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# Comparison of Embryo Transfer Techniques in Assisted Reproductive Technology (ART) Cycles

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## Abstract

**Capsule:** Different transfer techniques have been developed to optimize the embryo transfer process and maximize the probability of pregnancy after transfer. The purpose of this study is to compare the Afterload (AL) and the immediate Post-Mock (PM) Embryo Transfer (ET) techniques.

**Objective:** To determine if the AL ET technique results in higher Ongoing Pregnancy Rate (OPR) compared to the immediate PM ET technique.

**Design:** Retrospective cohort.

**Setting:** Clinic-based data.

**Patient(s):** The study population included 251 women between the ages of 18 and 49 at the time of transfer who underwent an autologous, fresh, or cryopreserved ET between July 01st, 2013 and September 01st, 2016 at our academic center.

**Intervention(s):** Embryo transfer was performed with either the AL or the immediate PM transfer technique.

**Main outcome measure:** OPR (presence of fetal cardiac activity on a first trimester ultrasound).

**Result(s):** There was no significant difference in OPR between patients that underwent AL transfers and PM transfers (AL 51%, PM 57%; P=0.378). OPR for frozen embryo transfers was superior for AL transfers compared to PM transfers (AL 68%, PM 31%; P=0.005). OPR was superior with the PM technique for fresh embryo transfers (AL 43%, PM 63%; P=0.002). OPR decreased with increasing age in the AL cohort, but not in the PM cohort (P=0.004).

**Conclusion:** There appears to be no overall difference in OPR between AL and PM transfer technique. However, with vitrified embryos, the AL technique demonstrated a higher OPR, and with fresh embryos, the PM technique resulted in a superior OPR.

**Keywords: Embryo transfer; Technique; AL; IVF**

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## Introduction

Embryo Transfer (ET) is the final and culminating event in the time consuming, emotionally challenging, and financially grueling *In-Vitro* Fertilization (IVF) cycle [1]. Various metrics have demonstrated a positive impact on successful ET such as catheter type, placement of embryos at a specific distance from the fundus, operator experience, ultrasound guidance, and transfer of cryopreserved embryos [2,3]. Despite numerous advances in IVF that have allowed for increased success of embryo implantation, little has changed in the general ET process [4]. Although embryo quality and a uterine environment are likely the most important factors in the success of IVF, the transfer technique itself is also recognized as an additional contributing factor [4].

Factors affecting failed transfer include disruption of the endometrium by the catheter, induction of uterine contractions, microbial contamination, traumatic transfer leading to the presence of blood in the transfer catheter, increased cervical mucus, deposition of the embryos in a suboptimal location, or damage to the embryos during the process [3,5]. The technique of the embryo transfer itself may also affect the success of ET. The Afterload technique (AL) is performed by placing an

empty catheter at or just beyond the internal cervical os [6,7]. The inner sheath of this catheter is removed and a second inner sheath containing embryos is passed. Alternatively, the immediate Post-Mock technique (PM) involves a mock ET that requires the passage of two separate catheters. This technique was initially published in the 1990's, and it involves a "practice" or mock transfer prior to the actual ET. During the mock transfer, performed on a separate date from ET, the clinician can assess the depth and contour of the cavity, and anticipate potential issues [8]. This technique has been further modified by performing a mock transfer immediately before the actual ET, to allow for similar transfer conditions [9]. Other transfer techniques include the non-guided direct transfer technique and ET following a pre-IVF cycle trial transfer, which have been shown to be inferior to an ultrasound-guided transfer [4].

Intuitively, the AL ET technique allows for easy navigation through the internal cervical os with minimal manipulation of embryos, and potentially reduced endometrial trauma [10,11]. However, the AL ET does not account for true assessment of the uterine cavity and early detection of unanticipated traumatic or difficult ET as the PM technique might. On the other hand, the PM ET immediately prior to the actual ET may cause detrimental uterine contractions, known to cause a hostile implantation environment and decreased rates of implantation [12]. Multiple experts have advocated the AL technique to be superior and the optimal ET method, but no study has directly compared the AL ET technique to the immediate PM ET, or established AL ET as the superior technique. Enhancing the ET process may maximize the probability of pregnancy after transfer. In order to compare AL and immediate PM techniques, we designed a retrospective cohort study to evaluate which technique results in a higher Ongoing Pregnancy Rate (OPR) after ET. Our study hypothesized that the AL ET technique would result in a higher ongoing OPR than immediate PM ET.

## Methods

This study was approved by Tripler Army Medical Center and complied with applicable regulations regarding human subjects' research.

A retrospective cohort study was designed comparing ART cycles in patients who underwent ET *via* the AL ET technique and those using the PM ET technique. The primary objective was to compare the OPR, defined as the presence of fetal cardiac activity on a first trimester ultrasound, between the two transfer types. We elected to use OPR due to our transient patient population, preventing timely and accurate collection of Live Birth Rate (LBR) data. All infertile female patients between the ages of 18 and 49 at the time of ET, who underwent ET using either AL or PM transfer techniques at Tripler Army Medical Center (TAMC) between July 01st, 2013 and September 01st, 2016 as recorded in the TAMC IVF secure database were included. At the time of data collection there were two fellowships trained reproductive endocrinology physicians performing embryo transfers. Both physicians completed more than 100 transfers in their careers when data collection began. Choice of transfer was dependent on clinical circumstances, catheter availability and ultimately was guided by physician preference. Cycles were excluded if patients underwent ET by any technique other than AL or PM, and those who were younger than 18 or older than 43 years of age. Our primary outcome of interest was OPR for each ET technique. Secondary outcomes of interest included the impact of different transfer techniques and the following demographics: Patient age, type of embryo (fresh *vs.* cryopreserved), number of embryos transferred, number of embryos cryopreserved, and transfer difficulty.

### Statistical analysis

Prior to the study it was determined that a sample size of 50 women in each ET group with an alpha equaling 0.05 would allow 80% power to detect a clinically meaningful 28% difference between OPR as determined by a post hoc power analysis.

Chi-square tests and Fisher's exact tests were used to compare demographics and pregnancy-related factors between ET technique groups and to assess unadjusted associations between categorical variables and ongoing pregnancy. Multivariable logistic regression was used to evaluate differences in OPR between the two types of ET techniques, adjusting for potential risk factors such as age, day of transfer, and number of embryos transferred. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

## Results

A total of 317 records were evaluated and assessed for eligibility with 250 meeting inclusion criteria. Of the records having had an embryo transfer, 21% were excluded from analysis secondary to missing necessary data. The mean age of patients was 34.4 (SD 4.6 years), with 18% of participants being 20 to 29 years of age (n=46), 66% of participants being 30 to 39 years of age (n=166), and 16% of participants being 40 to 49 years of age (n=39). In terms of transfer technique, 53% of patients underwent AL (n=133) and 47% underwent PM (n=118). A total of 64% of transferred cycles were of fresh embryos (n=160), while 36% were frozen (n=90). Table 1 shows the clinical comparison between the embryo technique groups.

In regards to the primary outcome, there was no significant difference in OPR between patients that underwent AL transfers and PM transfers (AL 51%, PM 57%; P=0.378). OPR was superior for AL transfers when frozen embryos were used compared with PM transfers (AL 68%, PM 31%; P=0.005). On the other hand, OPR was superior with the PM technique for fresh embryo transfers (AL 43%, PM 63%; P=0.002; Figure 1). OPR decreased with increasing age in the AL cohort, but not in the PM cohort (P=0.004). Table 2 shows the adjusted and unadjusted odds ratio comparing PM *vs.* ET, as well as the type of embryo used (fresh *vs.* frozen). When adjusting for age, day of transfer, and number of embryos transferred there was no significant difference in OPR between the AL and PM technique (OR=1.12, P=0.667). When the ET technique was compared to the embryo type, OPR for frozen embryo transfers was superior for AL transfers compared to PM transfers (OR 2.68, P=0.005). OPR was superior with the PM technique for fresh embryo transfers (OR 5.21,

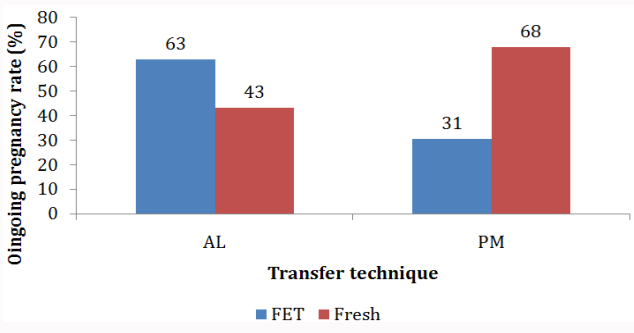


**Figure 1:** Ongoing pregnancy rate by transfer technique and type of embryo.

**Table 1:** Demographic comparison of patients in the AL and PM groups. The groups were similar (p>0.05) with respect to age, transfer type, day of embryo transfer and factors associated with difficult embryo transfer.

| | AL Group (n) | PM Group (n) | *P* |
|---|---|---|---|
| **Age (y)** | | | |
| 20 to 29 | 19 | 27 | 0.007 |
| 30 to 39 | 85 | 81 | |
| 40 to 49 | 29 | 10 | |
| **Transfer type** | | | |
| FET | 54 | 36 | 0.115 |
| Fresh | 79 | 81 | |
| **Day of transfer** | | | |
| 2 | 4 | 5 | 0.866 |
| 3 | 16 | 14 | |
| 5 | 113 | 98 | |
| **Number transferred** | | | |
| 1 | 25 | 15 | 0.298 |
| 2 | 90 | 90 | |
| 5-Mar | 18 | 13 | |
| **Blood in catheter** | | | |
| No | 125 | 116 | 0.307 |
| Yes | 5 | 1 | |
| Outside | 3 | 1 | |
| **Mucous in catheter** | | | |
| No | 130 | 114 | 0.307 |
| Yes | 3 | 2 | |
| Outside | 0 | 2 | |

**Table 2:** Unadjusted and Adjusted Odds Ratios comparing all embryo transfers and fresh and frozen embryo transfers. In all transfers comparison of the transfer techniques demonstrated equivalency (p<0.05).

| | Unadjusted OR (95% CI) | Adjusted OR (95% CI)* | *P* |
|---|---|---|---|
| All | 1.26 (0.76 to 2.07) | 1.12 (0.66 to 1.90) | 0.667 |
| Fresh embryo | 2.80 (1.47 to 5.34) | 2.68 (1.34 to 5.34) | 0.005 |
| frozen embyo | 0.26 (0.11 to 0.64) | 0.20 (0.08 to 0.55) | 0.002 |

*adjusted for age, day, and number transferred

P<0.001).

## Discussion

While an array of factors may impact the pregnancy success rate in Assisted Reproductive Technology (ART) cycles, the embryo transfer is likely the most crucial step. Embryo transfer is also the final step in a grueling and emotionally taxing process for couples trying to conceive in ART cycles. Small variations in the embryo transfer technique may make a significant difference in the OPR. Two embryo transfer techniques were compared in this retrospective study, the immediate post-mock technique, and the afterload technique [7]. The AL technique was first described by Neithardt et al. [7] in 2005, in an attempt to overcome the shortcomings of the PM technique, which include uterine trauma by passing two catheters, and the increased risk of uterine contractions [7]. They compared the AL technique to the direct transfer technique, and found it to be superior, but they did not compare it directly to the immediate PM technique.

The advantages of a PM transfer is that it allows for proper entry into the uterine cavity without putting the embryo at risk, as well as measurement of the uterine cavity and the correct position for transfer, usually with the aid of ultrasound guidance [8]. By passing two catheters there is more uterine manipulation which may lead to uterine contractions as demonstrated by various studies, and these have detrimental effects [10,11]. Furthermore, these contractions can last up to 45 min [12].

Only one catheter is passed in the AL technique, minimizing uterine trauma and also potentially decreasing the uterine contractility. There is also a benefit of decreased mucous and blood contamination in the catheter since the second catheter is threaded through the lumen of the first catheter, thus minimizing contact with the endocervical canal. Contamination with mucous and blood in the catheter has been suggested to affect the transfer rate [13-15].

Our study is the first to compare the immediate PM and AL embryo transverse technique. We also analyzed secondary outcomes which compared these techniques using fresh *vs.* frozen embryos. We hypothesized that the AL ET technique would be superior to the immediate PM technique. Our study did not show a statistically significant difference in the OPR between the two ET techniques. Interestingly, when sub-analyses were performed taking into consideration the type of embryo used; there was a statistically significant difference between the ET techniques. When frozen embryos were utilized, the AL technique was superior and had a higher OPR, and inversely when fresh embryos were utilized the immediate PM technique was superior.

Limitation to our study is a small sample size, as well as the retrospective nature of our study. Even though the results were adjusted for potential cofounders, there may have been confounders not adjusted which may have impacted the results.

Our study demonstrated no difference in ongoing pregnancy rate when using the AL or PM transfer technique. Prospective studies are needed to further evaluate the differences, if any, between the embryos transfer techniques.

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