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Reproductive Outcome is Optimized When an Embryo Transfer is Performed 1 to 3 Months after Cervical Dilation

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Abstract

Cervical dilatation improves the ease of access to the endometrial cavity in patients with a prior history of cervical stenosis and/or a difficult embryo transfer.

Objective: To evaluate IVF cycle outcome(s) of patients who underwent cervical dilatation (CD) prior to an embryo transfer (ET).

Material & Methods: Patients (n=68) at a private, academic reproductive medical center (July 2008 to December 2014) with a history of a difficult ET were included. A difficult ET is associated with cervical canal obstruction and requires the use of additional instrumentation (i.e. rigid transfer catheter). Patient cohorts were segregated by the time after CD to ET occurrence: <1 month; 1 to 3 months; and >3 months. Main outcome measure was live birth rate (LBR). Data was analyzed by student's t-test, Chi-square, Kruskal-Wallis and binary logistic regression using SAS.

Results: Seventy-one difficult ET cycles (n=69 patients) were identified, of which 11 (n=11 patients) had subsequent IVF cycles involved cryopreservation or a cycle cancellation. The remaining 60 cycles (n=58 patients) underwent CD prior to a subsequent ET. LBR was significantly increased in those patients who underwent ET 1 to 3 months (50.0%) post CD as compared to those patients pursuing at <1 month (10.5%, $p<0.05$) or >3 months (14.3%, $p<0.05$) cohorts.

Conclusions: Cervical dilatation improves the ease of access to the endometrial cavity in patients with a prior history of cervical stenosis and/or a difficult embryo transfer. Additionally, performing the embryo transfer 1-3 months after CD is correlated with higher LBRs.

Keywords: Cervical Dilatation; Cervical Stenosis; Embryo Transfer; Endometrial Cavity; In Vitro Fertilization; Live Birth Rate; Cervical Canal; Technique

Introduction

The success of an in vitro fertilization (IVF) cycle relies on clinical attention to patient age, infertility diagnosis and ovarian reserve markers; with the additional focus on stimulation protocol, response, embryo development and transfer technique [1,2]. Sperm's ability to fertilize an oocyte is susceptible to its ability to navigate through the cervical canal, a challenge made more arduous if the pathway is obstructed [3]. When undergoing assisted reproductive technologies (ART), clinicians seek a clear pathway when inserting a catheter through the cervical and endometrial canal during an intrauterine insemination (IUI) or embryo transfer (ET). Although successful implantation depends on a number of confluent factors, such as embryo and endometrial receptivity, the ease with which an embryo is transferred through these pathways is an important, ultimate factor influencing IVF outcome.

Anatomical distortion of the cervical canal can lead to challenges at time of ET which can alter the success of treatment. A large majority of difficult ETs occur in the setting of altered uterine anatomy, which may be due to fibroids, endometriosis or prior surgery, and cervical stenosis [4,5]. Cervical stenosis, a condition in which the cervical canal narrows or becomes completely obstructed, can occur due to congenital defects, agglutination, cervical cancer, or scar tissue following surgical procedures such as dilation and curettage (D&C) or cone biopsy [6,7]. Even in instances where an IVF clinic conducts a simulated transfer and finds limited barriers to a successful ET, unexpected difficulties can arise during true ETs. Difficult ETs, requiring additional instrumentation at the time of procedure, have been correlated with bleeding, uterine contractions (which can expulse or displace the embryo) and uterine contamination with microorganisms; all for which can prevent implantation [8-13].

Current ET techniques are performed with a full bladder [14,15], using ultrasound-guidance that enhances visualization of the catheter tip and release of the embryo at the top of the uterine cavity [16]. A variety of approaches have been described to overcome or prevent difficult ETs. While performing a simulated ET catheter trial in all patients is a strategy that helps to identify potential difficulties prior to the ET procedure, its true predictive value remains undefined; it cannot reliably prevent all of the possible challenges a physician may encounter during a subsequent ET [17,18]. Additionally, hysteroscopic canal shaving [19,20], hysteroscopic embryo transfer [21], ET with a malecot catheter [22], transmyometrial guided ET [23-26], intrafallopian embryo transfer [27] and the use of hygroscopic [28,29] or mechanical dilators [30,31] have been used with mixed results. Mechanical cervical dilation (CD) use has been shown to effectively improve the ease of access to the endometrial cavity in patients with cervical stenosis [29-30]. CD involves the use of a mechanical dilator, such as Hegar, Pratt and Denniston dilators, to mechanically widen the cervical canal. Additionally, there is a biochemical effect contributing to the dilation and relaxation of the cervical canal whereby pressure from the dilator on the cervical canal induces the release of endogenous prostaglandins [32].

There is limited data regarding whether CD has an influence on overall IVF cycle outcome and whether there is an optimal approach in the period between this treatment prior to ET practice for patients with cervical stenosis or a history of a difficult ET. There have been conflicting reports with regard to the influence of CD on the ease of ET and pregnancy outcomes. Abusheika et al. [8] reported that by using CD improved the ease of ET in 70% of the patients (judged by the performer) and increased pregnancy rates (PR): 40% versus 11.8% ($p<0.05$). In contrast, Tomas et al. [33] showed that difficulty of ET was an independent factor, postulating that PR were more reflective of physician intervention at ET and potential catheter-inflicted trauma to the uterine cavity or uterine contractions. Nevertheless, neither considered live birth as main outcome.

The study sought to evaluate IVF cycle outcomes of patients who had cervical stenosis and/or endured a difficult simulation or true transfer cycle, underwent CD and had a subsequent ET. This study seeks to confirm whether CD prior to an ET improves the ease of access to the endometrial cavity at the time of the procedure. Furthermore, this study aims to identify the optimal timing for patients to undergo CD prior to ET.

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Materials & Methods

Study population

Patients who underwent a simulated or true ET prior to an IVF cycle in which a "difficult" procedure prompted the need for CD procedure were included. Patients were identified from an electronic medical records database. Patients with previous ET prior to CD, difficult ET that had a cancelled cycle (diminished oocyte quantity, inadequate development of embryos or inadequate uterine lining development) or underwent a freeze-all cycle (for a subsequent cryo-natural or synthetic cycle) were excluded.

Treatment protocol

Patients underwent standard controlled ovarian stimulation (COH) with recombinant Follicle Stimulating Hormone (FSH) and/or Human Menopausal Gonadotropin (HMG) gonadotropins in either a down-regulation protocol with leuprolide acetate (Lupron®, AbbVie Inc., North Chicago, IL) a GnRH antagonist protocol (Ganirelix Acetate®, Organon USA Inc., Roseland, NJ or Cetrotide®, EMD Serono, Rockland, MA), or a Microflare protocol (Lupron®, AbbVie Inc., North Chicago, IL). When at least two follicles reached >18mm size, final oocyte maturation was induced with r-hCG alone (Ovidrel®, EMD Serono, Rockland, MA) or with 40 UI of leuprolide acetate (Lupron®, AbbVie Laboratories, Chicago, IL) with 1000-1500 IU of hCG (Novarel®, Ferring Pharmaceuticals, Parsippany, NJ) in patients with high ovarian response and/or in risk of ovarian hyperstimulation syndrome undergoing an antagonist protocol. Vaginal oocyte retrieval (VOR) was performed by using transvaginal ultrasound guidance 36 after hCG administration. Luteal phase support was administered with intramuscular progesterone (Progesterone in oil®, Watson Pharma Inc., Parsippany, NJ) or with micronized progesterone vaginally (Endometrin®, Ferring Pharmaceuticals Inc., Parsippany, NJ; or Crinone®, Actavis Pharma, Parsippany, NJ) and orally (Prometrium®, AbbVie Inc., North Chicago, IL) beginning the day after VOR.

Embryo selection

All embryos that showed signs of development between day 1 and day 5 were considered viable for transfer. Embryos that did not display any growth or development from day 1 to day 5 were discarded. Cleavage stage (day 3) and blastocyst stage (day 5) embryos were assigned a quality score. Blastocysts were classified according to a modified Gardner and Schoolcraft scale including D categories for inner cell mass and trophectoderm [34]. Each patient's highest quality embryo(s) were selected for ET.

Embryo transfer

Following localization and examination of the cervix, excess mucus was removed by use of a cotton swab soaked in modified HTF buffer (HEPES; Irvine Scientific, Santa Ana, CA, USA). One additional wash was administered, and the cervical canal content was aspirated with a sterile Teflon catheter (Malleable Stylet Wallace, SIMCARES, Lancing, West Sussex, UK) connected to a syringe.

A Wallace-Edwards catheter (SIMS Portex Ltd, Hythe, UK) was used to transfer the embryos under transvaginal ultrasound guidance. Patients were advised to arrive with a partially filled bladder to provide an acoustic window for optimal sonographic visualization of the uterus. The catheter was connected to an insulin syringe loaded with an embryo and transfer medium [50% synthetic serum substitute (Irvine Scientific) and IVF medium (IVF-50) or G2.2 medium (Scandinavian IVF Science, Gothenburg, Sweden)]. A physician inserted the loaded catheter through the cervical canal. The stiff outer sheath of the catheter was passed through the middle of the cervix and remained in the cervical canal, while the thin catheter was passed into the uterus with care to avoid fundal contact. After the embryo was expelled, the catheter was removed from the uterine cavity and passed to an embryologist who verified successful removal of the embryo from the catheter via stereo microscopy.

Becoming a candidate for CD

The CD procedure was performed in patients found to have a difficult simulated or true ET that resulted in the need to postpone the ET. A simulated ET catheter trial was considered difficult if required additional instrumentation with a firmer catheter (hard Wallace malleable stylet) or the placement of a tenaculum or Allis clamp on the external os to straighten the cervical canal and provide counter traction for catheter entry. A true ET was estimated difficult if required additional instrumentation with a firmer catheter (hard Wallace malleable stylet), required the use of a tenaculum or Allis clamp on the cervix, or the duration of the procedure exceeded 5 minutes. In either setting, CD was performed prior to subsequent ET.

Cervical dilation

Cervical dilation was performed using a Wallach Hegar Dilator Set (Wallach Surgical Devices, Trumbull, CT). Dilators were inserted through the cervix and held in place for 1 minute in a serial fashion, increasing in caliber from 3mm up to 10mm, if required.

Study groups

Patients were retrospectively segregated into 3 groups according to the interval of time from the CD procedure and ET: Group A) <1 month; Group B) 1-3 months; and Group C) >3 months.

Outcomes assessed

The primary outcome variable was live birth rate (LBR). The LBR was calculated as the number of live births occurring at >24 weeks gestation of the total number of patients that underwent ET. Secondary outcomes were pregnancy rate (PR), clinical PR, implantation rate (IR), early pregnancy loss rate and multiple PR. A pregnancy was defined as the detection of β-hCG ≥ 5m UI/mL 14 days after the oocyte retrieval. A clinical pregnancy was defined as the detection of a gestational sac (GS) on an ultrasound examination 22 to 25 days after the oocyte retrieval. Early pregnancy losses were defined as a positive pregnancy test and/or a GS with or without fetal heart activity that did not pass the 20th week of gestation. PR and clinical PR were calculated as the ratio of total pregnancies and ongoing clinical pregnancies, respectively, to the number of patients undergoing an ET. The IR was calculated as the ratio of the number of GS to the number of transferred embryos. Early pregnancy loss rate was calculated as the ratio of early pregnancy losses to the number of patients with a positive pregnancy. Multiple PR was calculated as the ratio of clinical pregnancies with ≥ 2 GSs to the number of patients with a clinical pregnancy.

Statistical analysis

Statistical analysis was performed using SAS (Statistic Applied Software) version 9.4 (by SAS Institute Inc., Cary, NC, USA). Measurement levels of descriptive data were compared by unpaired two-sided t-test with significance at $p<0.05$; results are expressed as mean ± standard deviation with 95% confidence intervals. Distributions between outcomes (Group A vs. B and Group B vs. C) were assessed by Chi Square test. Fisher exact test was computed on all contingency tables with significance at $p<0.05$ for samples less than 10. Groups were further analyzed with the Kruskal-Wallis one-way analysis of variance to determine if there were statistically significant differences between them. The Clopper-Pearson interval was used to calculate binomial confidence intervals of all reported proportions. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) for LBR, PR, clinical PR, IR, multiple PR and early pregnancy loss rate were calculated to evaluate the relative odds of each event.

This research was approved by the Western Institutional Review

Board (WIRB). Because of its retrospective nature, a formal consent was not required.

Results

A total of 69 patients who underwent 71 cycles from July 2008 to December 2014 with reported difficult simulated or true ETs were included in this study. Eleven patients (n=11 cycles) were excluded from further analysis due to a cancelled cycle or a cycle scheduled as a freeze-all cycle. The remaining 58 patients who underwent 60 cycles underwent a cervical dilation with a subsequent FET cycle.

Overall, patients had an average age of 39.4 ± 6.7 years, an average BMI of 24.6 ± 4.6, basal FSH levels were 9.5 ± 3.2, basal antral follicle count (AFC) was 8.3 ± 9.4, and average endometrial thickness at the ET of 9.7 ± 1.7 mm. Nineteen patients (31.7%) of the patients were transferred at the cleavage stage and 68.3% (n=41) were transferred at the blastocyst stage (Table 1). The main outcome measure of LBR was 26.7% (16/60) for all patients. Other evaluated clinical outcomes included PR (56.7%, 34/60), clinical PR (51.7%, 31/60), IR (33.6%, 42/125), multiple PR (16.7%, 10/60) and early pregnancy loss rate (18.3%, 11/60). No subsequent transfers were categorized as difficult or required additional instrumentation.

Group A: IVF within 1 month after CD

Nineteen transfers were performed within one month of a CD procedure. Patients' demographic characteristics are described in Table 1. Live birth rate for group A was 10.5% (2/19). PR was 57.9% (11/19), clinical PR was 47.4% (9/19), IR was 29.3% (12/41), multiple PR was 15.8% (3/19) and early pregnancy loss rate was 10.5% (2/19) (Figure 1 and Table 2).

Group B: IVF between 1 and 3 months after CD

Twenty transfers were performed between 1-3 months after the CD. Patients' demographic characteristics are described in Table 1. Live birth rate for group B was 50.0% (10/20). PR was 80% (16/20), clinical PR was 80% (16/20), IR was 59.0% (23/239), multiple PR was 30% (6/20) and early pregnancy loss rate was 25% (5/20) (Figure 1 and Table 2).

Group C: IVF after 3 months of CD

Twenty one transfers were performed after 3 months of CD. Patients' demographic characteristics are described in Table 1. Live birth rate for group C was 14.3% (3/21). PR was 33.3% (7/21), clinical PR was 28.6% (6/21), IR was 15.6% (7/45), multiple pregnancy rate was 4.8% (1/21) and early pregnancy loss was 19.0% (4/21) (Figure 1 and Table 2).

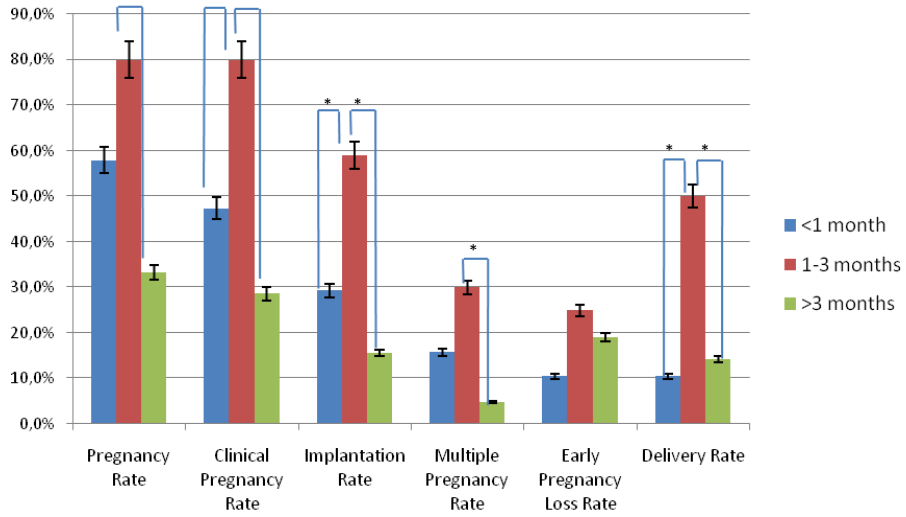
Main analysis

Baseline demographics and IVF cycle characteristics were similar among the three study groups except for the number of fertilized oocytes (8.1 vs. 10.2 vs. 5.2, respectively) and the proportion of cycles transferred in the blastocyst stage (63.2% (n=12) vs. 85.0% (n=17) vs.

Table 1: Demographic characteristics and embryological data.

Group	<1 month	1 – 3 months	>3 months	All	Kruskal-Wallis Test	
Cycles	n=19	n=20	n=21	n=60	Chi-Square	Pr>Chi Square
Oocyte's Age	33.4 ± 6.7	32.8 ± 6.7	36.0 ± 5.9	34.1 ± 6.5	2.8947	0.2352
Basal FSH	10.2 ± 3.2	8.7 ± 5.7	9.2 ± 4.0	9.3 ± 4.3	3.7844	0.1507
Basal AFC	8.3 ± 9.4	8.2 ± 6.2	10.1 ± 4.8	8.9 ± 6.9	3.1540	0.2066
BMI	25.9 ± 5.3	25.7 ± 6.5	22.8 ± 2.1	24.6 ± 4.9	1.1530	0.5619
Endometrial Thickness (mm)	9.3 ± 2.8	8.8 ± 1.9	8.1 ± 2.1	8.8 ± 2.3	2.2702	0.3214
Retrieved	9.1 ± 9.3	11.1 ± 12.3	5.7 ± 7.1	8.5 ± 9.8	2.2674	0.3218
2PN	8.1 ± 6.1	10.2 ± 5.9	5.2 ± 5.2	7.8 ± 6.0	6.2082	0.0449
Transferred	2.2 ± 1.3	2.0 ± 0.8	2.1 ± 1.3	2.0 ± 1.1	0.0662	0.9674
Transfer Stage						
Cleavage Stage	36.8 % (n=7)	15.0 % (n=3)	42.9 % (n=9)	31.7 % (n=19)		
Blastocyst Stage	63.2 % (n=12)	85.0 % (n=17)	57.1 % (n=12)	68.3 % (n=41)		

Results are expressed as mean ± standard deviation with 95% confidence intervals. Significance established at p<0.05.



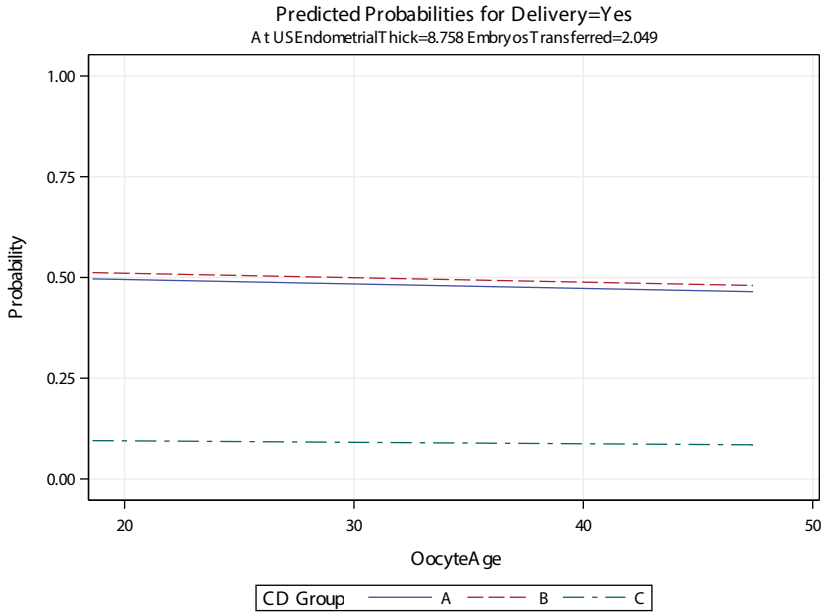
Error bars represent 95% CI by Clopper-Pearson method. *denotes p<0.05.

Figure 1: Clinical Outcomes between groups.

Table 2: Clinical Outcomes.

Group	<1 month	1 – 3 months	>3 months	All	A vs. B	A vs. C	B vs. C
Cycles	n=19	n=20	n=21	n=60			
Pregnancy Rate	57.9 % (11/19) (95% CI 35.7 – 80.1)	80.0 % (16/20) (95% CI 56.3 – 94.3)	33.3 % (7/21) (95% CI 14.6 – 57.0)	56.7 % (34/60) (95% CI 43.2 – 69.4)	NS, OR 2.9 (95% CI 0.7 – 12.1)	NS, OR 0.4 (95% CI 0.1 – 1.3)	p<0.05, OR 8.0 (95% CI 1.9 – 33.1)
Clinical Pregnancy Rate	47.4 % (9/19) (95% CI 24.9 – 69.8)	80.0 % (16/20) (95% CI 56.3 – 94.3)	28.6 % (6/21) (95% CI 11.3 – 52.2)	51.7 % (31/60) (95% CI 38.4 - 64.8)	p<0.05, OR 4.4 (95% CI 1.1 – 18.3)	NS, OR 0.4 (95% CI 0.1 – 1.6)	p<0.05, OR 10.0 (95% CI 2.3 – 42.5)
Implantation Rate	29.3 % (12/41) (95% CI 16.1 – 45.5)	59.0 % (23/39) (95% CI 42.1 – 74.4)	15.6 % (7/45) (95% CI 6.5 – 29.5)	33.6 % (42/125) (95% CI	p<0.05, OR 3.5 (95% CI 1.4 – 8.8)	NS, OR 0.5 (95% CI 0.2 – 1.3)	p<0.05, OR 7.8 (95% CI 2.8 – 21.8)
Multiple Pregnancy Rate	15.8 % (3/19) (95% CI 0.6 – 32.2)	30.0 % (6/20) (95% CI 11.9 – 54.3)	4.8 % (1/21) (95% CI 0.1 – 23.8)	16.7 % (10/60) (95% CI 8.3 – 28.5)	NS, OR 2.2 (95% CI 0.4 – 10.8)	NS, OR 0.3 (95% CI 0.02 – 2.8)	p<0.05, OR 8.5 (95% CI 0.9 – 79.3)
Early Pregnancy Loss Rate	10.5 % (2/19) (95% CI 3.3 – 24.3)	25.0 % (5/20) (95% CI 8.7 – 49.1)	19.0 % (4/21) (95% CI 5.4 – 41.9)	18.3 % (11/60) (95% CI 9.5 – 30.4)	NS, OR 2.8 (95% CI 0.4 – 16.8)	NS, OR 2.0 (95% CI 0.3 – 12.4)	NS, OR 1.4 (95% CI 0.3 – 6.2)
Live Birth Rate	10.5 % (2/19) (95% CI 3.3 – 24.3)	50.0 % (10/20) (95% CI 27.2 – 72.8)	14.3 % (3/21) (95% CI 3.0 – 36.3)	26.7 % (16/60) (95% CI 16.1 – 39.7)	p<0.05, OR 9.0 (95% CI 1.6 – 49.4)	NS, OR 1.5 (95% CI 0.2 – 10.1)	p<0.05, OR 6.0 (95% CI 1.3 – 27.0)

Binomial confidence intervals (CI) for all reported proportions. Adjusted odds ratios (OR) and their 95% CI by Clopper-Pearson method for pregnancy rata (PR), clinical PR, implantation rate, multiple PR, early pregnancy loss rate and live birth rate.



Error bars represent 95% CI. *denotes p<0.05.

Figure 2: Clinical Outcomes.

57.1%(n=12), respectively) (Table 1). The primary outcome measure of LBR was significantly higher in patients who underwent ET 1-3 months after the CD when compared to those who underwent ET at <1 month (50.0% vs. 10.5%, p<0.05) or >3 months after CD (50.0 % vs. 14.3%, p<0.05) (Table 2 and Figure 1). ETs performed 1-3 months after CD were 9 times more likely to achieve a live birth than those performed at <1 month (OR 9.0, 95% CI 1.6 – 49.4), and 6 times more likely than those performed at >3 months (OR 6.0, 95% CI 1.3 – 27.0) (Table 2).

PR was statistically higher when comparing Group B versus Group C (80.0% vs. 33.3%, p<0.05) (Figure 1), with patients 8 times more likely to become pregnant when ET was performed 1-3 months after CD vs. at >3 months after CD (OR 8.0, 95% CI 1.9 – 33.1) (Table 2). PR was increased in patients undergoing ET 1-3 months after CD compared with those that underwent ET at <1 month of CD (59.0% vs. 29.3%), however this did not reach statistical significance (Figure 1 and Table 2).

Clinical PR was statistically different when the ET was completed 1-3 months after the CD when compared to at <1 month (80.0% vs. 47.4%, p<0.05) and >3 months (80.0 % vs. 28.6%, p<0.05) (Table 2 and Figure 1). This significance was not demonstrated between <1 month and >3 months (47.4% vs. 28.6%, NS) (Table 2 and Figure 1). Patients who underwent an ET between 1 to 3 months were 4.4 times more likely to achieve a clinical pregnancy when compared to at <1 month (OR 4.4, 95% CI 1.1 – 18.3) and 10 times more likely when compared to at >3 months (OR 10.0, 95% CI 2.3 – 42.5) (Table 2).

IR was statistically significant when the ET was done 1-3 months after the CD when compared to at <1 month (59.0% vs. 29.3%, p<0.05) and >3 month (59.0 % vs. 15.6%, p<0.05), but not between <1 month and

>3 month (29.3% vs. 15.6%, NS) (Figure 1 and Table 2). Patients were 3.5 times more likely to have implantation if the ET was performed 1-3 months after the CD when compared to at <1 month, and 7.8 times more likely when compared to at >3 months (Figure 1 and Table 2).

Multiple PR was only statistically significant when comparing 1-3 months versus >3 months (30.0% 4.8%, $p<0.05$), with patient being 8.5 times more likely to have a multiple pregnancy when the ET was performed 1- 3 months after the CD. Early pregnancy loss rate was similar across all groups.

Conclusion

The embryo transfer is a critical step during an IVF cycle. Although preventative measures are in place to recognize, alleviate and optimize potential barriers of the procedure, the influence of any technical or anatomical modification are not well established. As clinicians attempt transcervical ET, technical difficulties can be encountered at time of IUI or ET, and this is most prevalently observed in patients diagnosed with cervical stenosis. If cervical stenosis goes unrecognized or untreated, it can obstruct an ET catheter from traversing the cervical and endometrial canal to reach approximately 5 to 7 mm from the uterine fundus. Because the transcervical ET is the preferred route in modern IVF programs, technical difficulties can be encountered at time of IUI or ET, most habitually in patients with cervical stenosis. Mechanical CD is the most common strategy to overcome this condition. The concept of a difficult ET and its impact on reproductive outcomes remains a focal point of contention within the field of reproductive medicine.

In this study, patients' were segregated into three groups according to the interval of time from the CD to subsequently performed ET. The study's results suggest that a live birth is more frequently achieved when an ET is performed 1-3 months after the CD procedure when compared to performing it at <1 month or >3 months after CD. It has been documented that CD may lead to trauma and bleeding of the cervix, which allows bloods cells to coat the embryos, and this may form an obstacle to connect with the endometrium. Bleeding also results in prostaglandin release, which may stimulate uterine contraction and expulse the embryo [35]. A period of time between the CD and the ET would allow any cervical or endometrial trauma to heal and to minimize the risk of expulsion of the embryos from the uterine cavity. This study's results support this perception.

Whether CD improves access to the uterine cavity and whether the timing of the procedure has any effect on clinical outcome has been debated and is not well established in the literature. Some authors have previously described that pregnancy outcomes improved as the length of time between CD and ET increased [36]. Abusheika et al. [8] and Prapas et al. [31] waited 1-3 months after CD to the ET; while Groutz et al. [30] performed CD on the day of the vaginal oocyte retrieval (VOR) and transferred 48 hours thereafter. Additionally, although some studies have suggested that difficult ETs correlate with lower pregnancy rates [37,38] while others suggest that it has minimal impact on clinical outcome [33,39,40], conflictions may be due to inconsistencies in what defines a difficult ET, the skill of the physician performing the ET, the embryo quality at transfer selection and the former study's sample size. Patients at the study's practice undergo a simulated ET catheter prior to their actual IVF-ET cycle [17,41]. Despite this preparation, a difficult ET can be encountered. When such circumstances present themselves, timed dilation is a useful and effective strategy to widen the cervical canal and is expected to ease the facilitation of a subsequent ET procedure.

The specific timing on when to perform the ET after CD has remained elusive. CD executed immediately before an IVF cycle or during the oocyte retrieval has been reported as means of improving outcomes in the presence of cervical stenosis. In one study, Groutz et al. [30] performed an ET 48 hours after CD. The authors reported almost all ETs were easier, nevertheless only 2.4% resulted in a clinical pregnancy. Abusheikha et al. [8] shared their experience when a post-CD ET was performed within two weeks. The authors reported that 31.6% of their patients achieved a clinical pregnancy, 40% of which had an ET classified as easy after the CD and 11.8% in those in which the ET was classified as difficult again. Lastly, Prapas et al. [25] waited 1-3 months to perform ET after CD, and found that 34.5% of the patients achieved a live birth. The current study evaluated and compared all such scenarios, using subjects with similar baseline demographics and IVF cycle characteristics, and the results suggest that the optimal lapse from CD to ET is 1-3 months.

Limitations of this study include its retrospective nature which creates a selection bias. Secondly, while CD is a simple procedure that is relatively inexpensive and safe, it does add another procedure to the treatment regimen, with associated time, cost, and risk. Known risks of CD include cervical tears, uterine perforation and future cervical insufficiency [42]. Third, the retrospective chart review includes patients treated over a six year period of time, during which treatment strategies have evolved drastically. This study's analysis included patients who underwent ET utilizing cleavage stage and blastocyst stage embryos. Advancements in extended culture methods [43] have successfully enabled the development of embryos to day 5 or 6 after vaginal oocyte retrieval (VOR). This has permitted the identification of blastocysts with little or no implantation potential [44], resulting in higher clinical PRs per transferred embryo. Fourth, a higher proportion of cycles in group B (1-3 months) were transferred at the blastocyst stage. Although in "good prognosis" patients blastocyst transfer results in increased LBRs compared to transfer of equal numbers of cleavage-stage embryos, in unselected populations it has not been shown to increase LBRs. Nevertheless, this difference can bias the results. Lastly, another limitation of the study was the relatively small sample size. For this reason, these findings cannot be generalized to the broader community based on this study alone.

In summary, patients with cervical stenosis and a difficult ET who underwent a cervical dilation procedure 30 to 90 days before a subsequent ET demonstrated higher live birth rates compared to patients who underwent the procedure less than a month or more than 3 months after the ET. Larger prospective studies are needed to better define the effects of a cervical dilation procedure on clinical outcomes and to optimize the use of mechanical dilation prior to or during an IVF cycle.

References

1. Hughes EG, King C, Wood EC. A prospective study of prognostic factors in in vitro fertilization and embryo transfer. Fertil Steril. 1989; 51:838-844.

2. Dinelli L, Courbière B, Achard V, Jouve E, Deveze C, Gnisci A, et al. Prognosis factors of pregnancy after intrauterine insemination with the husband's sperm: conclusions of an analysis of 2,019 cycles. Fertil Steril. 2014; 101:994-1000.

3. Vela G, Luna M, Sandler B, Copperman AB. Advances and controversies in assisted reproductive technology. Mt Sinai J Med. 2009; 76:506-20. doi: 10.1002/msj.20147.

4. Mains L, Van Voorhis BJ. Optimizing the technique of embryo transfer. Fertil Steril. 2010; 94:785–790.

5. Lass A, Abusheikha N, Brinsden P, Kovacs GT. The effect of a difficult embryo transfer on the outcome of IVF. Hum Reprod. 1999; 14:2417.

6. Suh-Burgmann EJ, Whall-Strojwas D, Chang Y, Hundley D, Goodman A. Risk factors for cervical stenosis after loop electrocautery excision procedure. Obstet Gynecol. 2000; 96:657-660.

7. Houlard S, Perrotin F, Fourquet F, Marret H, Lansac J, Body G. Risk factors for cervical stenosis after laser cone biopsy. Eur J Obstet Gynecol Reprod Biol. 2002; 104:144-147.

8. Abusheikha N, Lass A, Akagbosu F, Brinsden P. How useful is cervical dilatation in patients with cervical stenosis who are participating in an in vitro

fertilization-embryo transfer program? The Bourn Hall experience. Fertil Steril. 1999; 72:610-612.

9. Leeton J, Trounson A, Jessup D, Wood C. The technique for human embryo transfer. Fertil Steril. 1982; 38:156-161.

10. Englert Y, Puissant F, Camus M, Van Hoeck J, Leroy F. Clinical study on embryo transfer after human in vitro fertilization. J In Vitro Fert Embryo Transf. 1986; 3:243-246.

11. Goudas VT, Hammitt DG, Damario MA, Session DR, Singh AP, Dumesic DA. Blood on the embryo transfer catheter is associated with decreased rates of embryo implantation and clinical pregnancy with the use of in vitro fertilization-embryo transfer. Fertil. Steril. 1998; 70:878-882.

12. Diedrich K, Van der Ven H, Al-Hasani S, Krebs D. Establishment of pregnancy related to embryo transfer techniques after in-vitro fertilization. Hum Reprod. 1989; 4:111-114.

13. Visser DS, Fourie FL, Kruger HF. Multiple attempts at embryo transfer: effect on pregnancy outcome in an in vitro fertilization and embryo transfer program. J Assist Reprod Genet. 1993; 10:37-43.

14. Sharif K, Afnan M, Lenton W, Bilalis D, Hunjan M, Khalaf Y. Transmyometrial embryo transfer after difficult immediate mock transcervical transfer. Fertil Steril. 1996; 65:1071-1074.

15. Sundstrom P, Wramsby H, Persson PH, Liedholm P. Filled bladder simplifies human embryo transfer. Br. J. Obstet. Gynecol. 1984; 91:506-507.

16. Coroleu B, Carreras O, Veiga A, Martell A, Martinez F, Belil I, et al. Embryo transfer under ultrasound guidance improves pregnancy rates after in-vitro fertilization. Hum Reprod. 2000; 15:616-620.

17. Mansour R, Aboulghar M, Serour G. Dummy embryo transfer: a technique that minimizes the problems of embryo transfer and improves the pregnancy rate in human in vitro fertilization. Fertil Steril. 1990; 54:678-681.

18. Stafford-Bell MA. Which factors are important for successful embryo transfer after in-vitro fertilization? Hum Reprod. 1999; 14:2678-2679.

19. Noyes N. Hysteroscopic cervical canal shaving: a new therapy for cervical stenosis before embryo transfer in patients undergoing in vitro fertilization. Fertil Steril. 1999; 71:965-966.

20. Pabuccu R, Ceyhan ST, Onalan G, Goktolga U, Ercan CM, Selam B. Successful treatment of cervical stenosis with hysteroscopic canalization before embryo transfer in patients undergoing IVF: a case series. J Minim Invasive Gynecol. 2005; 12:436-438.

21. Kilani Z, Shaban M, Hassan LH. Live birth after hysteroscopic- guided embryo transfer: a case report. Fertil Steril. 2009; 91:2733e1–2733e2. doi:10.1016/j.fertnstert.2008.12.136.

22. Aust TR, Herod JJ, Gazvani R. Placement of a malecot catheter to enable embryo transfer after radical trachelectomy. Fertil Steril. 2005; 83:1842

23. Kato O, Takatsuka R, Asch RH. Transvaginal-transmyometrial embryo transfer: the Towako method; experiences of 104 cases. Fertil Steril. 1993; 59:51–53.

24. Sharif K, Afnan M, Lenton W, Bilalis D, Hunjan M, Khalaf Y. Transmyometrial embryo transfer after difficult immediate mock transcervical transfer. Fertil Steril. 1996; 65:1071–1074.

25. Groutz A, Lessing JB, Wolf Y, Azem F, Yovel I, Amit A. Comparison of transmyometrial and transcervical embryo transfer in patients with previously failed in vitro fertilization-embryo transfer cycles and/or cervical stenosis. Fertil Steril. 1997; 67:1073–1076.

26. Biervliet FP, Lesny P, Maguiness SD, Robinson J, Killick SR. Transmyometrial embryo transfer and junctional zone contractions. Hum Reprod. 2002; 17:347–350.

27. Tews G, Shebl O, Moser M, Ebner T. Successful pregnancy in vitrified/warmed blastocyst intrafallopian transfer. Fertil Steril. 2012; 98:52–54. doi:10.1016/j.fertnstert.2012.03.031

28. Serhal P, Ranieri D, Khadum I, Wakim R. Cervical dilation with hygroscopic rods prior to ovarian stimulation facilitates embryo transfer. Hum Reprod. 2003; 18:2618–2620.

29. Glatstein IZ, Pang SC, McShane PM. Successful pregnancies with the use of laminaria tents before embryo transfer for refractory cervical stenosis. Fertil Steril. 1997; 67:1172–1174.

30. Groutz A, Lessing J, Wof Y, Yoyel I, Azem F, Amit A. Cervical dilatation during ovum pick-up in patients with cervical stenosis: effect of pregnancy outcome in an in-vitro-fertilization embryo transfer programme. Fertil Steril. 1997; 67:909-911.

31. Prapas N, Prapas Y, Panagiotidis Y, Prapa S, Vanderzwalmen P, Makedos G. Cervical dilatation has a positive impact on the outcome of IVF in randomly assigned cases having two previous difficult embryo transfers. Hum Reprod. 2004; 19(8):1791-1795.

32. Reynolds SR. Uterine Contractility and Cervical Dilatation. Proc R Soc Med. 1951; 44:695-702.

33. Tomas C, Tikkinen K, Tuomivaara L, Tapanainen JS, Martikainen H. The degree of difficulty of embryo transfer is an independent factor for predicting pregnancy. Hum Reprod. 2002; 17:2632-2635.

34. Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Jansen R, Mortimer D, eds. Towards Reproductive Certainty: Infertility and Genetics Beyond. Carnforth: Parthenon Press. 1999; 378–88.

35. Ghazzawi IM, Al-Hasani S, Karaki R, Souso S. Transfer technique and catheter choice influence the incidence of transcervical embryo expulsion and the outcome of IVF. Hum Reprod. 1999; 14:677–682.

36. Akhtar MA, Netherton R, Majumder K, Edi-Osagie E, Sajjad Y. Methods employed to overcome difficult embryo transfer during assisted reproduction treatment. Arch Gynecol Obstet. 2015; 292:255-262.

37. Spandorfer SD, Goldstein J, Navarro J, Veeck L, Davis OK, Rosenwaks Z. Difficult embryo transfer has a negative impact on the outcome of in vitro fertilization. Fertil Steril. 2003; 79:654–655.

38. Marcus SF, Brinsden PR, Macnamee MC, Rainsbury PA, Elder KT, Edwards RG. Comparative trial between an ultra-short and long protocol of luteinizing hormone-releasing hormone agonist for ovarian stimulation in in vitro fertilization. Hum Reprod. 1993; 8:238–243.

39. Tur-Kaspa I, Yuval Y, Bider D, Levron J, Shulman A, Dor J. Difficult or repeated sequential embryo transfers do not adversely affect in-vitro fertilization pregnancy rates or outcome. Hum Reprod. 1998; 13:2452–2455.

40. Broussin B, Jayot S, Subtil D, Parneix I, Audebert A, Dubecq F, et al. Difficult embryo transfers: contribution of echography. Contracept Fertil Sex. 1998; 26:492–497.

41. Knutzen V, Stratton CJ, Sher G, McNamee PI, Huang TT, Soto-Albors C. Mock embryo transfer in early luteal phase, the cycle before IVF and embryo transfer: a descriptive study. Fertil Steril 1992; 57:156–162.

42. Newmann SJ, Dalve-Endres A, Diedrich JT, Steinauer JE, Meckstroth K, Drey EA. Cervical preparation for second trimester dilation and evacuation. Cochrane Database Syst Rev. 2010; 4:CD007310. doi: 10.1002/14651858.CD007310.pub2.

43. Thomas MR, Sparks AE, Ryan GL, Van Voorhis BJ. Clinical predictors of human blastocyst formation and pregnancy after extended embryo culture and transfer. Fertil Steril. 2010; 94:543-548.

44. Glujovsky D, Blake D, Farquhar C, Bardach A. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev. 2012; 7:CD002118.

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