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Heterogeneous reproductive benefits of pre-FET hysteroscopy: stratification analysis by intrauterine status and embryonic developmental stage

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Research Article

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Abstract

Background

Hysteroscopy serves as the gold standard for diagnosing and treating intrauterine lesions and is widely applied before Assisted Reproductive Technology (ART) embryo transfer. The benefit of office hysteroscopy(OH) in patients with recurrent implantation failure(RIF)has been increasingly acknowledged. Nevertheless, consensus remains absent on the impact of routine pre-frozen–thawed embryo transfer (FET) OH on subsequent pregnancy outcomes. This study sought to determine whether pre-FET hysteroscopic assessment combined with endometrial management improves patients' pregnancy outcomes.

Methods

This retrospective cohort study enrolled 496 patients (496 FET cycles) treated at the Reproductive Medicine Center of Tongji Hospital, Tongji University, from January 1, 2019 to May 31, 2025, with follow-up concluding on June 30, 2026. Participants were categorized into two groups: Subjects were allocated to OH group (308 cycles) and control group without hysteroscopy (188 cycles). Pregnancy outcomes, including antenatal complications and neonatal complications, were compared between the two groups. Subgroup analyses within the hysteroscopy group were conducted based on intrauterine status (normal vs abnormal cavity) and embryo transfer type.

Results

The hysteroscopy group exhibited significantly higher biochemical pregnancy rates (70.78% vs. 60.64%, $P < 0.05$) and clinical pregnancy rates (55.20% vs. 45.74%, $P < 0.05$) than the control group. Hysteroscopy did not increase adverse obstetric or perinatal risks, while gestational age and singleton neonatal birth weight differed significantly between the two groups ($P < 0.05$). Further stratified analyses within the hysteroscopy cohort showed comparable overall pregnancy outcomes between patients with normal and abnormal uterine cavities (all $P > 0.05$). In intra-cohort comparison of embryonic developmental stages, blastocyst transfer yielded numerically elevated biochemical and clinical pregnancy rates compared with cleavage-stage embryo transfer, though the differences were not statistically significant; notably, blastocyst transfer achieved a substantially higher live birth rate (47.15% vs. 22.22%, $P < 0.05$).

Conclusions

This study demonstrates that pre-FET hysteroscopy improves biochemical and clinical pregnancy rates without increasing adverse obstetric or perinatal risks. The reproductive benefit of hysteroscopy is heterogeneous, acting as a compensatory repair effect for pathological endometrium rather than conferring extra benefits for patients with normal uterine cavities. The long-term live birth benefit is

restricted to the subgroup of patients with uterine structural abnormalities receiving blastocyst transfer. These findings support hysteroscopy as a selective intervention instead of a universal strategy for all FET candidates. Individualized assessment based on baseline uterine status and embryonic developmental stage facilitates identification of high-benefit patients and guides the precise application of pre-FET hysteroscopy.

Background

Infertility currently afflicts 12–18% of couples worldwide[1]. Embryo implantation results from the highly coordinated interplay among embryonic developmental potential, endometrial receptivity, the intrauterine immune microenvironment, and local molecular signaling networks[2]. Occult intrauterine microlesions, chronic endometrial inflammation, inadequate decidualization, and intrauterine microbial dysbiosis may perturb the endometrial niche for implantation, thereby attenuating the efficiency of embryo adhesion and implantation. OH affords direct visualization for the diagnosis and management of intrauterine structural abnormalities and, via controlled mechanical stimulation of the endometrium, elicits reparative remodeling[3]. It presently serves as a pivotal preconditioning strategy for optimizing the intrauterine implantation microenvironment and improving embryo transfer success rates.

Existing clinical evidence has preliminarily substantiated that hysteroscopic intervention prior to FET is conducive to optimizing the conditions for embryo implantation and enhancing early pregnancy success rates[4]. Evidence indicates that hysteroscopy can not only correct structural uterine cavity abnormalities but also further optimize endometrial receptivity by modulating endometrial repair and the local microenvironment[5]. However, findings from other randomized controlled trials have demonstrated that hysteroscopy does not improve pregnancy outcomes either in patients with normal ultrasonographic findings undergoing their first IVF cycle or in those with a history of 2–4 failed embryo transfers[6]. Consequently, the optimal candidate population for hysteroscopic intervention, the differential responsiveness across embryonic developmental stages, and long-term perinatal safety have not yet coalesced into a unified and systematic clinical consensus, and further clinical evidence and mechanistic validation remain warranted.

Our study systematically evaluates the overall effects of hysteroscopic intervention prior to FET on early pregnancy, obstetric, and neonatal outcomes. By further conducting stratified analyses according to uterine cavity morphology and embryonic developmental stage, it aims to characterize the differential responses to hysteroscopic intervention across distinct populations and to elucidate the core effect profile and applicable indications of hysteroscopy in enhancing uterine receptivity. The findings are expected to provide robust clinical evidence for the individualized design of pre-FET intrauterine preconditioning strategies, the precise identification of patients most likely to benefit, and the safe and standardized implementation of hysteroscopic preconditioning in clinical practice.

Materials and methods

Study design and patients

This retrospective cohort study was conducted at the Reproductive Medicine Center of Tongji Hospital Affiliated to Tongji University. Both partners of each infertile couple underwent requisite examinations. Embryo-transfer cycles were performed between January 1, 2019 to May 31, 2025, with follow-up concluding on June 30, 2026. Only couples with infertility attributable to tubal factors, male-related factors or unexplained causes were enrolled.The inclusion criteria were as follows: (i) maternal age ≤ 40 years; (ii) body-mass index (BMI) ≤ 26 kg/m²; (iii) patients who requested OH were enrolled into the hysteroscopy group;(iv) normal peripheral blood karyotypes in both partners;(v) no prior hysteroscopy performed within the preceding 6 month. Exclusion criteria included: maternal age over 40 years; BMI > 26 kg/m²; coexistence of other uterine lesions, including intramural fibroids distorting the uterine cavity and adenomyosis prior congenital genital tract malformations (unicornuate uterus, septate uterus, didelphys uterus.

Hysteroscopic repair

All participants underwent preoperative investigations within one-week post-menstrual cessation. Surgical intervention was scheduled once the absence of surgical contraindications was confirmed.Hysteroscopic inspection was conducted sequentially to evaluate cervical configuration and patency of the endocervical canal, as well as the presence of cervical lesions. Intrauterine assessment encompassed global uterine-cavity morphology, patency of bilateral tubal ostia, endometrial hyperaemia, oozing, aberrant vascular distribution, surface smoothness, and focal hyperplastic or defective areas.Diagnoses were established in accordance with the hysteroscopic diagnostic criteria proposed by Guo Y et al. [7]. Endometrial samples were obtained under direct vision using biopsy forceps when inflammatory manifestations including mucosal hyperaemia, oedema and microscopic polyps were identified. If endometrial polyps or cervical polyps were identified intra-operatively, polyps were removed individually under hysteroscopic guidance and sent for histopathological examination. In cases of intrauterine adhesions, adhesiolysis was performed using micro-scissors. When irregular endometrial hyperplasia was detected, thorough intrauterine curettage was carried out, followed by repeat hysteroscopic inspection of the uterine cavity until a smooth endometrial surface was achieved.A small endometrial specimen was curetted from every patient after hysteroscopy. Hysteroscopic electrocoagulation repair was administered for caesarean-section scar defects. A resectoscope was deployed for isolated resection of the distal rim of the scar diverticulum, or combined resection of both proximal and distal margins. Bipolar or monopolar energy was used intra-operatively, and a ball-shaped electrode achieved haemostasis via electrocoagulation over fragile basal-segment vessels and the full diverticular wound bed[8]. All surgical procedures were performed by senior attending surgeons from our hospital.

Endometrium preparation protocol

Endometrium preparation protocol

Embryo transfer was performed using either a down-regulation cycle or a hormone-replacement therapy (HRT) cycle. For the down-regulation cycle, patients received an intramuscular injection of 3.75 mg gonadotrophin-releasing-hormone agonist (GnRH-a) (Diphereline, Ipsen Biopharmaceuticals, France) on day 2 or 3 of the menstrual cycle, followed by hormone-replacement therapy after an interval of 28 days. In the HRT cycle, patients took red-coloured Femoston tablets (estradiol/estradiol-dydrogesterone combination tablets; formulation: 2 mg:10 mg; Sovereign Pharmaceuticals, the Netherlands) orally at a dose of 2–4 mg/day starting on day 2 or 3 of menstruation. Transvaginal ultrasound and hormonal assessments were performed between days 7 and 10 of hormone-replacement treatment. Endometrial transformation was initiated when the endometrial thickness reached ≥ 7 mm. Patients were then administered 90 mg vaginal progesterone gel (Crinone, Merck Serono, Switzerland), vaginal suppositories, and yellow Femoston tablets at 6 mg/day. In women with regular menstrual cycles, a natural cycle(NC) protocol is employed.

Embryo Thawing and Transfer

Cleavage-stage embryo transfer was performed on day 5 of endometrial transformation, whereas blastocyst-stage transfer took place on day 7. On the day of transfer, embryos were thawed in the morning, and the transfer procedure was carried out 1–2 h post-thaw. Single-embryo transfer was implemented in all cycles. Following embryo transfer, patients received daily 90-mg vaginal progesterone gel (Crinone; Merck Serono, Switzerland) for luteal-phase support.

Definition of clinical outcomes

Primary observational indicator: Serum β-HCG testing was performed 2 weeks after the embryo transfer for all patients. Biochemical pregnancy was defined as a serum β-HCG level > 20 mIU/mL. Clinical pregnancy was defined as an intrauterine gestational sac at 7 weeks' gestation[9]. The secondary outcomes included embryologic, pregnancy, obstetric, and neonatal outcomes.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0. Categorical variables are presented as percentages (%). The Shapiro-Wilk test was used to assess normality. Non-normally distributed continuous data were expressed as median [interquartile range] (M [IQR]). For two-group comparisons, the Mann-Whitney U test was applied for non-normal continuous variables, while the chi-square test or Fisher's exact test was used for categorical variables.

Binary logistic regression was performed to evaluate the impact of cavity status (normal cavity group vs. abnormal cavity group) on FET pregnancy outcomes, including biochemical pregnancy, clinical pregnancy, live birth, and early miscarriage. Initially, univariate logistic regression analyses were

conducted. Subsequently, variables with a P-value < 0.1 in the univariate analysis, along with clinically relevant confounders (including maternal age, endometrial thickness, and embryo type et al), were included in the multivariate logistic regression model for adjustment. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).To evaluate whether the impact of cavity status on pregnancy outcomes was modified by embryo type, subgroup analyses were performed. The P-value for interaction was calculated by introducing a product term (cavity × embryo_type) into the multivariate logistic regression model. A P-value for interaction < 0.05 was considered statistically significant.

Results

Basic characteristics of the study population

Upon comparison, no significant differences were found in female age,BMI, baseline

follicle-stimulating hormone(FSH),anti-Müllerian Hormone(AMH), type of infertility, insemination method, FET protocals, embryo attributes between the two groups ($P > 0.05$). However, notable differences were observed in duration of infertility, endometrial thickness, NC-FET protocal($P < 0.05$). The duration of infertility was longer in the the control group [4.1(3.4, 4.9) years] compared with the hysteroscopy group [3.2(2.4, 4.0) years, $P < 0.05$]. Moreover, the endometrial thickness on the day of luteal transformation was significantly thicker in the control group than in the hysteroscopy group [8.35(8.02,9.12) mm vs.9.54(8.74,10.74) mm, $P < 0.05$]. The NC-FET protocals was significantly higher in in the control group than the hysteroscopy group [12.23%vs.4.87%, $P = 0.003$). The baseline characteristics of patients in each group are summarized in Table 1.

Table 1
Comparison of baseline characteristics:Control versus Hysteroscopy groups.

Variable	Control(n = 188)	Hysteroscopy(n = 308)	t/Z/χ2 value	*P* value
Female age(years)	32.86 ± 3.59	33.09 ± 3.22	0.64	0.53
Baseline FSH(mIU/ml)	6.60 (5.61, 7.59)	6.64 (5.68, 7.49)	−0.33	0.27
AMH(ng/ml)	3.88(2.42, 6.67)	3.51(2.68,6.33)	-0.70	0.48
BMI(kg/m^2)	21.89	22.79	-1.49	0.06
Duration of infertility(years)	4.1 (3.4, 4.9)	3.2 (2.4, 4.0)	−7.39	0.001
Type of infertility(%)			1.05	0.31
Primary infertility	48.40 (91/188)	53.89(166/308)		
Secondary infertility	51.60 (97/188)	46.10(142/308)		
Insemination method(%)			-0.69	0.49
IVF	34.57(65/188)	37.98(117/308)		
ICSI	65.43(123/188)	62.01(191/308)		
Endometrial thickness(mm)	8.35(8.02,9.12)	9.54(8.74,10.74)	9.82	0.001
FET protocals(%)				
HRT	47.87(90/188)	53.25(164/308)	1.35	0.25
GnRH-a + HRT	39.89(75/188)	41.88 (129/308)	0.19	0.66
NC	12.23(23/188)	4.87(15/308)	8.95	0.002
Embryo attributes(%)				
Cleavage embryo(D3)	27.13(51/188)	26.95(83/308)	0.001	0.97
Blastocyst embryo(D5)	61.17(115/188)	66.23(204/388)	1.30	0.25
D3 + D5	11.70(22/188)	6.82(21/308)	3.52	0.06

Embryological outcomes between the two groups

As shown in Table 2, No significant between-group differences were identified in the hysteroscopy group versus the control group for the number of MII-stage oocytes (n), number of 2-pronuclear zygotes (n), normal fertilisation rate (%), number of day-3 high- quality cleavage embryos (n), day-3 high-quality cleavage embryo rate (%), total number of cryopreserved blastocysts (n)(all $P > 0.05$). Comparable embry-laboratory outcomes were observed in both cohorts.

Table 2
Fertilization and embryologic outcomes: :Control versus Hysteroscopy groups.

Variable	Control(n = 188)	Hysteroscopy(n = 308)	t/Z/χ2 value	*P* value
No.of MII(n)	9(7,12)	10(8,13)	-1.86	0.06
No.of 2PN(n)	8(6.10)	8(7,10.25)	-1.87	0.06
Normal fertilisation rate(%)	84.04 ± 5.56	84.17 ± 4.18	0.00	0.98
No. of D3 high-quality cleavage embryos(n)	4(3,5.25)	5(4,6)	-1.84	0.07
D3 high-quality cleavage embryo rate(%)	48.1	48.4	0.21	0.65
No.of total cryopreserved Blastocyst(n)	2(1.3)	2(1,4)	-1.31	0.19

Pregnancy outcomes between the two groups

During the follow-up period of this study, no statistically significant inter-group differences in early miscarriage rate and live birth rate were observed between the two groups across FET cycles (all $P > 0.05$). Nevertheless, the hysteroscopy group exhibited higher biochemical pregnancy rate, clinical pregnancy rate than the control group (P = 0.020 and P = 0.041, respectively)as shown in Table 3.

Table 3
Pregnancy outcomes: :Control versus Hysteroscopy groups.

Variable	Control(n = 188)	Hysteroscopy(n = 308)	t/Z/χ2 value	*P* value
Biochemical pregnancy rate	60.64(114/188)	70.78(218/308)	5.42	0.02
Clinical pregnancy rate(%)	45.74(86/188)	55.20(170/308)	4.17	0.04
Live birth rate(%)	40.70(35/86)	50.00(85/170)	1.98	0.16
Early miscarriage rate(%)	10.47 (9/86)	12.35(21/170)	0.20	0.66

Antenatal complications and neonatal outcomes between the two groups

Antenatal complications and neonatal outcomes were compared between the hysteroscopy group and the control group. The preterm-birth rate was 0.00% in the hysteroscopy group and 2.94% in the control group, with no statistically significant difference between groups ($P > 0.05$). No cases of scar pregnancy, placenta previa, placenta accreta spectrum or uterine abnormalities occurred in either group. Encouragingly, neonatal outcomes were comparable between the two groups (Table 4). Obstetric safety profiles were similar across both groups, with no increased risk of preterm birth or congenital malformations.

Table 4
Obstetric and neonatal outcomes: :Control versus Hysteroscopy groups.

Variable	Control(n = 188)	Hysteroscopy(n = 308)	t/Z/χ2 value	*P* value
Gestational ages(days)	252.77 ± 4.91	255.14 ± 5.99	-2.13	0.03
Multiple births(twins)	2.86(1/35)	2.36(2/85)	0.03	0.87
Neonatal birth weight of singletons(g)	3394.85 ± 421.61	3244.35 ± 359.75	-2.00	0.04
Singleton(%)				
Preterm birth	2.94(1/34)	0.00(0/83)	2.46	0.12
Hypertensive disorders of pregnancy	2.94(1/34)	1.20(1/83)	0.43	0.51
Placenta previa	2.94(1/34)	0.00(0/83)	2.46	0.17
Placenta abruption	0.00(0/34)	1.20(1/83)	0.41	0.52
Low birthweight <2500g	2.94(1/34)	1.20(1/83)	0.43	0.51
Macrosomia>4000g	5.88 (2/34)	2.41(2/83)	0.88	0.35

Comparison of pregnancy outcomes between normal uterine and abnormal uterine cavity group

A total of 496 cycles were enrolled in the present study, among which 308 cycles belonged to the hysteroscopy group. According to hysteroscopic findings, the hysteroscopy group was further subdivided into two subgroups: the normal endometrium subgroup (107/308) and the abnormal endometrium subgroup (201/308). The abnormal endometrium subgroup was stratified into five sub-categories: thin endometrium(TE)(76/201), complex/atypical endometrial hyperplasia (45/201), cesarean-section scar diverticulum (22/201), concurrent cesarean-section scar diverticulum and thin endometrium (26/201), and unexplained intrauterine abnormalities (32/201). In the univariate logistic regression analysis, the abnormal cavity group showed no statistically significant differences in biochemical pregnancy, clinical pregnancy, live birth, and early miscarriage rates compared with the normal cavity group (all $P > 0.05$). **After adjusting for maternal age, BMI, AMH, duration of infertility, endometrial thickness, and embryo type, these differences remained non-significant in the multivariate logistic regression model** (all $P > 0.05$) (Table 5). These findings suggest that, despite the presence of an abnormal uterine cavity, FET pregnancy outcomes following hysteroscopic surgical intervention are comparable to those of patients with a normal uterine cavity.

Table 5
Univariate and multivariate logistic regression analysis of pregnancy outcomes between normal cavity and abnormal cavity groups.

Variable	Normal uterine (n = 107)n(%)	Abnormal uterine(n = 201) n(%)	Unadjusted Model OR (95% CI)	*P* value	Adjusted Model^a aOR (95% CI)	*P* value
Biochemical pregnancy rate	73.83(79/107)	68.66(138/201)	0.776(0.460–1.311)	0.344	0.797(0.470–1.351)	0.400
Clinical pregnancy rate	54.21(58/107)	53.22(111/201)	1.042(0.651–1.669)	0.864	1.086(0.675–1.748)	0.734
Live birth rate	51.72(30/58)	49.55(55/111)	0.967(0.573–1.632)	0.900	1.066 (0.619–1.834)	0.819
Early miscarriage rate^b	17.24(10/58)	15.32(17/111)	0.562(0.230–1.368)	0.264	0.606(0.245–1.501)	0.279
Note: Data are presented as n (%). OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.						
^a Adjusted for maternal age, BMI, AMH, duration of infertility, endometrial thickness, and embryo type.						
^b The analysis of live birth and early miscarriage rates was restricted to women who achieved a clinical pregnancy (i.e., only women with clinical pregnancy = 1 were included).						

Subgroup analysis of pregnancy outcomes stratified by embryo type

A total of 83 patients in the D3 cleavage-stage embryo group and 204 patients in the D5 blastocyst group who underwent hysteroscopic intervention were included in this analysis. As shown in Table 6, the biochemical pregnancy rate was 77.45% in the D5 group compared to 59.40% in the D3 group, with no statistically significant difference observed after adjusting for confounders (aOR = 1.283, 95% CI: 0.811–2.029, *P* = 0.288). The clinical pregnancy rate was higher in the D5 group (60.29%) than in the D3 group (43.37%), showing a marginal trend after adjustment (aOR = 1.457, 95% CI: 0.958–2.221, *P* = 0.080).

Table 6
Comparison of pregnancy outcomes between D3 cleavage-stage embryo and D5 blastocyst groups after hysteroscopic intervention.

Variable	D3(n = 83)n(%)	D5(n = 204)n(%)	Unadjusted Model OR (95% CI)	*P* value	Adjusted Model^a aOR (95% CI)	*P* value
Biochemical pregnancy rate	48(59.4)	158(77.45)	1.279(0.815–2.006)	0.284	1.283(0.811–2.029)	0.288
Clinical pregnancy rate	36(43.37)	123(60.29)	1.429(0.942–2.187)	0.093	1.457(0.958–2.221)	0.080
Live birth rate^b	8(22.22)	58(47.15)	2.249(1.374–3.680)	0.001	2.269(1.363–3.774)	0.002
Early miscarriage rate^b,^c	2(5.56)	17(13.82)	NA^c	0.125	NA^c	NA^c
^a Adjusted for maternal age, BMI, AMH, duration of infertility, endometrial thickness, etc.						
^b P for interaction was calculated by adding a product term (cavity status × embryo type) to the multivariate logistic regression model.						
^c The analysis of early miscarriage rate was restricted to women who achieved a clinical pregnancy.						

Notably, the D5 group demonstrated a significantly higher live birth rate compared to the D3 group (47.15% vs 22.22%; aOR = 2.269, 95% CI: 1.363–3.774, *P* = 0.002). Regarding the early miscarriage rate, it was 5.56% in the D3 group and 13.82% in the D5 group. Due to the limited number of events (n = 2 and n = 17, respectively), a multivariate logistic regression model could not be reliably fitted, and the adjusted odds ratio was not applicable (NA). Fisher's exact test showed no statistically significant difference in the early miscarriage rate between the two groups *(P* = 0.125).

Disscusion

This study systematically investigated the effects of OH prior to FET on early implantation, gestational maintenance, obstetric morbidities, and neonatal outcomes. Stratified multivariable-adjusted regression analyses were performed to elucidate the mechanistic basis underlying the heterogeneous reproductive efficacy of hysteroscopic intervention. Population-level analyses revealed that preoperative OH significantly improved biochemical and clinical pregnancy rates, verifying its capacity to enhance early embryonic implantation competency during FET. To date, the clinical utility of routine pre-FET hysteroscopy remains controversial. Accumulated studies have reported inconsistent live birth benefits, with emerging evidence challenging its universal, non-selective application in all FET candidates. Such literature discrepancies are primarily attributable to conventional homogeneous analytical strategies, which fail to account for baseline uterine pathological profiles and embryonic developmental characteristics that fundamentally determine endometrial–embryo crosstalk and implantation

competence. Against this background, the current study performed patient-stratified analyses based on baseline intrauterine status and embryonic developmental stage. By synthesizing clinical observations with established molecular and reproductive-biological knowledge, we offer biologically plausible explanations for the heterogeneous performance of preoperative hysteroscopy.

The present study demonstrated that, compared with patients who did not undergo OH, those who underwent OH examination prior to in vitro fertilization/intracytoplasmic sperm injection–embryo transfer (IVF/ICSI-ET) exhibited improved biochemical pregnancy rate (70.78% vs. 60.64%) and clinical pregnancy rate (55.20%vs.45.74%), with statistically significant differences ($P < 0.05$). These findings corroborate that hysteroscopic evaluation and endometrial management prior to FET can effectively enhance the biochemical pregnancy rate and clinical pregnancy efficiency.OH enables the precise identification and removal of occult intrauterine adhesions, minute polyps, focal endometrial hyperplasia, and other microlesions that are difficult to detect by conventional imaging, thereby alleviating mechanical barriers to implantation [10]. On the other hand, the minimal mild mechanical stimulation elicited by hysteroscopic procedures can induce a local inflammatory reparative response in the endometrium, modulate intrauterine cytokines, chemokines, and the immune microenvironment, promote orderly endometrial decidualization, and remodel endometrial receptivity, thereby creating more favorable conditions for embryo implantation[11]. Collectively, these observations indicate that the reproductive benefit conferred by hysteroscopy is not merely attributable to a single lesion-resection effect, but rather represents an integrated outcome of the correction of organic lesions combined with holistic optimization of the intrauterine microenvironment.

Studies have shown that the prevalence of TE among infertile patients ranges from 2–3% to 33%. In patients with recurrent implantation failure (RIF), the prevalence of TE varies from 14% to 66%, and multiple studies have consistently demonstrated that this condition is associated with lower implantation and live birth rates, suggesting that TE may be one of the factors contributing to pregnancy failure[12–13]. The impact of TE on embryo transfer is primarily manifested as impaired embryo implantation, reduced clinical pregnancy rates, and increased risk of miscarriage[14]. Hysteroscopic physical mechanical separation of scar adhesions can effectively repair intrauterine scar adhesions, facilitate postoperative endometrial blood flow reconstruction, improve uterine receptivity in TE, and restore uterine reproductive function[15–16]. Under direct visualization, hysteroscopy facilitates the resection of cesarean scar lesions and suturing of the scar with minimal blood loss. Meanwhile, intraoperative electrocoagulation of the diverticular endometrium and vessels protects the uterine cavity and cervical canal and exerts a mild stimulatory and irrigative effect on the intrauterine environment[17–18]. Minute endometrial polyps and submucosal uterine fibroids less than 1.0 cm in diameter sometimes appear on sonograms merely as endometrial thickening, enhancement, or abnormal echogenicity, lacking specificity[19]. Previously, the necessity of hysteroscopic evaluation prior to IVF/ICSI-ET remained highly controversial, especially among patients with normal findings on transvaginal sonography (TVS) or hysterosalpingography (HSG). In a retrospective cohort study by Zhang, hysteroscopy was shown to aid in diagnosing and treating intrauterine abnormalities among women with prior IVF failure, yielding improved pregnancy outcomes in

their subsequent FET cycles[20]. Nevertheless, several high-quality clinical studies published in recent years have drawn opposite conclusions, suggesting that pre-transfer hysteroscopy fails to improve embryo implantation rate or the ultimate live-birth rate. Pooling 10 RCTs, Hou JH et al. observed that hysteroscopy preceding ART was beneficial for clinical pregnancy and live-birth rates and did not raise miscarriage risk; subgroup comparisons showed comparable clinical pregnancy rates regardless of whether hysteroscopy identified intrauterine abnormalities[19]. Meanwhile, the large-sample meta-analysis by Vitale SG et al. including 5038 subjects supported that hysteroscopic correction of intrauterine lesions contributes to improved clinical pregnancy and live-birth outcomes among ART candidates[21].

Notably, the improved early implantation outcomes failed to translate into enhanced live birth rates in the overall cohort, with no significant differences in live birth or early miscarriage rates between the two groups ($P > 0.05$). This indicates that hysteroscopy exerts its biological effects primarily during the initial implantation stage. Post-implantation gestational maintenance, trophoblast invasion, decidualization and placental development are collectively modulated by embryonic competence and maternal feto-maternal immune tolerance[22]. While hysteroscopy partially rescues impaired endometrial receptivity and implantation defects, it cannot compensate for inherent placental developmental deficiencies, thereby defining the biological ceiling of its clinical efficacy[23]..

Stratified analyses showed no significant differences in pregnancy outcomes between subjects with normal uterine cavity and those with structural uterine abnormalities within the hysteroscopy cohort (all $P > 0.05$). This finding reveals a distinct mode of hysteroscopic action: it exerts a compensatory repair effect on pathological endometrium rather than inducing supraphysiological receptivity gains in normal endometrium. For patients with intrauterine lesions, hysteroscopy removes anatomical defects and modulates local inflammatory microenvironment to restore impaired endometrial receptivity and support embryo implantation[24]. In contrast, the endometrium–embryo crosstalk in patients with normal uterine cavities, who have intact decidualization and no occult intrauterine pathology, remains at optimal physiological homeostasis. Hysteroscopy cannot further boost implantation potential and yields no additional reproductive benefits[25–26].This mechanistic hypothesis challenges the conventional view that hysteroscopy universally improves endometrial receptivity. It explains why only selected subgroups benefit from pretransfer hysteroscopy and provides biological rationale to avoid unnecessary invasive intrauterine procedures.

Further stratified analysis of patients receiving hysteroscopy revealed marked temporal differences in how embryos at distinct developmental stages respond to optimized endometrial microenvironments. In hysteroscopy-pretreated cycles, blastocyst transfer yielded numerically higher biochemical pregnancy (77.45% vs. 59.40%) and clinical pregnancy rates (60.29% vs. 43.37%) than cleavage-stage embryo transfer, with a significantly superior live birth rate (47.15% vs. 22.22%, $P < 0.05$). This observation indicates that hysteroscopy eliminates anatomical barriers and local chronic inflammation, upregulates endometrial adhesion molecules, and creates a comparable early implantation niche for both embryo

types, resulting in similar chances of embryo adhesion and initial invasion. Nevertheless, trophoblast maturation determines the durability of post-implantation maternal–fetal crosstalk. Cleavage-stage embryos lack fully specified trophoblast lineages and only achieve superficial endometrial invasion, with limited capacity to drive decidual stromal remodeling and establish maternal–fetal immune privilege; even with improved endometrial conditions, subsequent placental developmental arrest remains likely[27]. In contrast, blastocyst trophectoderm is fully differentiated and equipped with complete molecular cascades to temporally regulate decidualization, remodel spiral arteries, and establish maternal immune tolerance[28].The stabilized endometrial niche after hysteroscopy provides essential stromal signals to sustain trophoblast invasion and placentation. This durable matching of maternal–fetal molecular communication ultimately translates into live birth benefit. These findings uncover a novel phenotype: endometrial repair homogenizes early implantation efficiency, whereas long-term gestational sustainability is governed exclusively by embryonic developmental competence.

This two-dimensional analysis integrating baseline uterine pathology and embryonic developmental stage identifies a context-dependent synergistic benefit of hysteroscopy. Hysteroscopy alone corrects uterine anatomical defects, reduces local endometrial proinflammatory signals and removes implantation-suppressing pathological cues, yet it cannot confer supraphysiological receptivity to normal endometrium. Its therapeutic efficacy is only realized when coupled with high-competence embryos with intact maternal–fetal crosstalk machinery. In the subgroup of patients with uterine structural abnormalities undergoing blastocyst transfer, hysteroscopy eliminates pathological substrates disrupting endometrial remodeling and reverses receptivity impairment induced by chronic inflammation. The mature trophectoderm of blastocysts senses cytokines and extracellular matrix signals within the restored endometrium, triggering orderly decidualization and spiral artery remodeling[29]. Pathological uterine repair and blastocyst trophoblast function act complementarily and synergistically: the former establishes a competent stromal microenvironment, while the latter exploits this niche to support placentation, jointly lowering the risk of post-implantation failure and pregnancy loss. By contrast, patients with normal uterine cavities lack pathological targets for intervention; cleavage-stage embryos possess insufficient trophoblast differentiation and cannot initiate stable placentation even in optimized endometrial conditions[30]. This mechanistic model overcomes the limitation of prior studies that separately evaluated uterine anatomy or embryo type, explaining why hysteroscopic benefit is restricted to this specific subgroup. Collectively, these findings refute the one-size-fits-all strategy of universal hysteroscopy for FET candidates and provide evidence-based support for individualized clinical decision-making.

At the level of perinatal and offspring safety, the study demonstrated that gestational age and singleton birth weight differed significantly between the hysteroscopy and control groups ($P < 0.05$), whereas the remaining obstetric and neonatal outcomes were generally comparable. Overall, no increased risk of adverse perinatal complications of any type was observed, thereby underscoring the temporal-window specificity of the biological effects of hysteroscopy. The regulatory effects of hysteroscopy are confined to the implantation window and the very early stage of pregnancy, primarily promoting embryo

implantation and the establishment of early pregnancy by remodeling the endometrial microenvironment and optimizing the decidualization process. Once clinical pregnancy is achieved, subsequent placental spiral artery remodeling, maintenance of placental function, and fetal growth and development are predominantly governed by maternal baseline status, genetic regulation, and intrinsic placental developmental mechanisms[31–32].OH does not alter the regulatory pathways of placental development and fetal growth in mid-to-late pregnancy, and therefore does not increase the risk of adverse perinatal outcomes such as preterm birth, low birth weight, and gestational complications, further corroborating the safety and reliability of this preconditioning strategy.

The present findings demonstrate that the reproductive benefits of pre-FET hysteroscopy are highly population-specific, rather than universally applicable to all FET candidates. Hysteroscopic pretreatment achieves maximal therapeutic efficacy in patients with uterine structural abnormalities undergoing blastocyst transfer, in whom endometrial microenvironmental restoration can be fully translated into improved implantation competency and sustainable live-birth outcomes. These results support a precision medicine paradigm, in which hysteroscopy is selectively administered to high-yield populations to reduce unnecessary invasive procedures and optimize clinical resource utilization.

Several limitations of this study warrant acknowledgment. This study was based on a single-center retrospective cohort design, which inherently entails potential selection bias and residual confounding despite rigorous multivariable adjustment. All subgroup analyses were exploratory, and mechanistic interpretations were inferred from clinical phenotypic data and published evidence, without direct histological or transcriptomic validation of endometrial biological alterations. Further large-scale prospective studies are warranted to confirm our stratified findings and substantiate the underlying biological mechanisms.

Cumulatively, pre-FET hysteroscopy exhibits heterogeneous reproductive effects that are jointly determined by baseline uterine pathological status and embryonic developmental characteristics. The therapeutic superiority of hysteroscopy primarily stems from the remediation of disordered endometrial microenvironments, with the most prominent incremental benefits confined to patients with uterine abnormalities receiving blastocyst transfer. This study clarifies the differential efficacy of hysteroscopy across FET populations and provides robust evidence to facilitate the paradigm shift from empirical universal intervention to individualized precision management in clinical FET practice.

Declarations

Ethics approval and consent to participate

The retrospective cohort study was approved by the the Ethics Committee of Shanghai Tongji Hospital(Tongji Hospital Affiliated to Tongji University (approval number K-2025-053). All procedures were performed in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Given the retrospective design and use of

fully de-identified clinical data, the requirement for written informed consent was waived by the review board.

Consent for publication Not applicable.

Data availability Datasets generated and / or analyzed during the current study are available from the corresponding authors upon reasonable request

Competing interests The authors declare no competing interests

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Authors' contributions Mingwen Wang was responsible for the study concept and design, scrutinized the patients' files, statistical analysis, wrote the manuscript, editing the manuscript, interpreting the results; Lihong Shi contributed to interpreting the results and editing the manuscript. All authors read and approved the final manuscript.

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