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Research Paper

Clinical outcomes of sildenafil application in patients of poor endometrial development

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ABSTRACT

Objective: To determine whether sildenafil has an effect on pregnancy outcomes in patients with poor endometrial development.

Methods: This study included 472 infertility patients who underwent *in vitro* fertilization/intracytoplasmatic sperm injection and frozen-thawed embryo transfer (IVF/ICSI-FET) and subsequently suffered from poor endometrial development during 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). We analyzed 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 the two groups.

Results: After adjusting for confounding factors, we found no significant differences in endometrial thicknesses and types on endometrial transformation day between the sildenafil group and the control group (0.79 ± 0.08 vs 0.81 ± 0.09, $P = 0.144$; 79.76% vs83.87%, $P = 0.402$). There were also no statistically significant differences in biochemical pregnancy rate (75.0% vs 76.8%, $P = 0.892$), clinical pregnancy rate (59.09% vs 69.53%, $P = 0.087$), early abortion rate (17.31% vs 14.61%, $P = 0.557$), late abortion rate (3.85% vs 4.49%, $P = 0.859$), or live birth rate (45.45% vs 55.47%, $P = 0.101$) between the two groups. In subgroup analysis, the application of sildenafil was unable to improve endometrial thickness (group one: 0.80 ± 0.08 cm vs 0.82 ± 0.08 cm; group two:0.78 ± 0.08 cm vs 0.80 ± 0.10 cm; group three:0.75 ± 0.11 cm vs 0.77 ± 0.08 cm, $p > 0.05$) and type endometrium on transformation day (group one: 78.57% vs 86.78%; group two: 80.65% vs 77.78%; group three: 81.82% vs 83.78%, $p > 0.05$). Moreover, sildenafil use was not closely associated with clinical pregnancy outcomes, clinical pregnancy rate, early abortion rate, late abortion rate, and live birth rate ($p > 0.05$).

Conclusions: Sildenafil did not benefit endometrial development and pregnancy outcomes in patients with poor endometrial development during the hormone replacement cycle.

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1. Introduction

In recent years, with the rapid development of assisted reproductive technology (ART), the pregnancy rate of infertility patients has greatly improved. 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 at increased risk of developing 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 a pregnancy depends on high-quality embryos and a synchronized uterine environment. Endometrium preparation 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 hormone secretion associated with 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 EM turns into a secretory period and is ready 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 EM reaches the transfer standard (commonly at least 8 mm thick).

Poor endometrial development is based on EM thickness and receptivity. An EM is considered poorly developed if it is less than 8 mm thick after 10 days of estrogen application during HRC. Accumulating evidence has demonstrated that a thinner EM is associated with lower clinical pregnancy rates. It is generally accepted that an EM < 7 mm or 8 mm hampers clinical pregnancy and live birth.[9,10] The underlying mechanisms of poor endometrial development are complex, and there is no specific remedy to prevent this from happening. Abnormal endometrial blood flow is thought to be an important cause of poor endometrial development. A number of drugs reported to increase endometrial blood flow, such as aspirin, low-molecular heparin, sildenafil and others, have been recommended for use in patients struggling with poor endometrial development.[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 *in vitro* fertilization/intracytoplasmatic sperm injection and frozen-thawed embryo transfer (IVF/ICSI-FET) cycles, and to provide a new clinical basis for improving pregnancy outcomes in patients with poor endometrial development.

2. Materials and methods

2.1. Study population

A total of 472 female infertility patients who were treated with IVF/ICSI-FET and had poor endometrial development in HRC were recruited from the Center for Reproductive Medicine of Shandong University between April 2017 and July 2019. Women with the following characteristics were included: patients with age<35 years old; EM less than 8 mm after 10 days with estradiol valerate application in HRC and high-quality blastocysts (Embryo scoring was based on the Gardner scoring system[15]); all patients underwent hysteroscopy prior to endometrial preparation. 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).

2.2. Study procedures

All patients were treated with oral estradiol valerate 4 mg/d from the 2nd to 4th day of menstruation for 5 days continuously, and 6 mg/day for the subsequent 5 days. Patients whose EM were less than 8 mm 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/day (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 not using sildenafil citrate were included in the control group (n = 384). Sildenafil citrate was stopped and endometrial transformation was initiated when EM ≥ 8 mm or the optimal thickness of the patient's previous treatment cycle had been reached. Two primary protocols were used for endometrial transformation and subsequent luteal phase support after FET. Protocol 1 was taking oral dydrogesterone (40 mg/d) combined with progesterone capsules (200 mg/d) for each patient. Protocol 2 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≤EM < 8 mm), group two (6≤EM < 7 mm), and group three (EM < 6 mm).

2.3. Outcome measures

The primary observation indicators were the EM thickness and type of EM on the day of endometrial transformation and the growth of the 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.[16] Type A meant three-line types with a 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 the EM was the difference between EM thicknesses measured the day after 10 days of estradiol valerate application and the day of endometrial transformation. The secondary observation indices 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.

2.4. Statistical analysis

SPSS software (version 26.0) was applied for statistical analysis. Continuous variables were expressed as mean ± standard deviation (x ±

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.

3. 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 in the thickness of EM after 10 days of estradiol valerate application (0.65 ± 0.08 vs. 0.68 ± 0.08, $P = 0.003$).

The thickness and type of EM on the day of endometrial transformation and the growth of the EM were compared in Table 2. The thickness of the 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 or the type of EM on the day of endometrial transformation or the growth of EM.

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 was shown not to 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 ($7 \leq EM < 8$ mm, $n = 277$), group two ($6 \leq EM < 7$ mm, $n = 145$), and group three ($EM < 6$ mm, $n = 50$). Table 3 exhibited the baseline characteristics of patients in the subgroups. In group one, the sildenafil group had a higher body mass index (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 was unable to provide prominent benefits for patients suffering from poor endometrial development.

Table 1
The baseline characteristics of all patients(x ± 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: follicle stimulating hormone; LH: luteinizing hormone; E2:estradiol; PRL: prolactin; To: androgen; TSH:thyroid stimulating hormone; AMH: Anti-Mullerian Hormone; EM:endometrium.

Table 2
Endometrial conditions and Pregnancy outcomes of all patients(x ± s, %).

Variable	Sildenafil group	Control group	P value	P-adjust[a]
EM on endometrial transformation day(cm)	0.79 ± 0.08	0.81 ± 0.09	0.035	0.144[b]
Type A endometrium on endometrial transformation day	79.76% (67/84)	83.87% (312/372)	0.364	0.402[c]
The growth of EM (cm)	0.14 ± 0.10	0.13 ± 0.10	0.706	0.144[b]
Biochemical pregnancy rate	75.0% (66/88)	76.8%(295/384)	0.716	0.892[c]
Clinical pregnancy rate	59.09% (52/88)	69.53%(267/384)	0.059	0.087[c]
Early abortion rate	17.31% (9/52)	14.61%(39/267)	0.618	0.557[c]
Late abortion rate	3.85% (2/52)	4.49%(12/267)	1.000	0.859[c]
Live birth rate	45.45% (40/88)	55.47%(213/384)	0.089	0.101[c]

Notes: EM: endometrium.
[a] Adjusted by the thickness of EM after 10 days of estradiol valerate application.
[b] Adjusted with multiple linear regression.
[c] Adjusted with binary logistic regression.

4. Discussion

This study demonstrated that sildenafil application could not better endometrial development and pregnancy outcomes in patients with poor endometrial development during the hormone replacement cycle.

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

Sildenafil citrate enhances the vasodilation effect of NO by preventing cGMP degradation and increasing the expression of β3 integrin and VEGF during the window period, which is important in both the decidualization and implantation process.[21] Sildenafil citrate was initially used as a vasoactive drug to treat erectile dysfunction in men.[22] the clinical applications of sildenafil citrate has gradually expanded to include

Table 3
Baseline characteristics of each group(x ± s,%).

Variable	Group one(7≤EM < 8 mm)			Group two(6≤EM < 7 mm)			Group three(6 mm < 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: AMH: Anti-Mullerian Hormone; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; To: androgen, TSH:thyroid stimulating hormone; EM: endometrium.

Table 4
Endometrial conditions and clinical outcomes of patients of every group (x ± s, %).

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

Notes: EM: endometrium.
[a] Adjusted by body mass index.
[b] Adjusted by basal FSH, number of previous abortions, the thickness of EM after 10 days of estradiol valerate application.
[c] Adjusted with Multiple linear regression.
[d] Adjusted with binary logistic regression.

treatment of issues in the cardiovascular, cerebrovascular, respiration, nervous, and other systems. Previous studies have mentioned that sildenafil citrate's therapeutic effects are likely mediated by improving blood flow perfusion in the corresponding tissues and organs, while some studies came to 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. They 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 through the mechanisms mentioned above .[29] When scholars administered sildenafil citrate to patients with primary dysmenorrhea, they discovered that sildenafil could relieve acute menstrual pain in patients with dysmenorrhea and that sildenafil treatment was associated with no adverse reactions as it acted to alleviate vasoconstriction caused by prostaglandin and reduce pain by inhibiting type 5 specific phosphodiesterase.[30] Jing et al. reported that sildenafil citrate could significantly increase the uterine arterial resistance index (RI) in patients with recurrent spontaneous abortion.[31] Sher et al. first used sildenafil to treat 4 patients with recurrent implantation failure attributed to thin EM in 2000, and detected that endometrial thickness increased and PI decreased after sildenafil treatment, resulting in 3 of the 4 patients achieving pregnancy.[32] Subsequently, Sher et al. expanded the samples size of patients to 105 in a 2002 follow-up study and came to a similar conclusion.[33] This finding that sildenafil can be used to treat patients with a history of implantation failure has also been confirmed by other researchers.[12,34] In a prospective study, sildenafil citrate was added during the endometrial preparation process of FET until the day of transplantation in 22 patients with thin EM and high blood flow resistance. The use of sildenafil significantly increased endometrial thickness and endometrial blood flow in this patient cohort, and consequently

improved pregnancy rate.[35] Takasaki et al. applied sildenafil to 12 patients who had a history of EM thickness <8 mm and uterine artery RI ≥ 0.81 as measured prior to ovulation induction. Compared with previous cycles without sildenafil, it was revealed that endometrial thickness and blood perfusion were increased.[36] A randomized controlled clinical trial conducted by Dehghani Firouzabadi et al. also discovered that patients suffering from poor endometrial development that were treated with sildenafil citrate had a higher endometrial thickness, proportion of type A endometrium, biochemical pregnancy, and clinical pregnancy rates compared to those that received routine programming cycles.[37]

However, in our study, we found that sildenafil did not improve either endometrial thickness or clinical pregnancy outcomes in patients experiencing 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 EM.[38] Paulus et al. assessed the effectiveness of sildenafil in 10 women with reduced uterine artery flow and poor endometrial development. These patients received 25g of sildenafil 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 of patients with two prior failed IVF/ICSI attempts and an endometrial thickness of <7 mm on hCG day in prior IVF/ICSI cycles in the sildenafil group were 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.[34] Some studies suggested that the limited clinical effect of sildenafil application in patients with poor endometrial development might be because those patients had an underlying dysfunction of vascular physiological activity, which could inhibit the production, activity, release, and availability of NO, or impair the response to downstream signals, such as cGMP.[40] It has also been suggested that some patients might have a history of endometritis, and previous endometritis might reduce the endometrial response to sildenafil.[33] 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%.[16] 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.

Many previous studies only looked at EM or clinical pregnancy rate as the main observed indicators.[34,39] This study further observed the effect of sildenafil on live birth rates and pregnancy loss rates. However, one primary limitation of this study lies in its retrospective characteristics. Moreover, endometrial blood flow was not included as a necessary clinical measurement to assess the effect of sildenafil citrate.

5. Conclusion

In summary, 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 hormone replacement cycle, 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.

Author contributions

GM and LJ conceived of the study under the supervision of YJ, GM designed the study and wrote the initial manuscript. XH performed ultrasound tests on the patients and obtained imaging data. YY, ZW and YN acquired the patients' clinical data. XM, LJ and ZQ revised the manuscript. GM, LJ, XH and YY contributed equally to this manuscript as first authors.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics approval

This study was approved by the Institutional Review Board of Center for Reproductive Medicine ([2019] IRB No. (131)), Shandong University and all individuals provided written informed consent.

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