

Correlation of technical difficulty during embryo transfer with rate of clinical pregnancy

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ABSTRACT

AIM: To correlate the ease or difficulty of embryo transfer and blood at catheter tip with pregnancy rate when embryo transfer (ET) was performed by the same operator using soft catheter. **MATERIALS AND METHODS:** A retrospective analysis of 342 patients who underwent *in vitro* fertilization or ICSI cycle from January 2008 to December 2010 in a single centre was done. The type of transfer was divided into two groups: 'easy' or 'difficult'. Transfer was considered difficult when additional instrumentation was required or firmer catheter was used or required changing of catheter. Patients undergoing cryo-preserved ET were excluded from the study. **RESULTS:** On the day of transfer in 284 (83%) patients, ET was easy and difficulty was encountered in 58 (17%) patients. Blood at catheter was seen in 101 (29.53%) patients. In the group of 58 difficult transfers, 10 pregnancies resulted with a clinical pregnancy rate of 17.2%, while 67 pregnancies resulted in 284 cycles of easy transfer with clinical pregnancy rate of 23.6% (P value = 0.045). While no significant difference was seen in pregnancies with blood on outer catheter and blood less transfer, there was significant reduction in pregnancy rate when blood was present on catheter tip compared to bloodless transfer (13.3% v/s 24.1; P value = 0.032). **CONCLUSION:** Reduction in clinical pregnancy rate is seen with difficult ETs, more when blood is present at the catheter tip.

KEY WORDS: Clinical pregnancy rate, difficult embryo transfer, embryo transfer, *in vitro* fertilization, mock transfer

INTRODUCTION

Embryo transfer (ET) is the final and critical step in the long pathway of *in vitro* fertilization (IVF) treatment. Despite recent advances in IVF, many controversies surround the procedure of ET.^[1]

Type of catheter used, ultrasound guidance versus clinical touch, trial transfer, easy or difficult transfer all have been variously studied to determine affect on pregnancy rate. Although implantation failure might be due to poor embryo quality or suboptimal endometrial quality, the ET technique is an important determinant.

Traditionally it has been thought that with increased manipulation required in ET, chances of pregnancy reduce. Also, 'blood at catheter tip' as a marker of difficult ET has been thought to be associated with reduced pregnancy rates. It has been said that with

use of vulsellum there is release of oxytocin, which stimulates uterine contractions.^[2-9] But in a few studies no correlation of difficult transfer has been seen with clinical pregnancy rate.^[10,11]

In this study, we aim to correlate the ease or difficulty of ET and blood at catheter tip with pregnancy rate when ET was performed by the same operator using soft catheter.

MATERIALS AND METHODS

A retrospective analysis of all patients who underwent IVF or ICSI cycle from January 2008 to December 2010 in a single center was done. The type of transfer was divided into two groups: 'easy' or 'difficult'. Transfer was considered difficult when additional instrumentation was required or firmer catheter was used or required changing of catheter. Patients undergoing cryo-preserved ET were excluded from the study.

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Stimulation protocol

Two main protocols were used for controlled ovarian hyper stimulation: the long agonist protocol and short antagonist protocol. In the long agonist protocol, pituitary desensitization with daily Subcutaneous (SC) administration of 1 mg leuprolide acetate (Lupride 4, Sun Pharmaceuticals, Gujarat, India) began in the mid-luteal phase of the previous menstrual cycle. This dose was continued until ovarian quiescence was confirmed by ultrasound examination in next menstruation, and estradiol values of less than 50 pg/ml and luteinizing hormone (LH), less than 2 mIU/ml. After which the dose of leupride was halved and stimulation with recombinant follicle stimulating hormone (FSH) (Gonal F, Merck Serono, Germany) was started until the day of human chorionic gonadotropin injection. In the short antagonist protocol, patients were scanned on second day of period to confirm quiescence and no ovarian cysts. Ovarian stimulation was initiated on second day of menstrual flow with recombinant FSH. A daily dose of 0.25 mg of GnRH antagonist (Cetrotide; Serono Laboratories, Germany) administration was initiated on day 6 of stimulation. Dosage of recombinant FSH was decided based on patient's age, antral follicle count, basal hormonal levels and response to previous stimulation. Dosages were adjusted according to response seen on vaginal ultrasound examination. Human chorionic gonadotropin (Ovitrelle; Serono Laboratories, Germany) was administered SC when at least two leading follicles reached a mean diameter R18 mms. Trans-vaginal oocyte retrieval was scheduled 36 hours later. Injectable progesterone 100 mg is started from the next day of pick up and continued till the day of pregnancy test. Embryo transfer (EET) was performed 2 to 3 or 5 to 6 days after oocyte retrieval via the vaginal route.

Technique of ET

A mock ET was done in all patients before recruiting patient for IVF cycle. During mock transfer, ease of transfer, need for instrumentation, direction of uterine cavity whether anteverted or retroverted was noted. On the day of ET, patient was asked to come with full bladder. Cooks soft catheter was used for ET in all patients and all transfers were done by single personnel with patient in lithotomy position. No anesthesia was used for the procedure. Under sterile condition, vaginal parts were cleaned with saline and draped and cusco speculum inserted to expose cervix. Cervical mucus was aspirated and cervix cleaned with sterile media. Cooks catheter was used for ET in all patients and all transfers were done by single personnel with patient in lithotomy position. The embryos were deposited in region of mid-portion of uterine cavity under ultrasound guidance [Figure 1]. In all cases, the catheter was left *in situ* for 30–60 seconds and then withdrawn gently avoiding negative pressure. It was then checked under a dissecting microscope for retained embryos. If these were found, they

were reloaded and transferred again (repeat transfer). The patients were asked to remain in bed for 15–30 min. ET was considered difficult when additional instrumentation was required or firmer catheter was used or required changing of catheter. Intramuscular micronized progesterone was continued for 15 days and b-hcg was done after 2 weeks.

Data analysis

SPSS version 10 (SPSS Inc., Chicago, IL) was used for data analysis. $P < 0.05$ was considered statistically significant. The chi-square test, the Fisher's exact test, and the chi-square test for independence for more than two groups were used to compare qualitative variables, and the Student's t-test to compare quantitative variables, as appropriate.

RESULTS

Three hundred and forty two IVF cycles or ICSI from our IVF database were studied. The mean age of the patient was 31.6 ± 3.98 years (range 24-45 years). In the pre-stimulation mock ET done in all patients, ET was easy in 268 patients and in 74 patients ET was difficult. For cases in which mock transfer was difficult due to cervical stenosis, dilation of the cervix was done before starting down-regulation or in the previous cycle. On the day of transfer, ET was easy in 284 (83%) patients and difficulty was encountered in 58 (17%) patients. The reduced incidence of difficult transfer at actual ET might be due to prior cervical dilation and also because of uterus becoming ante-verted as heavy stimulated ovaries sunk in the Pouch of douglas (POD). Blood at catheter was seen in 101 (29.53%) patients. An overall total of 77 pregnancies resulted with a clinical pregnancy rate of 22.51% in 342 cycles. A total of 950 embryos were transferred with a mean of 2.7 embryos transferred in each cycle.

Table 1 shows the cycle characteristics in group of difficult and easy transfer while Table 2 shows the differences between bloodless transfer and blood at catheter tip. In the



Figure 1: Embryo transfer catheter in the mid-portion of uterine cavity

group of 58 difficult transfers, 10 pregnancies resulted with a clinical pregnancy rate of 17.2%, while 67 pregnancies resulted in 284 cycles with clinical pregnancy rate of 23.6%. This difference did reach statistical significance (P value = 0.045). The difficulties encountered were difficulty in negotiation of cervix, use of volsellum or required changing of catheter.

Blood on catheter was seen in 101 (29.53%) patients. Out of these 101 patients, in 71 patients blood was seen on catheter wall while it was seen on catheter tip in 30 patients. A total of 19 pregnancies occurred (Clinical pregnancy rate (CPR) = 18.81%) in this sub-group with 15 pregnancies seen in patients with blood on catheter wall (CPR 21.12%) and 4 pregnancies in patients with blood on catheter tip (CPR = 13.33%). In patients with blood less transfer, 58 pregnancies occurred with clinical pregnancy rate of 24.1%. While no significant difference was seen in pregnancies with blood on outer catheter and blood less transfer, there was significant reduction in pregnancy rate when blood was present on catheter tip compared to bloodless transfer (13.3% vs 24.1; P value = 0.032)

DISCUSSION

An ET is considered successful when embryos are delivered a-traumatically to the site of maximal implantation in the uterus. It has generally been considered that chances of pregnancy are reduced if extra manipulation is required during ET. There have been reports both supporting as well as confounding this fact. In this study, we aimed to find whether difficult ET and blood at catheter tip are associated with reduced pregnancy rates.

We found that chances of pregnancy are reduced in a case of difficult transfer or when blood is present at catheter tip.

Table 1: Shows cycle characteristics between two groups of easy and difficult transfer

	Easy transfer (n = 284)	Difficult Transfer (n = 58)	P value
Age	31.56 ± 4.2	32.3 ± 3.8	NS
No. of oocytes retrieved	11.2 ± 5.6	11.6 ± 6.2	NS
No. of grade I embryos	6.4 ± 2.3	5.9 ± 2.9	NS
No. of embryos transferred	2.7 ± 0.5	2.7 ± 0.5	NS
Clinical pregnancy rate	23.6	17.2	0.045

Table 2: Characteristics of cycle between bloodless transfers and transfers with blood at outer catheter or catheter tip

	Bloodless transfer (n = 241)	Blood on outer catheter (n = 71)	Blood on catheter tip (n = 30)	P value
Age	31.29 ± 3.9	31.6 ± 4.12	31.8 ± 4.3	NS
No. of oocytes retrieved	11.6 ± 6.8	10.5 ± 6.9	11.9 ± 5.8	NS
No. of grade I embryos	5.4 ± 3.6	6.2 ± 3.4	5.8 ± 2.9	NS
No. of embryos transferred	2.7 ± 0.5	2.7 ± 0.5	2.7 ± 0.5	NS
Clinical pregnancy rate	24.1	21.2	13.3	0.032

This finding is similar to study by Sallam *et al.*^[12] in which blood at catheter tip was associated with reduced pregnancy rates. However, no difference was seen when transfer was difficult or extra manipulation like use of volsellum or cervical dilation was required.

In a large retrospective study by Tomas *et al.*^[13] in which a total of 4807 ET were studied, easy or intermediate transfers were associated with 1.7 fold increased pregnancy rate then difficult transfers (P value < 0.0001). Increased manipulation or touching of the fundus during difficult transfers might stimulate uterine contraction reducing CPR.

The role of mock transfers in reducing difficult ETs has been controversial. Mock Transfer can be done at the time of start of ovarian stimulation or at oocytes retrieval or at the time of actual transfer. In the initial studies by Mansour *et al.*,^[14] trial transfers have been shown to reduce the incidence of difficult transfers. However in a study by Henne *et al.*,^[15] it has been shown that uterine length and position changes with ovarian stimulation challenging the role of trial transfer. In the present study, mock transfers were done in all patients before ovarian stimulation.

The success of ET also depends on the operator as seen in the study by Hearn-Stokes *et al.*^[16] in which clinical pregnancy rate varied significantly with the clinician performing the embryo transfer. In the present study all embryo transfers were done by a single clinician, hence eliminating this confounding factor.

The next most important factor considered is the role of ultrasound guidance.^[17] Ultrasound guidance helps in depositing embryos a-traumatically to the mid-portion of the uterus without touching the fundus. A meta-analysis of 17 Randomized controlled trials (RCT) studies conducted by Cochrane^[18] comparing ultrasound vs. clinical touch showed increased pregnancy rate with ultrasound guidance. In the present study, all ETs were done under ultrasound guidance.

To conclude, all efforts should be made to reduce difficult transfers. Difficult transfer and blood at catheter tip are associated with reduced CPR. In case of difficulty encountered during transfer a stepwise approach with minimal endometrial trauma should be used. There are no conflicts of interest.

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