ± 0.02	0.50 ± 0.06	NS
Type A endometrium after 10 days of estradiol valerate application	90.48% (38/42)	91.49% (215/235)	NS	94.12% (32/34)	87.39% (97/111)	NS	83.33% (10/12)	76.32% (29/38)	NS

Notes: EM indicates endometrium.

Table 4
Endometrial conditions and clinical outcomes of patients of every group ($\bar{x} \pm s, \%$)

variable	Group one (7 ≤ EM<8mm)				Group two (6 ≤ EM<7mm)				Group three (6<EM)		
	Sildenafil group (n = 42)	Control group (n = 235)	P value	P-adjust ^f	Sildenafil group (n = 34)	Control group (n = 111)	P value	P-adjust [†]	Sildenafil group (n = 12)	Control group (n = 38)	P value
EM on transformation day(cm)	0.80 ± 0.08	0.82 ± 0.08	NS	NS*	0.78 ± 0.08	0.80 ± 0.10	NS	NS*	0.75 ± 0.11	0.77 ± 0.08	NS
A type endometrium on transformation day	78.57% (33/42)	86.78% (197/227)	NS	NS #	80.65% (25/31)	77.78% (84/108)	NS	NS #	81.82% (9/11)	83.78% (31/37)	NS
The growth of EM(cm)	0.08 ± 0.08	0.09 ± 0.08	NS	NS*	0.16 ± 0.08	0.17 ± 0.09	NS	NS*	0.24 ± 0.12	0.26 ± 0.10	NS
Biochemical pregnancy rate	73.81% (31/42)	80.43% (189/235)	NS	NS #	76.47% (26/34)	71.17% (79/111)	NS	NS #	75% (9/12)	71.05% (27/38)	NS
Clinical pregnancy rate	61.90% (26/42)	72.34% (170/235)	NS	NS #	52.94% (18/34)	63.94% (71/111)	NS	NS #	66.67% (8/12)	68.42% (26/38)	NS
Early abortion rate	23.08% (6/26)	15.88% (27/170)	NS	NS #	16.67% (3/18)	14.08% (10/71)	NS	NS #	0% (0/8)	7.69% (2/26)	NS
Late abortion rate	3.85% (1/26)	4.12% (7/170)	NS	NS #	0.00% (0/18)	7.04% (5/71)	NS	NS #	12.5% (1/8)	0% (0/26)	NS
Live birth rate	42.86% (18/42)	56.60% (133/235)	NS	NS #	44.12% (15/34)	50.45% (56/111)	NS	NS #	58.33% (7/12)	63.16% (24/38)	NS

Notes: EM indicates endometrium. ^f Adjusted by body mass index. [†] Adjusted by basal FSH, number of previous abortions, the thickness of EM after 10 days of estradiol valerate application. * Adjusted with Multiple linear regression. # Adjusted with binary logistic regression

Discussion

This study demonstrated that sildenafil application could not better endometrial development and pregnancy outcomes in patients with poor endometrial development.

EM is an important indicator used to assess endometrial receptivity in IVF patients by ultrasound. It is generally accepted that EM is closely related to pregnancy outcomes and poor endometrial development usually predicts lower clinical pregnancy and live birth rates[16]. The etiology of poor endometrial development is complex, which can be caused by acute and chronic endometrium inflammation, repeated uterine operations, and the use of drugs that affect endometrium development, such as clomiphene. Despite extensive investigation, there are still some patients without identifiable factors and labeled idiopathic[17]. Previous studies have reported that endometrial growth is dependent on uterine blood perfusion[18]. Patients with poor endometrial development are usually accompanied by increased uterine artery blood flow resistance. When the uterine artery resistance is increased, the growth of glandular epithelial cells is impaired and the expression of vascular endothelial growth factor (VEGF) is decreased. It is expected to result in vascular dysplasia, a decrease in endometrial blood flow and blunted endometrial development[19]. Abnormal blood perfusion is considered to be one of the primary causes of thin endometrium[20]. Whether drugs that improve blood perfusion can optimize endometrial development and subsequent pregnancy outcomes in patients suffering thin endometrium remains elusive.

Sildenafil citrate enhances the vasodilation effect of NO by preventing cGMP degradation, and increases the expression of β_3 integrin and VEGF during the window period, which plays a role in both decidualization and implantation process[21]. Sildenafil citrate was initially used as a vasoactive drug to treat erectile dysfunction in men[22]. With further investigations on sildenafil citrate, the application scope of sildenafil citrate has gradually expanded to cardiovascular, cerebrovascular, respiration, nervous and other systems. Most studies mentioned that sildenafil citrate could achieve therapeutic effects by improving blood flow perfusion of corresponding tissues and organs, while some studies got the opposite conclusion[23–27]. Trapani et al. compared maternal uterine artery and umbilical cord blood flow before and after using sildenafil citrate in 35 single pregnancies with fetal growth restriction, and found that uterine artery blood flow pulsatility index (PI) and fetal umbilical cord blood PI decreased significantly after the application of sildenafil[28]. It was speculated that sildenafil might meliorate maternal

uterine artery and umbilical cord blood flow by enhancing uterine artery perfusion [29]. Some scholars applied sildenafil citrate to patients with primary dysmenorrhea, and discovered that sildenafil could relieve the acute menstrual pain in patients with dysmenorrhea with no adverse reactions observed via alleviating vasoconstriction caused by prostaglandin and reducing pain successfully by inhibiting type 5 specific phosphodiesterase[30]. Jing et al. reported that sildenafil citrate could increase significantly the uterine arterial resistance index (RI) in patients with recurrent spontaneous abortion[31]. Sher et al. first employed sildenafil to 4 patients with recurrent implantation failure attributed to thin endometrium in 2000, and detected that endometrial thickness increased and PI decreased after treatment and 3 of 4 patients obtained pregnancy[32]. Subsequently, Sher et al expanded the samples size of patients to 105 in 2002 and came to the similar conclusions[33]. And this conclusion has been confirmed by other researchers[34, 12]. In a prospective study, sildenafil citrate was added in endometrial preparation process of FET until the day of transplantation in 22 patients with thin endometrium and high blood flow resistance. The use of sildenafil significantly increased endometrial thickness and endometrial blood flow, and consequently improved pregnancy rate[35]. Takasaki et al. applied sildenafil to 12 patients who had a history of EM < 8mm and uterine artery RI \geq 0.81 in previous ovulation induction cycle from the 1st day of the menstrual cycle until the day of injecting hCG and measured endometrial thickness and uterine artery RI before ovulation induction. Compared with the previous cycles without sildenafil, and revealed that endometrial thickness and blood perfusion were heightened[36]. A randomized controlled clinical trial conducted by Dehghani Firouzabadi et al. also discovered that patients of poor endometrial development after using sildenafil citrate had higher endometrial thickness, proportion of type A endometrium, biochemical pregnancy and clinical pregnancy rates compared with those received routine programming cycles[37].

However, in our study, we found that sildenafil did not improve both endometrial thickness and clinical pregnancy outcomes in patients exposed to poor endometrial development. Our conclusion is consistent with some earlier studies. Check J H et al. announced that neither sildenafil nor vaginal estradiol could enhance endometrial thickness in patients with thin endometria after taking oral estradiol in graduating dosages[38]. Paulus et al. assessed the effectiveness of sildenafil in 10 women with reduced uterine artery flow and poor endometrial development. These patients received sildenafil 25g every time and 4 times per day from the 3rd day of ovulation induction until ovulation retrieval, and there was no statistically significant difference in endometrial blood flow before and after treatment[39]. Moini A et al. pointed out that the endometrial thickness on hCG day of patients with two prior failed IVF/ICSI attempts and endometrial thickness < 7mm on hCG day in prior IVF/ICSI cycles in the sildenafil group was not statistically different from the placebo group. Although the pregnancy rate was higher in the sildenafil group than the placebo group, there was no statistical difference[40]. Some studies suggested that the limited clinical effect of sildenafil application in patients of poor endometrial development might be because that those patients might already have vascular physiological function dysfunction, which could inhibit the production, activity, release, and availability of NO, or impair the response to downstream signals, such as cGMP [41]. It has also been suggested that some patients might have a history of endometritis, and previous endometritis might reduce the endometrial response to sildenafil[42]. Further, there is a growing realization that when type A or B endometrial patterns are observed, the negative predictive value of pregnancy occurrence is 90.5%[43]. In this study, all groups of patients were diagnosed with type A or B endometrial type, and the difference between the two groups was not clinically significant.

Most of the previous studies just chose EM or clinical pregnancy rate as the main observed indicators[39, 40]. This study further observed the effect of sildenafil on the live birth and pregnancy loss rates. However, one primary limitation of this study lied in its retrospective characteristics. Moreover, endometrial blood flow was not included as a necessary clinical measurement to assess the effect of sildenafil citrate.

Conclusion

To sum up, we discovered that sildenafil citrate was not effective in improving endometrial development and pregnancy outcomes in patients with poor endometrial development during their IVF/ICSI-FET cycles, regardless of how thin the EM was. At the same time, further randomized controlled studies with a larger sample size could be worthwhile to investigate the effect of sildenafil in patients with poor endometrial development.

Abbreviations

The full name	abbreviations
assisted reproductive technology	ART
controlled ovarian hyperstimulation	COH
cyclic guanosine monophosphate	cGMP
Endometrium	EM
frozen-thawed embryo transfer	FET
hormone replacement cycle	HRC
human chorionic gonadotropin	hCG
in vitro fertilization/intra-cytoplasmic sperm injection and frozen-thawed embryo transfer	IVF/ICSI-FET
nitric oxide	NO
ovarian hyperstimulation syndrome	OHSS
pre-implantation genetic testing	PGT
pulsatility index	PI
resistance index	RI
vascular endothelial growth factor	VEGF

Declarations

Ethics approval: The study was approved by the Institutional Review Board of Center for Reproductive Medicine, Shandong University and all individuals provided written informed consent.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: There is no conflict of interest in this study.

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Authors' contributions: Meiling Guo and Jianan Lv conceived of the study under the supervision of Junhao Yan. Meiling Guo designed the study and wrote the initial manuscript. Xinhua performed ultrasound tests on the patients and obtained imaging data. Yuchen Yan, Wei Zhou and Na Yu acquired the patients' clinical data. Mingdi Xia, Jing Li and Qian Zhang revised the manuscript. Meiling Guo, Jianan Lv, Hua Xin and Yuchen Yan contributed equally to this manuscript as first authors.

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