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Original Article

Impact of uterine cavity manipulation history on clinical and neonatal outcomes for *in vitro* fertilization-embryo transfers with donor sperm

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Abstract: Objective: To evaluate the effect of prior uterine cavity procedures on clinical and neonatal outcomes in patients undergoing first-time in vitro fertilization-embryo transfer with donor sperm (IVF-ET with DS). Methods: This retrospective cohort study included 599 infertility patients receiving their first IVF-ET with DS. Patients were categorized into two groups: those with a history of uterine cavity operation group (n=457) and the group with no history (n=142). The former was further subdivided into curettage (n=67), hysteroscopy (n=292), and complex uterine operations (n=98). Primary outcomes included clinical pregnancy outcomes (implantation rate, clinical pregnancy rate, miscarriage rate, and live birth rate) and neonatal outcomes (gestational age, birth weight and length, incidence of being small for gestational age [SGA], large for gestational age [LGA], and preterm birth). Results: No significant differences were found in clinical pregnancy outcomes between the non-operative, curettage, and complex operation groups (all $P > 0.05$). However, the hysteroscopy group showed significantly lower miscarriage rates and higher implantation, clinical pregnancy, and live birth rates (all $P < 0.05$). Multivariate analysis confirmed that hysteroscopy history was independently associated with improved pregnancy outcomes and reduced miscarriage rates, particularly in both age groups (< 35 and ≥ 35 years). No significant differences in neonatal outcomes were observed across all groups (all $P > 0.05$). Conclusion: A history of hysteroscopy is associated with improved implantation, clinical pregnancy, and live birth rates, and a lower miscarriage rate in patients undergoing first IVF-ET with DS, without affecting neonatal outcomes.

Keywords: History of intrauterine operation, in vitro fertilization-embryo transfer, pregnancy outcome, neonatal outcome

Introduction

In vitro fertilization and embryo transfer (IVF-ET) is a widely used clinical treatment for infertility. Successful clinical pregnancy after IVF-ET depends on multiple factors, among which the uterine environment plays a critical role. An abnormal uterine environment can impair embryo implantation and pregnancy maintenance, leading to poor outcomes after embryo transfer [1, 2].

Uterine surgery is a common gynecological intervention used for diagnosis and treatment, including procedures such as dilation and curettage (D&C), surgical abortion, diagnostic curettage, and hysteroscopic surgery [3]. Procedures like surgical abortion may increase the risk of pelvic inflammatory disease (e.g., salpingitis) and damage the endometrial environment, thereby contributing to infertility [4, 5]. Some studies suggest that a history of uterine surgery is associated with reduced success rates in assisted reproduction [6]. However, the impact of prior uterine manipulation on pregnancy and neonatal outcomes after IVF-ET remains controversial. For example, a study by Ozgur et al. [7] reported that surgical abortion adversely affects pregnancy outcomes within six months of the procedure, while other studies found no significant impact of uterine evacuation history on subsequent IVF-ET outcomes [8].

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Therefore, the effect of different types of uterine interventions on clinical and neonatal outcomes in IVF-ET cycles remains unclear. This study aims to minimize the confounding effects of male age and sperm quality by focusing on IVF-ET cycles using donor sperm (IVF-ET with DS), to assess the influence of various uterine procedures on clinical pregnancy and neonatal outcomes, and to explore potential mechanisms, thereby providing theoretical support for improving IVF-ET success rates and neonatal health.

Materials and methods

General information

This retrospective study included 599 infertility patients who underwent first-time IVF-ET with DS between January 2015 and December 2023 at the Third Affiliated Hospital of Guangxi Medical University and the Second People's Hospital of Nanning City. The study was approved by the Ethics Committee of the Second People's Hospital of Nanning City (Ethics Approval No. Y2022015).

Inclusion criteria: (1) patients who received the gonadotropin-releasing hormone (GnRH) agonist long protocol for controlled ovarian hyperstimulation; (2) first-time fresh embryo transfer; (3) complete clinical, diagnostic, treatment, embryo, and outcome data.

Exclusion criteria: (1) congenital uterine anomalies (e.g., septate, bicornuate, unicornuate, or hypoplastic uterus); (2) adenomyosis or endometrial tuberculosis; (3) tubal effusion; (4) sonographic evidence of endometrial polyps; (5) intrauterine fluid, adhesions, etc.; (6) positive serology for hepatitis B, hepatitis C, HIV, or syphilis; (7) ovarian hyperstimulation syndrome; (8) chromosomal abnormalities.

Group classification

Patients were grouped based on their history of intrauterine procedures, including induced abortion, curettage, dilation and curettage, hysteroscopic surgery, or intrauterine device placement/removal. The cohort was divided into a history of uterine cavity operation group (n=457) and a no history group (n=142). The operation group was further classified into three subgroups: Curettage group (n=67): patients who underwent induced abortion, curettage, or dilation and curettage; Hysteroscopy group (n=292): patients with hysteroscopic surgery only; Complex uterine operation group (n=98): patients with multiple types of intrauterine procedures.

Sperm source

Sperm samples were obtained from the following certified sperm banks: Xiangya Reproductive and Genetic Specialty Hospital, the Zhejiang Provincial Institute of Family Planning Science and Technology, Renji Hospital Affiliated to Shanghai Second Medical University, the First Affiliated Hospital of Guangxi Medical University, the Third Affiliated Hospital of Zhengzhou University, and the Affiliated Hospital of Nanchang Medical Science Research Institute. All institutions are licensed by the National Health Commission of China. All sperm donation procedures strictly adhered to national laws, ethical standards, and relevant regulations.

Methods

Controlled ovarian hyperstimulation protocol: All patients received the luteal phase long protocol using GnRH-a (Diphereline, 1.2-1.5 mg). After 14-18 days of downregulation, ovarian stimulation began when downregulation criteria were met: LH < 5 IU/L, estradiol (E2) < 50 pg/mL, endometrial thickness < 4-5 mm, and absence of functional cysts. Gonadotropins (Gonal-F or Ovidrel) were initiated at 150-300 IU/day depending on antral follicle count, age, AMH, and BMI. When follicles reached 13-14 mm, LH (HMG or recombinant LH) was added based on follicular growth, LH and E2 levels, and follicle count. Trigger was performed using human chorionic gonadotropin (8000-10000 IU) or Ovidrel (250 U), and oocyte retrieval was conducted 36-38 hours later under transvaginal ultrasound guidance.

In vitro fertilization and embryo transfer: Oocytes were fertilized with donor sperm. Embryo quality was assessed by two experienced embryologists based on blastomere development, cell number, uniformity, and fragmentation rate. The highest-quality day 3 cleavage embryos or day 5 blastocysts were selected for fresh transfer. A transvaginal ultrasound was performed 28 days post-transfer to con-

firm clinical pregnancy, defined as the presence of a gestational sac. Intrauterine pregnancy was confirmed if the gestational sac was located within the uterus. Miscarriage was defined as pregnancy loss before 28 weeks of gestation [9, 10].

Observational indicators and data collection

(1) Basic information: Age, duration of infertility, body mass index (BMI), basal follicle-stimulating hormone (bFSH), basal estradiol (bE_2), basal luteinizing hormone (bLH), endometrial thickness on the trigger day, number of oocytes retrieved, number of high-quality embryos, and number of embryos transferred.

(2) Pregnancy outcomes [9, 10]: ① Clinical pregnancy rate: calculated as the number of clinical pregnancies divided by the total number of embryo transfer cycles. ② Embryo implantation rate: calculated as the number of implanted embryos divided by the number of embryos transferred. Implanted embryos were defined as those with gestational sacs identified by transvaginal ultrasound 28 days post-transfer. ③ Miscarriage rate: calculated as the number of miscarriages divided by the number of clinical pregnancies. ④ Live birth rate: calculated as the number of live births divided by the total number of embryo transfer cycles.

(3) Neonatal outcomes: Gestational age (weeks at delivery), birth weight, birth length, incidence of being small for gestational age (SGA), large for gestational age (LGA), and preterm birth. In this study, SGA and LGA were defined based on birth weight percentiles [11], with SGA referring to neonates whose birth weight was below the 10th percentile, and LGA to those above the 90th percentile for the corresponding gestational age. Preterm birth was defined as delivery before 37 weeks of gestation.

A total of 599 patients undergoing IVF-ET with DS were included, of which 261 resulted in live births. Among them, 201 were singleton live births and 60 were twin live births. Due to the complex and heterogeneous factors influencing twin births, neonatal outcome analysis was limited to singleton live births.

Data collection: Basic demographic and treatment-related information was extracted from the electronic medical record system and laboratory information management system of the Third Affiliated Hospital of Guangxi Medical University.

Statistical analysis

All statistical analyses were performed using SPSS version 23.0. Continuous variables with normal distribution are presented as mean ± standard deviation; those with non-normal distribution are reported as median (interquartile range), denoted as M (P25, P75). Group comparisons were performed using independent sample t-tests, one-way ANOVA, or non-parametric tests, as appropriate. Categorical variables are expressed as n (%), and group differences were analyzed using chi-square or Fisher's exact tests. Multivariable logistic regression was conducted to assess the association between a history of uterine cavity procedures and pregnancy or neonatal outcomes. A p-value < 0.05 was considered statistically significant.

Results

Comparison of general information

Endometrial thickness on the trigger day was significantly lower in the complex group compared to the no history and hysteroscopy groups ($P < 0.05$). No significant differences were observed among the groups in terms of age, duration of infertility, number of oocytes retrieved, number of high-quality embryos, number of embryos transferred, BMI, bFSH, bE_2, or bLH levels (all $P > 0.05$). For details, see **Table 1**.

Comparison of pregnancy outcomes of IVF-ET with DS

There were no statistically significant differences in embryo implantation rate, clinical pregnancy rate, miscarriage rate, or live birth rate between the history of uterine cavity operation group and the no history group (all $P > 0.05$). However, the hysteroscopy group demonstrated significantly higher embryo implantation, clinical pregnancy, and live birth rates, and a significantly lower miscarriage rate compared to the no history, curettage, and complex groups (all $P < 0.05$). For details, see **Table 2**.

Table 1. Comparison of General information [$\bar{x}$±s, M (P25, P75), n (%)]

General information	No history of uterine cavity operation group (n=142)	Uterine cavity operation history group (n=457)	Curettage group (n=67)	Hysteroscopy group (n=292)	Complex uterine operation group (n=98)
Age (years)	32.91±4.73	32.55±4.15	32.28±4.46	32.33±4.11	33.31±4.00
Duration of infertility (years)	6.00 (5.00, 8.00)	5.00 (4.00, 8.00)	5.00 (4.00, 7.00)	5.00 (3.00, 8.00)	6.00 (4.00, 8.00)
BMI (kg/m^2)	21.51±2.57	21.24±2.91	21.57±3.05	21.16±2.82	21.23±3.08
bFSH (mIU/ml)	5.58±1.52	5.72±1.86	5.64±1.50	5.76±1.83	5.64±2.07
bE_2 (pg/ml)	30.00 (22.00, 42.75)	33.00 (24.00, 47.00)	33.00 (23.50, 51.50)	33.00 (24.00, 47.25)	32.00 (22.00, 46.00)
bLH (mIU/ml)	3.06 (2.42, 4.14)	3.28 (2.48, 4.63)	3.24 (2.49, 4.96)	3.42 (2.54, 4.60)	3.16 (2.31, 4.64)
Endometrial thickness on the trigger day (mm)	12.43±2.66	12.06±2.56	12.00±2.41	12.32±2.69	11.41±2.20^{*,a}
Number of oocytes retrieved	10.00 (8.00, 12.25)	10.00 (7.00, 13.00)	10.00 (7.00, 12.00)	10.00 (7.00, 13.00)	10.00 (7.00, 12.00)
Number of high-quality embryos	3.00 (1.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)
Number of embryos transferred	1.92±0.27	1.86±0.36	1.90±0.31	1.84±0.38	1.89±0.32

Note: $^*P < 0.05$: compared to the No history of uterine cavity operation group; $^aP < 0.05$: compared to the hysteroscopy group; BMI: Body mass index, bFSH: Basal Follicle-Stimulating Hormone, bE_2: Basal Estradiol, bLH: Basal Luteinizing Hormone.

Table 2. Comparison of pregnancy outcomes of IVF-ET with DS [%, (n)]

Group	Embryo implantation rate	Clinical pregnancy rate	Miscarriage rate	Live birth rate
No history of uterine cavity operation group (n=142)	30.40 (83/273)	44.37 (63/142)	19.05 (12/63)	35.92 (51/142)
Uterine cavity operation history group (n=457)	38.09 (323/848)	52.08 (238/457)	11.76 (28/238)	45.95 (210/457)
Curettage group (n=67)	32.28 (41/127)	44.78 (30/67)	16.67 (5/30)	37.31 (25/67)
Hysteroscopy group (n=292)	41.79 (224/536)$^{*,\#}$	57.19 (167/292)$^{*,\#}$	8.38 (14/167)$^{*,\#}$	52.40 (153/292)$^{*,\#}$
Complex uterine operation group (n=98)	31.35 (58/185)^a	41.84 (41/98)^a	21.95 (9/41)^a	32.65 (32/98)^a

Note: $^*P < 0.05$: compared to the No history of uterine cavity operation group; $^\#P < 0.05$: compared to the curettage group; $^aP < 0.05$: compared to the Hysteroscopy group; IVF-ET with DS: In Vitro Fertilization-Embryo Transfer with Donor Sperm.

Table 3. Comparison of neonatal outcomes in IVF-ET with DS [$\bar{x}$±s, n (%)]

Neonatal outcome	No history of uterine cavity operation group (n=42)	Uterine cavity operation history group (n=159)	Curettage group (n=23)	Hysteroscopy group (n=106)	Complex uterine operation group (n=30)
Gestational age (weeks)	38.26±1.73	38.27±1.47	38.48±1.83	38.16±1.46	38.50±1.20
Preterm infants	5 (11.90)	12 (7.55)	2 (8.70)	7 (6.60)	3 (10.00)
Birth weight (g)	3070.24±372.63	3067.64±505.88	3224.78±481.71	3039.48±500.27	3196.67±400.12
SGA	6 (14.29)	10 (6.29)	2 (8.70)	7 (6.60)	1 (3.33)
LGA	3 (7.14)	15 (9.43)	3 (13.04)	10 (9.43)	2 (6.67)
Birth length (cm)	49.76±1.43	50.05±2.08	49.82±2.46	50.11±1.95	50.07±2.14

Note: SGA: small for gestational age, LGA: large for gestational age, IVF-ET with DS: In Vitro Fertilization-Embryo Transfer with Donor Sperm.

Comparison of neonatal outcomes in IVF-ET with DS

There were no significant differences in gestational age, incidence of preterm birth, neonatal birth weight, SGA, LGA, or birth length between patients with or without a history of uterine procedures, or among the uterine operation subgroups (all P > 0.05). See **Table 3** for details.

Impact of history of uterine operation on clinical outcomes in IVF-ET with DS

A multivariate logistic regression model was constructed to assess the impact of different types of uterine operations on pregnancy and neonatal outcomes, with endometrial thickness on the trigger day included as a covariate. The results indicated that, both before and after adjustment, a history of hysteroscopic surgery was independently associated with improved clinical pregnancy, implantation, and live birth rates, and with a reduced miscarriage rate (all P < 0.05). See **Table 4** for details.

Age-stratified analysis: clinical characteristics and outcomes by age group

To assess age-related differences, patients were stratified into age-appropriate (< 35 years) and advanced age (≥ 35 years) groups. In the age-appropriate group, endometrial thickness on the trigger day was significantly lower in the complex group compared to the no history group (P < 0.05). The hysteroscopy group had a significantly lower miscarriage rate and higher live birth rate compared to the complex and no history groups (both P < 0.05). See **Table 5** for details.

In the advanced age group, endometrial thickness on the trigger day was significantly lower in the complex group compared to the hysteroscopy group (P < 0.05). The hysteroscopy group showed significantly higher rates of embryo implantation, clinical pregnancy, and live birth than the other three groups (all P < 0.05). See **Table 6** for details.

Impact of different uterine operation types on clinical outcomes by age

Among women < 35 years of age, those with a history of hysteroscopic surgery had a significantly lower miscarriage rate (Odds Ratio [OR] =0.308, 95% Confidence Interval [CI]: 0.101-0.935) and a significantly higher live birth rate (OR =1.840, 95% CI: 1.118-3.028) compared to those without such a history.

Among women ≥ 35 years of age, those with a history of hysteroscopic surgery had significantly higher clinical pregnancy (OR =2.124, 95% CI: 1.021-4.416), embryo implantation (same OR as above), and live birth rates (OR =2.289, 95% CI: 1.061-4.941) than those without a hysteroscopy history. See **Tables 7** and **8** for details.

Discussion

Donor sperm in vitro fertilization is indicated for men with azoospermia, severe oligozoospermia, or poor sperm quality, as well as for men with genetic disorders that render them unfit for childbearing [12]. Cryopreserved donor sperm is selected for fertility treatments, with all donors being under 45 years of age and meeting the semen quality standards established by the Ministry of Health. This ensures good sperm homogeneity, thereby minimizing male-related confounding factors. After excluding male-related factors, embryo quality and endometrial receptivity are critical determi-

Table 4. Analysis of the impact of different types of uterine operation history on clinical outcomes of IVF-ET with DS

Clinical outcomes	Model 1 [OR (95% CI)]				Model 2 [OR (95% CI)]			
	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation
Clinical pregnancy/embryo implantation rate	1	1.017 (0.567-1.824)	1.675 (1.118-2.510)*	0.902 (0.536-1.518)	1	1.015 (0.565-1.821)	1.673 (1.117-2.507)*	0.995 (0.935-1.059)
Miscarriage rate	1	0.850 (0.270-2.679)	0.389 (0.169-0.895)*	1.195 (0.453-3.155)	1	0.854 (0.271-2.693)	0.390 (0.169-0.898)*	1.235 (0.456-3.340)
Live birth rate	1	1.062 (0.582-1.940)	1.964 (1.300-2.967)*	0.865 (0.502-1.490)	1	1.060 (0.580-1.936)	1.961 (1.298-2.964)*	0.862 (0.499-1.487)

Note: *P < 0.05; Model 1: no adjustment factor added; Adjustment 2: endometrial thickness on the trigger day was used as an adjustment factor. Because both implantation and clinical pregnancy occurred in this study, the regression analysis parameters for implantation and clinical pregnancy rates were the same, and therefore, only 1 row of the table is presented to show the data; IVF-ET with DS: In Vitro Fertilization-Embryo Transfer with Donor Sperm, OR: Odds Ratio, 95% CI: 95% Confidence Interval.

Table 5. Comparison of clinical characteristics and outcomes among different groups of age-appropriate patients [$\bar{x}\pm s$, M (P25, P75), n (%)]

Clinical features and clinical outcomes	No history of uterine cavity operation group (n=91)	Uterine cavity operation history group (n=310)	Curettage group (n=37)	Hysteroscopy group (n=218)	Complex uterine operation group (n=55)
Age (years)	30.18±3.13	30.28±2.87	29.92±3.06	30.49±2.82	30.38±2.58
Duration of infertility (years)	5.00 (4.00, 7.00)	5.00 (3.00, 7.00)	4.00 (3.00, 6.00)	5.00 (3.00, 7.00)	5.00 (4.00, 8.00)
BMI (kg/m^2)	21.66±2.69	21.16±2.77	21.13±3.12	21.10±2.73	21.41±2.74
bFSH (mIU/ml)	5.48±1.45	5.80±2.11	5.68±1.64	5.82±1.99	5.79±2.75
bE_2 (pg/ml)	29.00 (22.00, 45.50)	33.00 (24.00, 46.00)	28.00 (21.25, 39.75)	34.00 (24.00, 49.00)	32.00 (23.00, 47.00)
bLH (mIU/ml)	3.16 (2.49, 4.10)	3.42 (2.58, 4.65)	3.24 (2.55, 4.96)	3.53 (2.56, 4.70)	3.18 (2.22, 4.97)
Endometrial thickness on the trigger day (mm)	12.64±2.73	12.08±2.53	12.02±2.45	12.31±2.61	11.63±2.29*
Number of oocytes retrieved	11.00 (8.00, 13.00)	10.00 (7.00, 13.00)	11.00 (6.50, 14.50)	10.00 (7.00, 13.00)	10.00 (8.00, 14.00)
Number of high-quality embryos	3.00 (1.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.50, 6.00)	4.00 (2.00, 6.25)	3.00 (1.00, 5.00)
Number of embryos transferred	1.92±0.27	1.84±0.37	1.84±0.37	1.83±0.38	1.85±0.36
Clinical pregnancy rate (%)	48.35 (44/91)	55.81 (173/310)	51.35 (19/37)	58.72 (128/218)	47.27 (26/55)
Embryo implantation rate (%)	35.43 (62/175)	41.83 (238/569)	38.23 (26/68)	43.86 (175/399)	36.27 (37/102)
Miscarriage rate (%)	15.91 (7/44)	8.09 (14/173)	10.53 (2/19)	5.47 (7/128)*	19.23 (5/26)[a]
Live birth rate (%)	40.66 (37/91)	51.29 (159/310)	45.95 (17/37)	55.50 (121/218)*	38.18 (21/55)[a]

Note: *P < 0.05: compared to the No history of uterine cavity operation group; [a]P < 0.05: compared to the Hysteroscopy group. BMI: Body mass index, bFSH: Basal Follicle-Stimulating Hormone, bE_2: Basal Estradiol, bLH: Basal Luteinizing Hormone.

Table 6. Comparison of clinical characteristics and outcomes among different groups of age-advanced patients [$\bar{x}\pm s$, M (P25, P75), n (%)]

Clinical features and clinical outcomes	No history of uterine cavity operation group (n=51)	Uterine cavity operation history group (n=147)	Curettage group (n=30)	Hysteroscopy group (n=74)	Complex uterine operation group (n=43)
Age (years)	37.78±2.38	37.03±2.07	36.50±1.38	37.42±2.41	36.74±1.69
Duration of infertility (years)	7.00 (6.00, 9.00)	6.00 (5.00, 9.00)	7.00 (5.00, 10.00)	6.00 (5.00, 9.00)	6.00 (4.00, 9.00)
BMI (kg/m^2)	21.25±2.32	21.46±3.12	22.11±2.91	21.35±3.07	21.20±3.35
bFSH (mIU/ml)	5.76±1.64	5.50±1.28	5.59±1.34	5.60±1.21	5.50±1.33
bE_2 (pg/ml)	33.00 (24.00, 41.00)	34.00 (25.00, 50.25)	40.00 (30.00, 69.50)	28.00 (24.00, 37.00)	34.00 (18.50, 47.00)
bLH (mIU/ml)	2.34 (2.82, 4.43)	3.13 (2.30, 4.58)	2.92 (2.31, 5.01)	3.13 (2.35, 4.29)	2.96 (2.34, 4.52)
Endometrial thickness on the trigger day (mm)	12.06±2.50	11.98±2.63	11.99±2.40	12.36±2.92	11.34±2.13[a]
Number of oocytes retrieved	9.00 (8.00, 12.00)	9.00 (6.50, 12.00)	9.00 (6.75, 12.00)	10.00 (6.75, 13.00)	10.00 (7.00, 12.00)
Number of high-quality embryos	3.00 (1.00, 5.00)	3.00 (2.00, 5.00)	3.00 (1.00, 5.00)	3.00 (1.00, 6.00)	3.00 (2.00, 5.00)
Number of embryos transferred	1.92±0.27	1.90±0.33	1.97±0.18	1.85±0.39	1.93±0.26
Clinical pregnancy rate (%)	37.25 (19/51)	44.22 (65/147)	36.67 (11/30)	52.70 (39/74)[*,#]	34.88 (15/43)[a]
Embryo implantation rate (%)	21.43 (21/98)	30.47 (85/279)	25.42 (15/59)	35.77 (49/137)[*,#]	25.30 (21/83)[a]
Miscarriage rate (%)	26.32 (5/19)	21.54 (14/65)	27.27 (3/11)	17.95 (7/39)	26.67 (4/15)
Live birth rate (%)	27.45 (14/51)	34.69 (51/147)	26.67 (8/30)	43.24 (32/74)[*,#]	35.58 (11/43)[a]

Note: [*]P < 0.05: compared to the No history of uterine cavity operation group; [#]P < 0.05: compared to the curettage group; [a]P < 0.05: compared to the Hysteroscopy group. BMI: Body mass index, bFSH: Basal Follicle-Stimulating Hormone, bE_2: Basal Estradiol, bLH: Basal Luteinizing Hormone.

Table 7. Analysis of the effect of different types of uterine operation history on clinical outcomes of IVF-ET with DS in the age-appropriate group

Clinical outcome	Model 1 [OR (95% CI)]				Model 2 [OR (95% CI)]			
	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation
Miscarriage rate	1	0.622 (0.117-3.314)	0.306 (0.101-0.928)[*]	1.259 (0.355-4.465)	1	0.625 (0.117-3.333)	0.308 (0.101-0.935)[*]	1.307 (0.354-4.823)
Live birth rate	1	1.241 (0.574-2.679)	1.821 (1.108-2.991)[*]	0.901 (0.454-1.790)	1	1.259 (0.582-2.725)	1.840 (1.118-3.028)[*]	0.920 (0.462-1.834)

Note: [*]P < 0.05; Model 1: no adjustment factor added; Adjustment 2: endometrial thickness on the trigger day was used as an adjustment factor; IVF-ET with DS: In Vitro Fertilization-Embryo Transfer with Donor Sperm, OR: Odds Ratio, 95% CI: 95% Confidence Interval.

Table 8. Analysis of the effect of different types of uterine operation history on clinical outcomes of IVF-ET with DS in the age-advanced group

Clinical outcome	Model 1 [OR (95% CI)]				Model 2 [OR (95% CI)]			
	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation	No history of uterine cavity operation	History of curettage	History of hysteroscopy	History of Complex uterine operation
Clinical pregnancy rate/embryo implantation rate	1	0.975 (0.383-2.483)	2.093 (1.009-4.340)[*]	0.902 (0.387-2.102)	1	0.972 (0.381-2.478)	2.124 (1.021-4.416)[*]	0.875 (0.374-2.048)
Live birth rate	1	0.961 (0.348-2.655)	2.246 (1.044-4.834)[*]	0.908 (0.362-2.281)	1	0.958 (0.346-2.650)	2.289 (1.061-4.941)[*]	0.875 (0.347-2.207)

Note: [*]P < 0.05; Model 1: no adjustment factor added; Adjustment 2: endometrial thickness on the trigger day was used as an adjustment factor. Because both implantation and clinical pregnancy occurred in this study, the regression analysis parameters for implantation and clinical pregnancy rates were the same, and therefore, only 1 row of the table is presented to show the data; IVF-ET with DS: In Vitro Fertilization-Embryo Transfer with Donor Sperm.

nants of IVF-ET success. While criteria for assessing embryo quality are well established, the impact of endometrial receptivity remains a major concern for reproductive physicians [13, 14].

Endometrial receptivity refers to the endometrium's ability to support embryo localization, adhesion, penetration, and implantation [15]. It is influenced by various factors, including sex hormone levels, controlled ovarian hyperstimulation regimens, uterine blood flow, and immune status, all of which affect embryo transfer outcomes. Endometrial thickness, blood flow, and volume are key indicators of endometrial receptivity.

Historically, researchers have sought to determine whether endometrial thickness can predict clinical pregnancy rates. Previous studies have shown that patients with thinner endometriums tend to experience lower implantation, clinical pregnancy, and live birth rates, and higher miscarriage rates in IVF-ET cycles [16]. In this study, we observed no significant difference in endometrial thickness between the hysteroscopy and curettage groups compared to the no history group. However, the Complex group had significantly thinner endometriums compared to the no history group. This finding aligns with Liu et al. [17], who reported that repeated and severe intrauterine procedures may cause endometrial damage and thinning.

Despite these findings, our study revealed no significant differences in embryo implantation rate, clinical pregnancy rate, miscarriage rate, or live birth rate between the no history group and the history group. Specific analysis of subgroups with a history of uterine procedures also showed no significant differences in these outcomes between the complex group and the no history group. Interestingly, the hysteroscopy group exhibited significantly higher rates of implantation, clinical pregnancy, and live birth, and significantly lower miscarriage rates compared to the no history, curettage, and complex groups. These findings are consistent with those of Tam et al. [18] and Vitale et al. [19]. A meta-analysis examining the relationship between endometrial thickness and pregnancy rates in artificial insemination [20] also found no significant correlation between the two. This suggests that, within a certain range, endometrial thickness may not have a direct impact on pregnancy outcomes.

In this study, we found no significant differences in gestational age at delivery, birth weight, birth length, SGA, LGA, or preterm birth between the history group and its subgroups, compared to the no history group. These findings suggest that a history of uterine manipulation in infertile patients undergoing IVF-ET with DS cycles is not associated with adverse neonatal outcomes. Specifically, the presence or absence of a history of intrauterine manipulation does not appear to increase the risk of adverse neonatal outcomes. This is consistent with the findings of Tada et al. [21], who reported that uterine cavity operations, such as induced abortion, induced labor, and hysteroscopy, do not increase the likelihood of adverse outcomes like preterm birth or fetal growth restriction in pregnant women undergoing embryo implantation.

By performing multifactorial logistic regression analysis, we further explored the effects of different histories of uterine manipulation on embryo implantation rate, clinical pregnancy rate, miscarriage rate, and live birth rate. The results showed that, both before and after adjusting for endometrial thickness on the trigger day, a history of hysteroscopy improves the clinical pregnancy rate, implantation rate, and live birth rate in IVF-ET with DS cycles, while reducing the miscarriage rate. These findings are in agreement with a study by Kilic et al. [22].

Several potential mechanisms could explain these results. The detection rate of uterine cavity abnormalities is higher with hysteroscopy in patients who appear normal on vaginal ultrasound, particularly among older women [23, 24]. These abnormalities may cause mechanical or inflammatory damage to the endometrium, interfering with its normal endocrine function and negatively impacting endometrial receptivity [25]. Hysteroscopy allows for the diagnosis and treatment of undetected uterine abnormalities, improving endometrial tolerance and, by extension, the uterine environment. This improvement may enhance overall treatment outcomes [26, 27]. Additionally, some studies suggest that minor endometrial damage from hysteroscopy may stimulate proliferative endometrial metaplasia and alter the secretion of endometrial cytokines and growth

factors, improving endometrial tolerance and reducing miscarriage rates [28, 29]. Another theory proposes that hysteroscopy may induce immune system and gene expression changes that enhance endometrial receptivity and implantation [30]. However, studies by Ben et al. [31] and Marchand et al. [32] found no benefit of hysteroscopy for infertile women undergoing IVF-ET. Differences in study design, patient selection, surgical technique, and postoperative management may explain these divergent conclusions.

This study also demonstrated that hysteroscopy or hysteroscopic treatment significantly improves pregnancy outcomes in IVF-ET with DS, especially in women of advanced age. Specifically, hysteroscopy improved live birth rates in women of all ages, increased embryo implantation and clinical pregnancy rates in women aged ≥ 35 years, and reduced the miscarriage rate in women aged < 35 years. These findings suggest that hysteroscopy may offer greater benefits for women aged ≥ 35 undergoing IVF-ET with DS. One potential explanation is that older women have a higher detection rate of uterine abnormalities, and treatment of these abnormalities may improve embryo implantation rates and pregnancy outcomes by enhancing endometrial receptivity [27].

The study's strength lies in its use of a standardized long protocol of gonadotropin-releasing hormone agonist for ovulation induction, which minimizes the impact of varying ovulation induction protocols on IVF-ET with DS outcomes. Additionally, stratified analyses by age group were conducted to assess clinical outcomes. However, this study has limitations: being a retrospective study, it is difficult to exclude all potential confounding factors. Moreover, as a single-center study, the generalizability of the results may be limited. Prospective, multicenter studies are needed to further validate these findings.

In conclusion, this study suggests that repeated and severe intrauterine surgery may lead to endometrial damage and thinning; however, no clear direct association was found between endometrial thickness and pregnancy or neonatal outcomes. A history of intrauterine operation does have an impact on IVF-ET with DS clinical outcomes. Hysteroscopy and hysteroscopic treatment can improve embryo implantation rates, clinical pregnancy rates, live birth rates, and reduce miscarriage rates. However, no association was found between a history of intrauterine manipulation and neonatal outcomes in IVF-ET with DS cycles.

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Disclosure of conflict of interest

None.

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References

[1] Moradi Alamdarloo S, Razavi B, Motamedifar M, Hashemi A, Samsami A, Homayoon N, Ghasempour L, Davoodi S, Homayoon H, Mohebi S, Hadadi M and Hessami K. The effect of endocervical and catheter bacterial colonisation during in vitro fertilisation and embryo transfer (IVF-ET) on IVF success rate among asymptomatic women: a longitudinal prospective study. J Obstet Gynaecol 2022; 42: 333-337.

[2] Zhou F, Zhao F, Jin X, Li C and Zhang S. Factors affecting clinical outcomes after IVF-ET for infertile young patients with ovarian endometrioma: a 5-year retrospective cohort study. Medicine (Baltimore) 2022; 101: e29793.

[3] Zhang Y, de Ziegler D, Hu X, Tai X, Han Y, Ma J, Zhang Y and Luo H. Previous caesarean delivery and the presence of caesarean scar defects could affect pregnancy outcomes after in vitro fertilization frozen-thawed embryo transfer: a retrospective cohort study. BMC Pregnancy Childbirth 2022; 22: 769.

[4] Zhang S, Tang H and Zhou M. Association between previous surgical termination of pregnancy and pregnancy outcomes in frozen-thawed embryo transfer cycles of IVF/ICSI: a retrospective cohort study. Sci Rep 2024; 14: 6579.

[5] Tu P and Pei K. Prior surgical uterine evacuation of pregnancy and infertility: protocol for systematic review and meta-analysis. BMJ Open 2020; 10: e034837.

[6] Zhang YF, Luo HN, Zhang YJ, Shi R, Ma JF and Zhang YS. Effect of the number of previous spontaneous abortions on the first in vitro fertilization cycle. Zhonghua Fu Chan Ke Za Zhi 2019; 54: 803-807.
[7] Ozgur K, Bulut H, Berkkanoglu M, Basegmez FO and Coetzee K. Six-month recovery needed after dilation and curettage (D and C) for reproductive outcomes in frozen embryo transfer. J Obstet Gynaecol 2018; 38: 1150-1157.
[8] Meng J, Zhu M, Shen W, Huang X, Sun H and Zhou J. Influence of surgical evacuation on pregnancy outcomes of subsequent embryo transfer cycle following miscarriage in an initial IVF cycle: a retrospective cohort study. BMC Pregnancy Childbirth 2019; 19: 409.
[9] Hu LL, Huang GN, Sun HX, Fan LQ, Feng Y, Shen H and Sun Y. CSRM consensus on key indicators for quality control in ART clinical operation. J Reprod Med 2018; 27: 828-35.
[10] Sun Q, Huang GN, Sun HX, Fan LQ, Feng Y and Shen H. CSRM consensus on key indicators for quality control in IVF laboratory. J Reprod Med 2018; 27: 836-51.
[11] Schlaudecker EP, Munoz FM, Bardají A, Boghossian NS, Khalil A, Mousa H, Nesin M, Nisar MI, Pool V, Spiegel HML, Tapia MD, Kochhar S and Black S; Brighton Collaboration Small for Gestational Age Working Group. Small for gestational age: case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine 2017; 35 (48 Pt A): 6518-6528.
[12] Segal TR and Giudice LC. Before the beginning: environmental exposures and reproductive and obstetrical outcomes. Fertil Steril 2019; 112: 613-621.
[13] Zhang HX, Li F, Jin H, Song WY, Su Y and Li G. Effect of retained embryos on pregnancy outcomes of in vitro fertilization: a matched retrospective cohort study. BMC Pregnancy Childbirth 2023; 23: 5.
[14] Kadour-Peero E, Tulandi T, Feferkorn I, Hiszkiahu R and Buckett W. Effects of embryo retention during embryo transfer on IVF outcomes. J Assist Reprod Genet 2022; 39: 1065-1068.
[15] Wang Q, Ai H, Li X, Tian H, Ning B, Zhang M and La X. Association of miRNA-145 with the occurrence and prognosis of hydrosalpinx-induced defective endometrial receptivity. Bosn J Basic Med Sci 2021; 21: 81-92.
[16] Liao Z, Liu C, Cai L, Shen L, Sui C, Zhang H and Qian K. The effect of endometrial thickness on pregnancy, maternal, and perinatal outcomes of women in fresh cycles after IVF/ICSI: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2022; 12: 814648.
[17] Liu T, He B and Xu X. Repairing and regenerating injured endometrium methods. Reprod Sci 2023; 30: 1724-1736.
[18] Tam WH, Tsui MH, Lok IH, Yip SK, Yuen PM and Chung TK. Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage. Hum Reprod 2005; 20: 3355-9.
[19] Vitale SG, Angioni S, Parry JP, Di Spiezio Sardo A, Haimovich S, Carugno J, Alonso Pacheco L, Perez-Medina T, Moawad N, De Franciscis P and Riemma G. Efficacy of hysteroscopy in improving fertility outcomes in women undergoing assisted reproductive technique: a systematic review and meta-analysis of randomized controlled trials. Gynecol Obstet Invest 2023; 88: 336-348.
[20] Weiss NS, van Vliet MN, Limpens J, Hompes PGA, Lambalk CB, Mochtar MH, van der Veen F, Mol BWJ and van Wely M. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. Hum Reprod 2017; 32: 1009-1018.
[21] Tada Y, Kitaya K, Amano N, Kobatake M, Hayashi T, Taguchi S, Funabiki M and Nakamura Y. A pilot survey on obstetric complications in pregnant women with a history of repeated embryo implantation failure and those undergoing single local endometrial injury. Clin Exp Obstet Gynecol 2015; 42: 176-8.
[22] Kilic Y, Bastu E and Ergun B. Validity and efficacy of office hysteroscopy before in vitro fertilization treatment. Arch Gynecol Obstet 2013; 287: 577-81.
[23] El-Mazny A, Abou-Salem N, El-Sherbiny W and Saber W. Outpatient hysteroscopy: a routine investigation before assisted reproductive techniques? Fertil Steril 2011; 95: 272-6.
[24] Monteiro CS, Cavallo IK, Dias JA, Pereira FAN and Reis FM. Uterine alterations in women undergoing routine hysteroscopy before in vitro fertilization: high prevalence of unsuspected lesions. JBRA Assist Reprod 2019; 23: 396-401.
[25] Saare M, Lawarde A, Modhukur V, Mikeltadze I, Karro H, Minajeva A, Salumets A and Peters M. The expression pattern of endometrial receptivity genes is desynchronized between endometrium and matched endometriomas. Reprod Biomed Online 2022; 45: 713-720.
[26] Tamura H, Yoshida H, Kikuchi H, Josaki M, Mihara Y, Shirafuta Y, Shinagawa M, Tamura I, Taketani T, Takasaki A and Sugino N. The clinical outcome of dienogest treatment followed by in vitro fertilization and embryo transfer in infertile women with endometriosis. J Ovarian Res 2019; 12: 123.
[27] Mao X, Wu L, Chen Q, Kuang Y and Zhang S. Effect of hysteroscopy before starting in-vitro fertilization for women with recurrent implantation failure: a meta-analysis and systema-

tic review. Medicine (Baltimore) 2019; 98: e14075.
[28] Palomba S, Vitagliano A, Marci R and Caserta D. Endometrial scratching for improving endometrial receptivity: a critical review of old and new clinical evidence. Reprod Sci 2023; 30: 1701-1711.
[29] Siristatidis C, Kreatsa M, Koutlaki N, Galazios G, Pergialiotis V and Papantoniou N. Endometrial injury for RIF patients undergoing IVF/ICSI: a prospective nonrandomized controlled trial. Gynecol Endocrinol 2017; 33: 297-300.
[30] Inagaki N, Stern C, McBain J, Lopata A, Kornman L and Wilkinson D. Analysis of intra-uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer. Hum Reprod 2003; 18: 608-15.
[31] Ben Abid H, Fekih M, Fathallah K, Chachia S, Bibi M and Khairi H. Office hysteroscopy before first in vitro fertilization. A randomized controlled trial. J Gynecol Obstet Hum Reprod 2021; 50: 102109.
[32] Marchand GJ, Masoud AT, Ulibarri H, Parise J, Arroyo A, Coriell C, Goetz S, Moir C and Moberly A. Effect of the decision to perform hysteroscopy on asymptomatic patients before undergoing assisted reproduction technologies-a systematic review and meta-analysis. AJOG Glob Rep 2023; 3: 100178.