Evaluation of a strategy for difficult embryo transfers from a prospective series of 2,046 transfers

Lionel Larue, M.D., Ph.D.,[a] Laure Bernard, M.D.,[a] Julie Moulin, M.D.,[a] Anne Massari, M.D.,[a] Nino-Guy Cassuto, Ph.D.,[b] Dominique Bouret, M.D.,[b] and Gwenola Keromnes, M.D.[a]

[a] Centre de Fertilité - Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France, and [b] Laboratoire Drouot, Paris, France

Objective: To evaluate an embryo transfer strategy for difficult transfers (DiTs).
Design: Prospective, nonrandomized, observational, cohort study
Setting: A hospital fertility center in France.
Patient(s): Data were collected on all embryo transfers conducted using the strategy between February 2014 and February 2020.
Intervention(s): Anatomical characteristics that could cause DiT were identified by transvaginal ultrasound and the catheter was adapted accordingly. Transfer was guided by transvaginal ultrasound. After passage through the cervix, a rest period was introduced to allow any contractions to stop before embryo deposition in the uterus.
Main Outcome Measure(s): The primary criterion was the percentage of pregnancies per transfer (P/T) after an easy transfer (EaT) or a DiT. The secondary criteria included the anatomical causes of DiT and the patients' levels of discomfort.
Result(s): Of 2,046 transfers, 257 (12%) were DiTs: minor difficulties (n = 152; 7.4%), major difficulties (n = 96; 4.7%), very significant difficulties (n = 7; 0.3%), or impossible (n = 2; 0.1%). The most common causes of DiTs were endocervical crypts (54%), tortuous cervical canal (36%), and marked uterine anteversions (30%). Several causes were often responsible for DiTs. There was no statistically significant difference in the P/T between the EaTs (n = 1,789, 41%) and all degrees of DiT (n = 257, 37%). In addition, there was no statistically significant difference between the level of patient-reported discomfort in the EaT and DiT groups.
Conclusion(s): This study demonstrated that an adapted embryo transfer strategy, monitored by transvaginal ultrasound, led to similar pregnancy rates regardless of whether the transfer was easy or difficult. (Fertil Steril Rep® 2021;2:43–9. ©2020 by American Society for Reproductive Medicine.)
Key Words: Embryo transfer, difficult transfer, in vitro fertilization, transvaginal ultrasound, personalized healthcare

The outcome of assisted reproductive technology (ART) mainly depends on 3 factors: embryo quality, uterine receptivity, and the quality of the embryo transfer (1, 2). Most previous studies found that success rates were lower when the transfer was difficult (1–6). A study conducted by Listijono et al. (6) on a large series of 6,484 transfers found a statistically significant difference between clinical pregnancy rates for easy transfers (EaTs) and difficult transfers (DiTs; 30.7% vs. 24.6%) . Similar results were obtained from the analysis of 7,714 transfers by Kava-Braverman et al. (4), with pregnancy rates of 38.2% for EaTs compared with 27.1% for DiTs and a progressive decline in pregnancy rates as the level of difficulty of the transfer increased (i.e., transfers requiring the use of a sheath, a stylet, or forceps). The development of appropriate strategies to make the embryo transfer as easy as possible is therefore an important approach for improving outcomes.

The embryo transfer strategy used in the current study was based on identifying the anatomical cause responsible for each DiT, adapting the equipment used to perform the transfer accordingly, and using ultrasound to guide and monitor the procedure in real time. The main aim of the study was to evaluate the pregnancy outcomes in a large prospective series of embryo transfers carried out using this strategy.

MATERIALS AND METHODS

This prospective observational study of embryo transfers was conducted between February 2014 and February 2020 in the Fertility Centre of the

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Reprint requests: Lionel Larue, M.D., Ph.D., Centre de Fertilité – Groupe Hospitalier Diaconesses Croix Saint Simon, 18, Rue du Sergent Bauchat, 75012 Paris, France (E-mail: llarue@hopital-dcss.org).

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Diaconesses Croix Saint Simon Hospital Group (France). All transfers were performed according to a standardized procedure and, with the exception of cases where transfer was unsuccessful even after several attempts, all transfers were performed by the same operator.

The primary evaluation criterion was the percentage of pregnancies per transfer (P/T) after an EaT or a DiT. The secondary evaluation criteria included describing the causes of DiT and their frequency, the feasibility of the technique based on the number of cases for which transfer proved impossible (impossible transfer: ImT), and the level of discomfort reported by the patients during embryo transfer.

Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and good clinical practice guidelines (CPMP/ICH/135/95). The study was approved by the institutional review board of the Diaconesses Croix Saint Simon hospital group in accordance with the Jarde law (Article L1121-4 of the French public health code). The data were collected anonymously according to the applicable reference methodology (MR003) issued by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés), and each participant provided signed informed consent before inclusion. Consent for the use of anonymized data was obtained systematically in addition.

Materials

From February 2014 to November 2017, first attempts at embryo transfer were made with the use of the "soft" monoblock angled catheter (Elliocath; Ellios Biotek Laboratory, Paris, France) directly loaded with the embryos. If the transfer was not straightforward, this catheter was withdrawn, the embryos were returned to culture, and a reinforced catheter with a sheath (TDT set; CCD Laboratory, Paris, France) was used. From November 2017 to February 2020, a "soft" ultra-flexible catheter with a sheath was used in all cases (Guardia Embryo Transfer Catheter; COOK Laboratory, Brisbane, Australia). A malleable mandrel was used in the case of persistently difficult transfers. The ultrasound system used throughout the study was a Voluson E8 (General Electric International Inc, New York, NY).

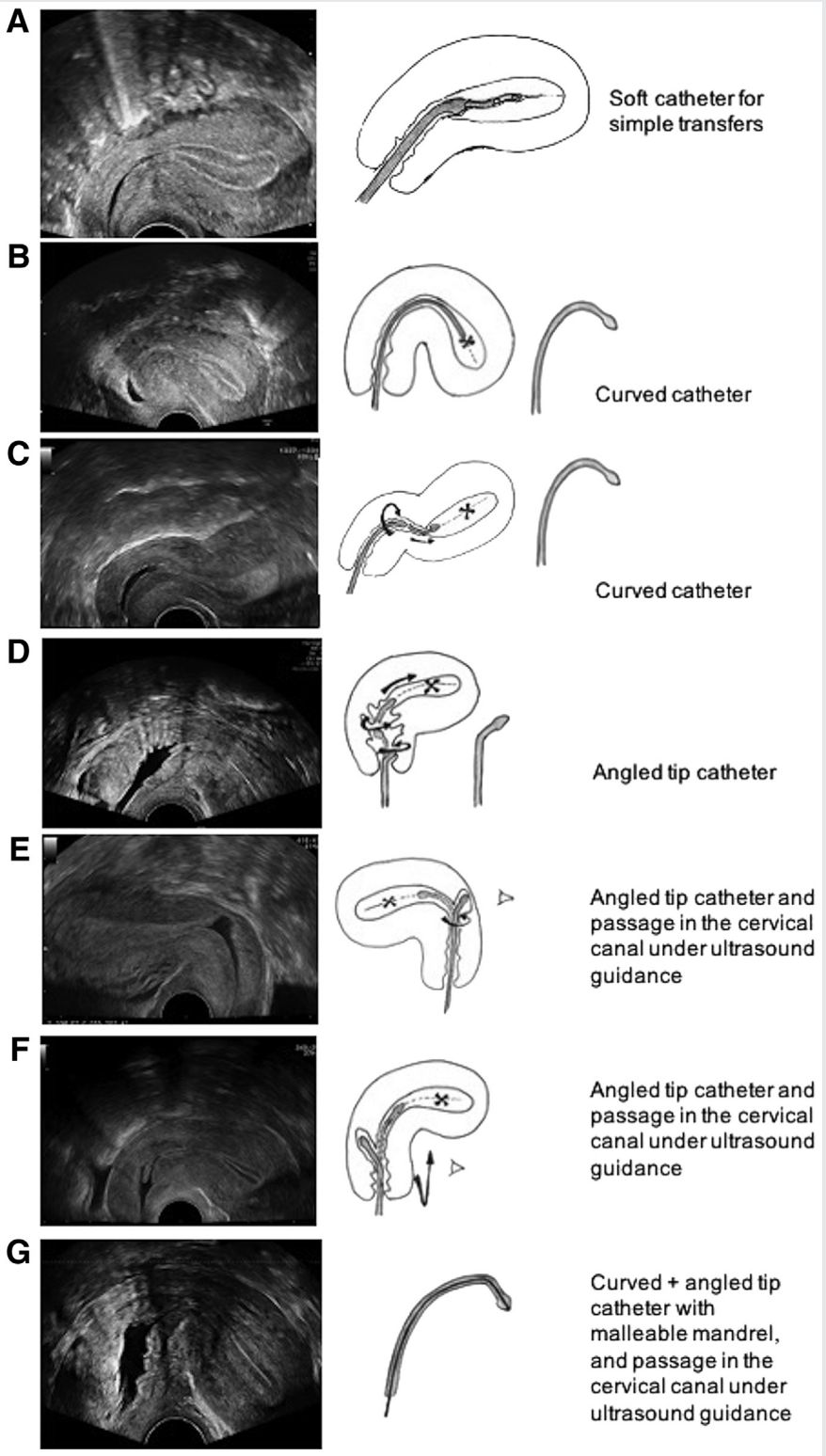
Transfer Technique

The transfer technique used was based on that described by Kojima et al. (7) in 2001. The transfer was performed in 2 stages. After exposure and preparation of the cervix under speculum (washing with physiological serum and aspiration of excess mucus if necessary), the first step consisted of inserting the catheter into the external cervical os and then guiding it manually toward the internal os. The speculum was then removed and a transvaginal transducer was introduced. Ultrasound guidance was then used to determine when the internal cervical os had been reached. A rest period (lasting approximately 1 to 5 minutes) was then observed before the transfer was completed. The duration of the rest period was adapted according to the needs of the patient, allowing time for the patient to relax and for any pelvic discomfort or abdominal contractions to stop. The second step was the deposition of the embryo: the position of the catheter tip was adjusted in terms of its height and width to allow the embryo to be deposited precisely in the middle third of the cavity and between the 2 layers of the uterine mucosa. Once the deposition was complete, the catheter was removed gently, followed by the ultrasound transducer. After the procedure, the patient was instructed to rest for approximately 10 minutes but was then allowed to return to normal daily life.

Assessment of the Difficulty of the Transfer

The definition of a difficult transfer used in this study was based on the criteria described previously by Kava-Braverman et al. (4). The transfer was considered an EaT when the catheter passage was rapid and unimpeded through the cervix and into the cavity. It was considered a DiT in all other cases. If the transfer was difficult, the catheter was removed and a more detailed vaginal ultrasound was performed to analyze the anatomical characteristics of the patient and search for the most common anomalies: endocervical crypts, tortuous cervical canal, marked uterine anteversions, and cesarean-induced isthmoceles (8), or other causes (stenosis of the external or internal os, false passages, malformations, anomalies resulting from conizations, cervical endometriosis, and poor cervical exposure). If necessary, the size of the speculum was adjusted to improve the cervical exposure, and dilation of the external os was performed in case of external cervical os stenosis. Similarly, bladder filling was used to correct marked anteversion. The catheter pathway was then adapted according to the anatomical information gained from the ultrasound, and a new attempt at transfer was performed. If this transfer was easy, it was considered a simple DiT (SDiT); if transfer was still not possible, it was considered a persistently difficult transfer (PDiT). For all cases of PDiT, the next attempt at transfer was performed with the use of a catheter with a malleable mandrel that had been modeled and adapted to the anatomical features of the patient: a small bend was introduced at the end of the catheter to allow it to cross crypts or false passages with successive rotations, whereas a more global curve was introduced to adapt the catheter for use in patients with a tortuous cervical canal or anteversion (Fig. 1). The progression of the catheter was monitored and guided by transvaginal ultrasound. Antispasmodic drugs (oral tablets containing 80 mg phloroglucinol and 80 mg trimethylphloroglucinol) were used in the case of spasm, suspected on the basis of patient reports of discomfort or contractions (1). If transfer was still not possible once the internal os of the cervix had been reached, the transfer was considered a very persistent difficult transfer (VPDiT). If transfer remained impossible (ImT), even after repeated attempts taking as much time as needed to allow passage of the catheter and after a further attempt at performing the transfer by another operator, the embryos were frozen. Neither dilation of the cervical canal nor cervical forceps were used as part of the procedure as the use of these techniques may induce cervical contractions.

FIGURE 1



The visualization of the uterine anatomy by transvaginal ultrasound and the personalization of the embryo transfer based on the anatomical characteristics of the uterus. Images of the midsagittal sections of the uterus, with the ultrasound probe positioned below and the front of the uterus toward the right. (**A**) Normal uterus. (**B** to **G**) The anatomical characteristics of the uterus causing difficult transfer: (**B**) marked anteversion; (**C**) tortuous cervical canal; (**D**) crypts; (**E**) cesarean-induced isthmoceles; (**F**) individual causes: false cervical passages (**G**) the most frequent association of characteristics causing difficult transfers: crypts + marked anteversion + canal bend of >90°.

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Subjective Patient Assessment of Discomfort During the Transfer

A subjective assessment of the level of discomfort felt by the patient during the procedure was conducted for each embryo transfer. This assessment was based on a five-point verbal rating scale: 4 = pain, 3 = marked discomfort, 2 = mild discomfort, 1 = passage of the catheter was felt without pain or discomfort, 0 = transfer achieved without any sensations.

Statistical Methods

The main criteria known to affect the outcomes of ART—i.e., the patient's age, ovarian reserve, type of ART (in vitro fertilization, intracytoplasmic sperm injection, or frozen embryo transfers), and embryonic stage—were compared in the 2 groups (EaT and DiT) to ensure the absence of statistical bias. The criterion used to assess the ovarian reserve was the number of usable oocytes obtained during puncture. The P/T rates were calculated with pregnancy being determined by a β-human chorionic gonadotropin level >100 IU/mL. Statistical comparisons were performed using Pearson's chi-square test and the R Program software (9). For all analyses, $P<.05$ was considered statistically significant.

RESULTS

A total of 2,046 embryo transfers were conducted during the study period: 12% of these were DiTs (257/2,046) and 88% were EaTs (1,789/2,046). The demographic and clinical data of the patients are presented in Supplemental Table 1 (available online). The 5 most common anatomical features in cases of DiT were as follows (Table 1 and Fig. 1): endocervical crypts (54%), tortuous cervical canal (36.6%), marked uterine anteversions (30%), cesarean-induced isthmoceles (22%), and other various causes (26%). These anatomical features frequently occurred in association (53.3% of DiTs). Of the 2,046 embryo transfers, 152 (7.4%) were considered as a SDiT, 96 (4.7%) as a PDiT, 7 (0.3 %) as a VPDiT, and 2 (0.1%) as an ImT.

Overall, there was no statistically significant difference between the P/T ratios of the EaTs and the DiTs (41% vs. 37%, $P=.25$, Table 2). This result was found regardless of the type of catheter used. In addition, there was no statistically significant difference between the percentages of births per transfer for the EaTs and the DiTs (33% vs. 29%, Supplemental Table 1, available online). Similarly, there was no statistically significant difference in P/T results between the EaTs and the subtypes of DiT with various degrees of difficulty, i.e., SDiT, PDiT, and SDiT+PDiT (Table 2). Because of the small sample size, no statistical analysis was performed for the VPDiT alone group (n = 7, 2 pregnancies obtained) or for the 2 cases of ImT.

Statistically significant differences in P/T were observed within the EaT group according to the catheter used (Table 3): the pregnancy rate was significantly higher when a "soft" catheter was used compared with that when a rigid monoblock catheter (Elliocath) was used (P/T of 45% vs. 37%, $P=.0005$). For the overall DiT group, there was no statistically significant difference in the pregnancy rate with the TDT set and that with the "soft" catheter (P/T of 35% vs. 38%, $P=.6$). However, for the persistent DiTs, there was a statistically significant difference in the pregnancy rate between the types of catheter, with the pregnancy rate being higher when the "soft" catheter vs. when the rigid catheter was used (P/T of 42% vs. 23% $P=.04$). For the "soft" catheter, no statistically significant differences in results were observed between the EaTs and all DiTs (n = 878, P/T = 45% vs. n = 146, P/T = 38%, $P=.12$). Finally, there was no statistically significant difference between the EaT and DiT groups in the level of discomfort felt during the procedure (Supplemental Table 2, available online).

TABLE 1

The identified causes of difficult embryo transfers.

Causes of difficulties (difficult transfers = 257)	Number and percentage
Main causes[a]	
Endocervical crypts	138 (53.7)
Tortuous cervical canal	94 (36.6)
Uterine anteversion	76 (29.6)
Cesarean-induced isthmoceles	57 (22.2)
Various other causes	66 (25.7)
Type of other causes	
False pathways	16 (24.2)
Stenosis of external cervical os	14 (21.2)
Stenosis of internal cervical os	10 (15.1)
Malformation	8 (12.1)
Conization	8 (12.1)
Cervical endometriosis	6 (9.1)
Poor cervical exposure	4 (6.1)
No. of associated causes	
1 only	120 (46.7)
2 or more	137 (53.3)
2	96 (37.3)
3	38 (14.8)
4	3 (1.2)

[a] Each difficult transfer may have been associated with multiple causes.

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TABLE 2

The pregnancy per transfer (P/T) results according to the degree of difficulty of the embryo transfer.

Types and subtypes of embryo transfer	Transfer number and percentage	Pregnancy No. (%)	P/T (%)	*P* value[a]
Type of embryo transfer				
All	2,046 (100.0)	829 (100.0)	40.5	
EaT	1,789 (87.4)	734 (88.5)	41.0	
DiT	257 (12.6)	95 (11.5)	37.0	.25
Subtype of DiT				
SDiT	152 (7.4)	59 (7.1)	38.8	.60
PDiT	96 (4.7)	34 (4.1)	35.4	.20
SDiT+PDiT	248 (12.1)	93 (11.2)	37.5	.28
VPDiT	7 (0.3)	2 (0.2)	28.6	ND
ImT	2 (0.1)	0 (0.0)	0.0	ND

Note: DiT = difficult transfer; EaT = easy transfer; ImT = impossible transfer; ND = not determined; P = pregnancy number; PDiT = persistently difficult transfer; SDiT = simple difficult transfer; T = transfer number; VPDiT = very persistent difficult transfer.

[a] *P* value for the comparison of P/T between EaTs and DiTs as a whole, and each type of DiT, using Pearson's chi-square test. $P<.05$ was considered significant.

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TABLE 3

The pregnancy per transfer (P/T) results according to the type of catheter used for the embryo transfer.

Type of transfer	Type of catheter	Transfer No. (%)	Pregnancy No. (%)	P/T (%)	*P* value[c]
All transfers (N = 2,046)	Rigid catheter[a]	1,022 (50.0)	377 (45.5)	36.9	
	Soft catheter[b]	1,024 (50.0)	452 (54.5)	44.1	.0008
Easy transfers (N = 1,789)	Rigid catheter[a]	911 (50.9)	338 (46.0)	37.1	
	Soft catheter[b]	878 (49.1)	396 (54.0)	45.1	.0005
Difficult transfers (N = 257)	Rigid catheter[a]	111 (43.2)	39 (41.0)	35.1	
	Soft catheter[b]	146 (56.8)	56 (59.0)	38.4	.6
Subtype of difficult transfer (DiT)					
Simple DiT	Rigid catheter[a]	68 (44.7)	29 (49.2)	42.6	
	Soft catheter[b]	84 (55.3)	30 (50.8)	35.7	.38
Persistent DiT (PDiT+VPDiT+ImT)	Rigid catheter[a]	43 (41.0)	10 (27.8)	23.3	
	Soft catheter[b]	62 (59.0)	26 (72.2)	41.9	.04

Note: DiT = difficult transfer; EaT = easy transfer; ImT = impossible transfer; P = pregnancy number; PDiT = persistently difficult transfer; T = transfer number; VPDiT = very persistent difficult transfer.

[a] From February 2014 to November 2017, the rigid Elliocath was used for easy transfers, and the TDT set was used for difficult transfers.

[b] The soft catheter from the COOK Laboratory was used in all cases from November 2017 to February 2020. A malleable mandrel was used for the PDiT, VPDiT, and ImT subtypes.

[c] *P* value for the comparison of P/T between rigid and soft catheters, using Pearson's Chi-square test. $P < .05$ was considered significant.

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DISCUSSION

Previous studies have indicated that the success rates for ART are on average 10% lower after a DiT than after an EaT (3–5, 10, 11). The most common explanations are endometrial trauma and the occurrence of induced uterine contractions (2). Our prospective study evaluated an embryo transfer strategy that could be adapted in the case of DiT. The 2 key innovations were the adaptation of the transfer procedure based on a rigorous analysis of the anatomical characteristics identified by transvaginal ultrasound and the division of the transfer into 2 stages. The first stage involved passage through the cervical canal, with the degree of difficulty encountered varying among patients. This step was followed by a rest period to allow any uterine contractions to subside before the precise deposition of the embryo in the optimal region of the uterine cavity. In addition, antispasmodics that act on the smooth muscle (phloroglucinol and trimethylphloroglucinol) were administered to limit further uterine contractions. Our study showed that there was no overall difference between the pregnancy outcome for EaTs and DiTs when the embryo transfer was carried out using the strategy described.

There is a lack of consensus concerning the definition of a DiT. Therefore, the reported frequency of DiT varies depending on the study. Indeed, embryo transfers have often been defined as difficult when they required the use of specific tools such as catheters with sheaths and rigid mandrels. According to this definition, DiT frequency has been reported to vary from 7% to 10% (4, 5). This rate is similar to that found in our study, as 12% of transfers were classified as difficult. However, other investigators have defined DiTs as those that required the use of a tenaculum or involved cervical dilation or transmyometrial transfer. In these studies, the frequency of DiT ranged from 2% to 5% (2, 4–6). In our study, these transfers would have been classed as PDiTs (4.7%), although a tenaculum was never used as part of our strategy, and neither routine cervical dilation nor transmyometrial transfer were performed.

The embryo transfer technique has changed little over time (12). Identifying the causes of DiT allows innovative strategies to be developed, including the advent of alternative techniques and new equipment, to overcome specific difficulties. Some studies have identified cervical stenosis and pronounced anteversions of the uterus as causes of DiT, leading to the suggestion that embryo transfer could be improved by performing a dilation before the transfer (5). To date, only one prospective study has been conducted to identify correlations between anatomical characteristics, based on morphological examinations (ultrasound and hysteroscopy), and the difficulty of embryo transfer (8). The investigators identified 5 main anatomical causes for DiT: crypts, marked anteversions, tortuous cervical canal, cervical spasms, and other individual abnormalities. These anatomical characteristics were observed in similar proportions in our current study, although the frequency of isthmoceles (22%) was higher than that previously reported. Cervical stenosis was infrequent (5%) in the current study, and although anteversions (30%) were identified as a source of difficulty, retroversions were not (Table 1). The association of several of these anatomical characteristics was observed frequently when the transfer was difficult (Fig. 1).

Abdominal ultrasound has been found to improve transfer results in the majority of studies (1, 13, 14) (Scottish Intercollegiate Guidelines Network grade A). No consensus has been reached yet concerning the superiority of transvaginal ultrasound for monitoring this procedure because only a few studies on the subject have been published (1, 15, 16). However, transvaginal ultrasound appears to be a more suitable method for monitoring embryo transfer than abdominal ultrasound; the high frequency of the probes and the proximity of the target improves the quality of the image (Figure 1) (16), allowing more detailed analysis of the endocervical abnormalities and providing precise guidance throughout the entire transfer procedure. Moreover, transvaginal ultrasound has the benefit of being a more comfortable procedure for the patients because the bladder does not need

to be full (15). This technique can be used routinely for all embryo transfers and can be repeated as often as necessary during the optimization of DiTs. Although transvaginal ultrasound requires training and regular practice for optimal use during difficult transfers, we have not identified yet any disadvantages of using this technique in all cases.

The type of catheter used evolved over the study period. From February 2014 to November 2017, embryo transfers were performed routinely with monoblock catheters (Elliocath, n = 911). The curved end of these catheters facilitated transfer in some cases, particularly when DiTs were caused by crypts and false cervical passages. However, once they have passed through the internal os, these rigid catheters can scratch the mucous membrane, and may even result in submucosal transfers. When difficulties were encountered during this period of the study, subsequent transfer attempts were made with the use of the TDT catheter set (n = 111). The classification of the TDT catheter set varies among publications, with some studies classing these catheters as rigid because of their metal mandrel, and others classing them as "soft" because of their flexible secondary catheter. We found that the TDT catheter set worked well when the DiT was simple (SDiT), but that this catheter was associated with lower P/T percentages when the DiT was more difficult (PDiT; Table 3). From November 2017 to February 2020, all transfers (n = 1,024) were performed with the use of a curved "soft" catheter with a distal olive that allowed endocervical obstacles to be overcome without causing tissue trauma. The results of our study showed that using this catheter in combination with our two-stage transfer procedure guided by transvaginal ultrasound was an effective management strategy for DiT. Notably, this strategy appeared to reduce the differences in P/T results between SDiT and more difficult transfers (PDiT+VPDiT+ImT; Table 3). Our findings were consistent with those obtained in previous studies in which higher pregnancy rates were observed when a "soft" catheter was used (1, 17–19).

There was no overall difference between the EaT and DiT groups in the level of discomfort reported by the patients; this may have been related to the systematic rest period introduced between the passage of the catheter through the cervix and the transfer of the embryo.

Only 2 ImTs were observed during the course of our study. In both cases, the embryos were frozen while an exploration of the cervix was performed under hysteroscopy followed by surgical correction to improve the ease of transfer (20). The embryos of the first patient did not survive thawing and the patient stopped the ART process. The second patient had 2 postoperative transfers evaluated as simple: one resulted in a spontaneous miscarriage and the other in an evolutive pregnancy.

The main limitation of this prospective study was the absence of randomization. Our study is the largest of its kind to be published in the field to date. Despite the large number of transfers evaluated, the low frequency of DiT made randomization very difficult. Another limitation was that all the transfers performed in our study were conducted by the same operator with the exception of the 2 cases of ImT in which the transfer was attempted by a second operator, and therefore further evaluations involving a larger number of operators are required to ensure the generalizability of our findings.

In conclusion, this large prospective study demonstrated that an adapted embryo transfer approach, based on the analysis of uterine anatomy and transvaginal ultrasound guidance, allowed similar pregnancy rates to be obtained regardless of whether the transfer was easy or difficult.

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