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## Original Article

# Hysteroscopic cervical features associated with difficult embryo transfer in unselected patients undergoing in vitro fertilization

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## ABSTRACT

**Background:** The most appropriate diagnostic tests for the assessment of the uterine cavity in patients undergoing standard infertility evaluation in daily practice remain unclear. Routine hysteroscopic uterine cavity evaluation before an in vitro fertilization-embryo transfer (IVF-ET) cycle is not a uniformly accepted procedure. However, cervical findings associated with difficult ET have rarely been reported in previous hysteroscopic studies. The main objective of this study was to examine the relationship between cervical finding under flexible outpatient hysteroscopy (OH) and difficult ET.

**Methods:** A cohort clinical study was conducted with 650 patients undergoing their first in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) from January 2010 to December 2017. Of them, 605 women with available embryos underwent transfer cycles. Outpatient hysteroscopies were scheduled during the follicular phase of the menstrual cycle, 1–3 months before starting IVF/ICSI treatment.

**Results:** Among the 650 women who underwent transvaginal sonography (TVS) and OH, abnormal sonographic findings were observed in 51 women (7.8%) in which submucous myoma, endometrial polyp, and endometrial hyperplasia were the most common. Abnormal hysteroscopic intracavitary findings were observed in 158 cases (24.3%) in which endometrial polyp, submucous myoma, and intrauterine adhesions were the most common. These results showed that TVS was specific (100%) but not sensitive (32.3%) compared with OH. Embryo transfer (ET) was difficult in 25% of women with cervical stenosis (CS) or tortuous cervical canal (TC) and was significantly more difficult in women in the TC group (30.7%) than in the CS group (19.6%).

**Conclusion:** OH can identify cervical characteristics associated with a high incidence of difficult ET.

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### At a glance commentary

#### Scientific background on the subject

Routine hysteroscopic uterine cavity evaluation before an in vitro fertilization-embryo transfer (IVF-ET) cycle is not a uniformly accepted procedure. However, little or no studies validate the efficacy of OH in predicting ET difficulty. Cervical findings associated with difficult ET have rarely been reported in previous hysteroscopic studies.

#### What this study adds to the field

Outpatient hysteroscopy can identify cervical lesions associated with difficult ET in women undergoing initial IVF/ICSI procedures. Cervical dilatation and mock ET in patients with cervical lesions result in easier subsequent ultrasound-guided ET. Routine OH prior to IVF can be cost-effective in avoiding difficult ET.

Outpatient hysteroscopy (OH), which enables direct visualization of the uterine cavity without anesthesia, has been recommended as a routine procedure in assessing the causes of infertility [1]. OH of infertile women with normal transvaginal sonography (TVS) findings or who have failed previous in vitro fertilization–embryo transfer (IVF-ET) cycles have shown that the incidence of abnormalities of the uterine cavity (such as polyps, myoma, and adhesions) is relatively high (approximately 20–40%) [1–15]. Moreover, correction of these OH-detected abnormalities markedly improves outcomes in these patients [16,17].

Two randomized controlled trials reported that OH in women with two or more failed IVF treatment cycles increased pregnancy rates by up to 13% [9,10]. However, routine hysteroscopy for uterine cavity evaluation before an IVF-ET cycle is not a uniformly accepted procedure [18].

The ET technique has a major impact on the pregnancy rates of assisted reproductive technologies, with poor execution estimated result in 30% of IVF failures [19]. Guidelines have been developed for the performance of the major steps of ET [20]. ET is frequently difficult due to forbidding cervix [21], including tortuosity and/or stenosis of the cervical canal. Unfortunately, the ease of the ET procedure in individual patients is largely unpredictable. The only diagnostic tool available to date is mock transfer, but its reliability is questionable.

Little or no studies validate the efficacy of OH in predicting ET difficulty. Recently, Larue et al. conducted an observational study to detect anatomical anomalies by assessing the cervix and uterus using TVS and rigid hysteroscopy [22]. They found that the most common anatomical characteristics associated with difficult ET were abnormal crypts in the cervical canal (86%) and tortuosity of the cervical canal (68%). The findings by Larue et al. were consistent with our previous clinical observation regarding

the difficulty of ET. This retrospective cohort study evaluated the relationship between OH findings and the difficulty of ET. OH was used to assess the anatomical state of the cervix and determine the feasibility of predicting difficult embryo transfer (ET).

## Methods

### Participants

This study included all women undergoing their first IVF/intracytoplasmic sperm injection (ICSI) by K.C. Lan service at our institution between January 2010 and December 2017. All IVF/ICSI couples underwent the standard infertility work-up, consisting of medical history, physical examination, hormone status, semen analysis, TVS, and OH [Fig. 1].

The rationale involving OH is as follows: OH should be part of the infertility workup before ART, even in patients with normal HSG and/or TVS [1]. In addition, mock ET can be performed by OH better than traditional blind sounding and patients less suffering.

TVS of the uterine cavity was performed to evaluate the regularity of the endometrial lining and to measure the double layer of the endometrium in both the sagittal and transverse planes, thereby determining the presence of features associated with predefined abnormalities (polyps, submucous myoma, adhesions, or septa).

### Hysteroscopy procedure and uterine cavity assessment

OH were scheduled during the follicular phase of the menstrual cycle, 1–3 months before starting IVF/ICSI treatment. The cervix was cleaned with povidone-iodine solution. No premedication or local anesthetic was administered.

All OH procedures were performed by a single examiner (K.C. Lan) with the patient in a semi-recumbent position in an electronic gynecological examination chair. Panoramic hysteroscopy was performed using a 3.8-mm diameter flexible hysteroscope (HYF-V, Olympus, Tokyo, Japan) without mechanical or drug-induced dilatation. Images of the cervical canal and the uterine cavity were viewed on a high-resolution color television monitor. Normal saline 0.9% was used as the distending medium and was propelled by an electronic pump (Endomat, Storz, Tuttlingen, Germany), with intrauterine pressure maintained at 45 mmHg. Illumination was provided by a halogen light source with a fiber-optic cable. After hysteroscopy, the cervical canal, tubal ostium, uterine cavity, and endometrium were examined. Any detected pathologies were recorded.

Women with any of these intracavitary abnormalities underwent subsequent diagnostic or therapeutic hysteroscopy to resolve these abnormalities prior to starting treatment for infertility. In case of the operator could not accomplish the OH examination due to cervical stenosis (CS) or tortuous cervical canal (TC), therapeutic hysteroscopy was also scheduled for cervical dilatation and mock ET by sounding under general

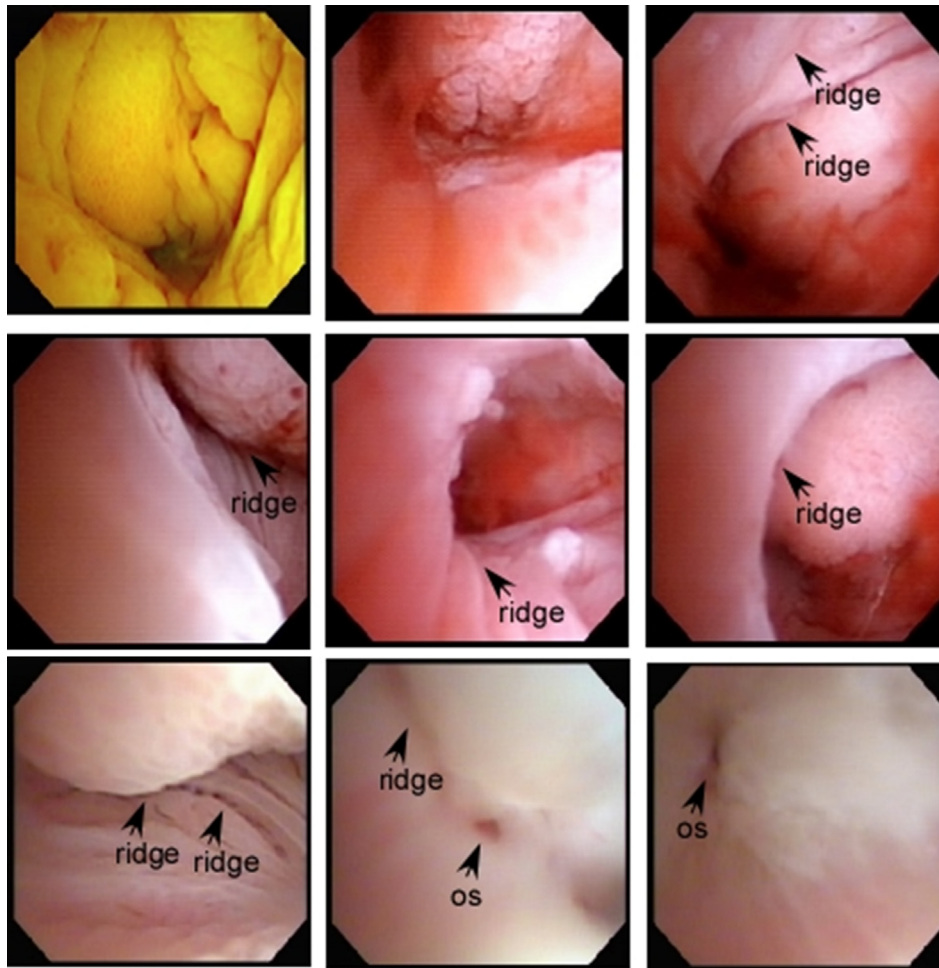


Fig. 1 Flow chart of study population.

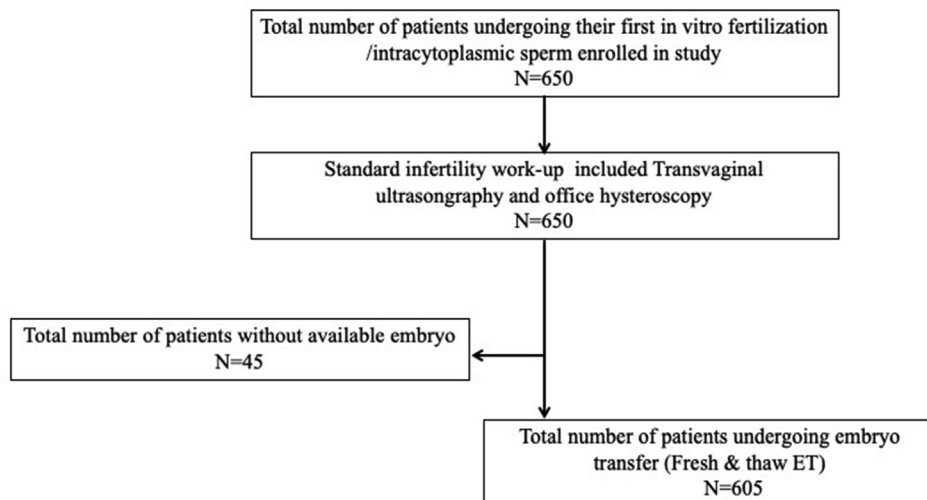


Fig. 2 Hysteroscopic images, showing various characteristics of tortuous cervical canals, including with crypts and ridges.

anesthesia later. If polyps or myomas were detected, the diagnosis was confirmed histopathologically. Hysteroscopic findings for characteristic chronic endometritis include the presence of local or diffuse hyperemia, edema of the stroma, and presence of micropolyps [17].

We defined the following conditions during the procedure or post-procedure 1 week as a hysteroscopic-related complication: severe uterine pain cannot tolerate, massive vaginal bleeding, pelvic inflammatory disease, uterine perforation, shock, or pulmonary emboli.

The passage through the cervical canal studied was marked by three reference points: the internal and external os of the cervix, and a virtual reference point defined as the midpoint between the two orifices. The passage through the cervical canal was considered as direct when the three reference points were aligned, and as tortuous when the reference points were not aligned [22].

### Tortuous cervical canal (TC) and cervical stenosis (CS)

In our study, tortuous cervical canal (TC) was defined as hysteroscopic images of a TC with complex crypts and ridges [Fig. 2].

Cervical stenosis (CS) was defined as following condition:

1. A flexible hysteroscope fails to enter the external os (less than 3.8-mm in diameter) during the initial outpatient procedure.
2. The affected part of the cervical canal or the entire canal from the external to the internal os [23] but without a TC.

### Embryo transfer (ET)

The laboratory facilities, clinical strategy, and protocol for controlled ovarian hyperstimulation have been described [24,25]. Briefly, ETs were performed on day 3 or 5 (blastocyst) of development. Patients were placed in the lithotomy position and then exposed to the cervix with a speculum.

All ET procedures were performed by a single operator (K.C. Lan). Transabdominal ultrasound was performed by an assisted staff, with the bladder full, to visualize the endometrial lining and the endocervical angle. A Labotect (Labotect, GmbH, Germany) or Kitazato (Kitazato, Tokyo, Japan) catheter loaded with the embryos was inserted into the cervical os through the endocervical canal and into the uterine cavity. The embryos, suspended in 20  $\mu$ L of transfer medium in a syringe, were gently injected into the uterine cavity by the embryologist, and the catheter was slowly withdrawn a few seconds later. After microscopic inspection of the catheter for retained embryos, the speculum was removed. The patient remained in supine position for 15 min.

### ET difficulty

The ET procedure was defined as difficult if (i) it required additional instrumentation, such as a tenaculum; (ii) if it required additional time (more than 3min) or (iii) effort or firmer catheters; or (iv) if any resistance to negotiating the internal cervical os was encountered.

ET was defined as severely difficult if all four factors were present [19,26].

### Statistics

Categorical variables (reported as proportions) were compared using the chi-square or Fisher's exact test, where appropriate. Accuracy was represented using sensitivity (true positive/true positive + false negative) and specificity (true negative/true negative + false positive). Continuous variables are expressed as mean  $\pm$  standard deviation (SD). All *p*-values were two-sided with *p* < 0.05 considered statistically significant. The

power was larger than 90% when we recruited 402 patients to detect a difference of proportion of 0.282 between the cervical tortuous group and the normal group, using the two-sided *t*-test with a significance level of 5%.

## Results

A total of 650 women were scheduled for hysteroscopy at our institute prior to their first IVF/ICSI treatment cycle [Fig. 1]. The demographic characteristics and causes of infertility are shown in Table 1. The mean patient age was  $35.7 \pm 4.2$  years. Forty-six (7.1%) patients failed OH because of marked CS and/or a tortuous canal. No procedure was aborted due to a patient's inability to tolerate the procedure, and none of the women experienced early or late complications of OH.

Abnormal sonographic findings were observed in 51 women (7.8%) in which submucous myoma, endometrial polyp, and endometrial hyperplasia were the most common. Abnormal hysteroscopic intracavitary findings were observed in 158 cases (24.3%) in which endometrial polyp, submucous myoma, and intrauterine adhesions were the most common. These results showed that TVS was specific (100%), but not sensitive (32.3%) compared to OH [Table 2] in the detection of major differences in endometrial polyps.

Hysteroscopic intracavitary pathologies were observed in 158 patients, including endometrial polyps in 88 patients (13.5%), submucosal myoma in 21 (3.2%), Mullerian duct anomalies in eight (1.2%), intrauterine adhesions in 11 (1.7%), chronic endometritis in 3 (0.5%), Cesarean section scar in 7 (1.1%), and endometrial hyperplasia in 7 (1.1%). The remaining 13 (2.0%) patients had more than one abnormality.

**Table 1** Demographic characteristics of the 650 women who underwent initial IVF/ICSI.

Number who underwent IVF	344
Number who underwent ICSI	306
Age of female partner (years)	$35.7 \pm 4.2$ (21–48).
Body mass index (kg/m <sup>2</sup> )	$22.5 \pm 3.4$ (15.6–40.7)
Infertility (No)	
Primary	368
Secondary	382
Duration of infertility (years)	$3.9 \pm 2.9$ (1–20)
No. of mature or approaching mature oocytes retrieved	$6.6 \pm 3.8$ (1–22)
Endometrial thickness on day of hCG (mm)	$1.3 \pm 0.2$
Estradiol (pg/mL) on hCG day	$2157.7 \pm 1369.9$
Progesterone (pg/mL) on hCG day	$0.9 \pm 0.6$
Number of indications	
Tubal factor	108
Male	211
Endometriosis	33
Ovulatory factor	128
Unexplained and others	68
Combined factors	102
Normal fertilization rate	79.8%
Number of embryos transferred	$2.1 \pm 0.7$ (1–4)
Clinical pregnancy rate/transfer cycle	40.2% (243/605)
Implantation rate	26.0% (312/1198)

Note: Values are mean  $\pm$  SD (range), number, or proportion.

**Table 2 Transvaginal sonography (TVS) and hysteroscopic intracavitary findings in the 650 first IVF/ICSI women included in this study.**

Findings	TVS (n = 650)	Hysteroscopy (n = 650)
Endometrial polyps	11(1.7%)	88 (13.5%)
Submucosal myoma	21 (3.2%)	21 (3.2%)
Mullerian anomalies	4 (0.6%)	8 (1.2%)
Adhesions	4 (0.6%)	11(1.7%)
Cesarean section scar	2 (0.3%)	7 (1.1%)
Endometrial hyperplasia	7 (1.1%)	7 (1.1%)
Endometritis	0	3 (0.5%)
Combined lesions	2 (0.3%)	13 (2.0%)
Total findings	51 (7.8%) <sup>a</sup>	158 (24.3%)

<sup>a</sup> Sensitivity, 32.3%; specificity, 100% versus hysteroscopy.

**Table 3A Cervical evaluation by Hysteroscopy in the 605 women with embryos transfer included in this study.**

No. of unremarkable finding	350 (57.8%)
No of abnormal Intracavity finding but with normal cervix	147 (24.3%)
No. of Cervical stenosis	56 (9.3%)
No. of Tortuous Cervical canal	52 (8.6%)

As shown in Fig. 1 and 45 patients had no available embryos for transfer and 605 underwent ET. Table 3A shows the cervical evaluation by hysteroscopy findings in these 605 ET patients. Intracavitary abnormal findings, but normal cervix, CS, and tortuous cervical canal were observed in 147 (24.3%), 56 (8.6%), and 52 (6.6%) patients, respectively.

The relationship between hysteroscopy findings and transfer difficulty is shown in Table 3B. Patients with CS or TC, including the aforementioned OH failure, all had received ET. Among the remaining 605 transfer cycles, 39 (6.4%) were classified as difficult. Difficult ET was significantly more frequent in patients with CS or tortuous cervical canal (25%) than in patients with intracavity lesions (2.0%) and normal patients (2.6%). Difficult ET was also significantly more frequent in patients with TC (30.7%) than in patients with CS (19.6%), but the frequency of severely difficult ET in these two groups was similar (11.6% vs. 14.2%).

## Discussion

The most appropriate diagnostic tests for the assessment of the uterine cavity in patients undergoing standard infertility evaluation in daily practice remain unclear. Although TVS and hysteroscopy are both utilized, hysteroscopy is generally considered the gold standard in the diagnosis of intrauterine pathology [11,27]. It is therefore necessary to identify subgroups that may benefit most from OH.

The present study found that TVS did not reveal any of the predefined intracavitary abnormalities revealed by hysteroscopy in 107 (16.5%) patients. The prevalence of such unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to IVF, ranges from 20% to 45% [8,13–15], which is much higher than the 11% reported in a previous study [12]. These discrepancies may be due to differences in study design, patient inclusion criteria, and types of intrauterine pathologies included. Furthermore, differences in the prevalence of abnormalities may be due to variations in the interpretation of hysteroscopy findings. The most frequently detected abnormality in the current study was endometrial polyps, consistent with previous findings. However, the incidence of this abnormality (13.5%) was higher than that previously reported [1,3,6,12]. The effects on fertility of polyp number, size, and location remain unclear, as well as the effects of polypectomy [28]. To date, there is little evidence showing whether correction of endometrial polyps improves IVF outcomes.

We had 11 patients with IUA. Hysteroscopy is currently considered the gold standard treatment because it allows simultaneous diagnosis and treatment [29]. Currently, the treatment of IUA relies on the mechanical methods of surgical lysis and the barrier applied between to prevent adhesion reformation. Repeated hysteroscopy with adhesion prevention is still the gold standard and a known way to attain success in IUA treatment. As IUA has been questioned not merely as a surgical disease, sound knowledge of endometrial regeneration and adhesion prevention are needed to find better treatment strategies [27]. However, subfertile patients with Asherman's syndrome undergoing adhesiolysis should be appropriately informed about the risk of associated life-threatening complications and preterm delivery [30].

The ease of the ET procedure has been reported to influence its success [19]. There is no universal definition of difficult ET, complicating efforts to accurately compare subjective

**Table 3B ET Findings of the 605 hysteroscopies included in this study.**

	Normal	Abnormal Intracavity finding but with normal cervix	Cervix stenosis	Tortuous cervical canal
Number of patients	350	147	56	52
Difficult ET	2.6% (9)	2.0% (3)	19.6% (11) <sup>a</sup>	30.7% (16) <sup>a,b</sup>
Severely difficult ET	1.1% (4)	0.7% (1)	14.2% (8) <sup>a</sup>	11.6% (6) <sup>a</sup>

(n): number of patients.

<sup>a, b</sup>  $p < 0.05$ .

<sup>a</sup> Compared with the normal and intrauterine groups.

<sup>b</sup> Compared with the cervical stenosis group.

evaluations among studies [19,31]. The prevalence of difficult ET has been reported to be approximately 7% [19], similar to our finding. Compared with past OH studies, the present study highlights cervical findings associated with difficult ET. Strategies to overcome anatomic impediments to hysteroscopy have been proposed, but the study did not assess the relationship between overcoming these impediments and ET difficulty [23]. The anatomic features causing difficult transfer detected during assessments of the cervix and uterus by TVS, rigid hysteroscopy, and mock transfer [22], were similar to those detected using flexible OH in our study.

The prevalence of CS was recently reported to be 29.9% [23]. Using OH, we found that 108 (16.6%) patients had cervical lesions, including tight internal or external cervical os projecting ridges within the cervical canal, TC, or an acutely anteфлекed or retroфлекed uterus. ET can be complicated by tortuosity and/or stenosis of the cervical canal. In contrast to OH, cervical ultrasound elastography is less effective in predicting the ease of ET [32], and our results suggested that ultrasound was less effective in predicting cervical lesions.

Our results indicate that the rate of difficult ET is significantly higher in patients with cervical lesions than in those without them, especially in those with TC. Indeed, to optimize IVF outcomes, women in our infertility clinic have regularly undergone OH prior to IVF since 2011. Amelioration of cervical canal obstruction and optimization of the ET procedure has reduced the incidence of very difficult ET in patients with TC, making its incidence similar to that in patients in the CS subgroup.

Patients found to have CS or TC can undergo a destructive or invasive procedure, such as cervical canal resection by shaving or morcellation [33,34]. Our center does not favor these procedures. Rather, patients in our center with CS or TC are treated with cervical dilatation and mock ET, with or without the application of tenaculum and different hardness ET catheter. We found that these procedures lead to easier subsequent ultrasound-guided ET.

Two recent high-quality trials demonstrated that routine hysteroscopy did not improve live birth rates in infertile women undergoing initial IVF treatment or in those with a history of unsuccessful IVF treatment cycles but normal TVS findings [35–37]. However, an increasing number of experimental and clinical studies have emphasized the importance of uterine and intrauterine pathology for spontaneous and post-ART fertility [38]. Office hysteroscopy is a feasible, non-invasive and highly effective diagnostic and therapeutic procedure for allowing the resolution of female infertility related to these pathologies [39]. A systematic review and meta-analysis found moderate evidence that hysteroscopy increases pregnancy rate if performed before IVF, regardless of intrauterine abnormalities [4,16]. Although the efficacy of regular hysteroscopy prior to IVF has been questioned due to lack of definitive evidence, IVF itself is accompanied by psychological, physical, and financial burdens that increase with every failed IVF treatment cycle. Efforts should be made to minimize the number of cycles a patient must undergo, and the balance between the tolerability of OH and the burden that accompany IVF/ICSI must therefore be determined. Moreover,

a thorough cost-effectiveness analysis would help physicians in creating an optimal strategy for each patient [40].

Although OH failed in 46 of our patients, recent technical and technological innovations, along with a higher level of experience of the operator, allowed for OH to overcome even severe CS. Thus, this significantly reduces the rate of failed procedures and the need for surgery and general anesthesia. Safety, ease of use, high diagnostic accuracy, and high patient tolerability have made OH an ideal procedure for patients undergoing IVF/ICSI [41]. In evaluating the relationship between cervical lesions and ET, we found that flexible hysteroscopy is a feasible and valid procedure when performed in an outpatient setting without anesthesia [42,43]. However, studies are needed to determine the efficacy of OH in specific subsets of patients undergoing IVF. In addition, randomized trials are needed to confirm the effectiveness of hysteroscopy in avoiding difficult ET.

The clinical application suggests that the OH can be used as a routine assessment tool before IVF treatment and ET. Patients with repeated IVF failures or a history of complicated procedures (such as artificial insemination; Hysterosalpingogram, or contraceptive device insertion) should use hysteroscopy as an assessment tool because these patients are highly suspected for difficult ET if they undergo IVF.

Our study highlighted the application of flexible OH for difficult ET and evaluated the frequency of these characteristics as causes of difficulty during ET by a single expert operator, and to propose a detailed review of this subject that can be used in clinical practice. However, the retrospective design, the conduction in a single center, the small number of patients recruited, and a slightly subjective definition of ET difficulty and cervical findings are limitations of our study. In addition, our study involved only one operator in order to avoid inter-personal differences.

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## Conclusion

In conclusion, this study showed that OH can identify cervical lesions associated with difficult ET in women undergoing initial IVF/ICSI procedures. Cervical dilatation and mock ET (with or without the application of tenaculum) in patients with cervical lesions result in easier subsequent ultrasound-guided ET. Routine OH prior to IVF can be cost-effective in avoiding difficult ET.

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## Ethics approval and consent to participate

Written informed consent was obtained from all patients, and this study was approved by the Ethics Committee of CGMH and the local institutional review board (CGMH201601539B0 and 201601539B0C601).

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## Conflicts of interest

Drs. Kuo -Chung Lan and Yu-Che Ou and Kuan-Hui Huang have no conflicts of interest or financial ties to disclose.

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