

Pregnancy Rates of Embryo Transfer: Measuring the Uterus Length with Transvaginal Ultrasound in Art Freeze Cycles Compared with the Conventional Experimental Method

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Abstract

Background: This study is conducted to compare the pregnancy rate among patients with embryo transfer using the conventional experimental method with those using measurement of uterine length with transvaginal ultrasound before transfer in freeze ART cycles.

Methods: In this cohort study, all participants were subjected to the cycle of ovulation stimulation according to the antagonist protocol; consequently, after oocyte recovery, the embryos were frozen following the next cycles. If they were ready, they were subjected to the cycle of endometrial preparation with estradiol protocol. In case of having one to three embryos of good quality (based on the patients' selection), they were placed in two groups of embryo transfer using the conventional method (clinical touch) or embryo transfer after measuring the length of the uterus with transvaginal ultrasound. Then, all patients were treated with vaginal progesterone and oral estradiol; two weeks later, a pregnancy test was performed, and if it was positive, they were followed up for ultrasound and pregnancy outcomes. Statistical analysis was performed using Student's t-test and Chi-square or Fisher's exact test in SPSS 16 software. A significance level of less than 0.05 was considered.

Results: There are no statistically significant differences between the two groups in variables such as the type of stimulation, the type of gonadotropin, the number of retrieved eggs, the number of transferred embryos, the thickness of the endometrium, the length of the uterus, and easy or difficult transfer. Although the pregnancy rate was higher in the group of ET with measuring the length of the uterus (38.5% versus 34.0%), this difference was not statistically significant ($p=0.681$).

Conclusion: The use of the embryo transfer method using transfer guidelines which were guided by transvaginal ultrasound and determining the location of the embryo deposition by experienced doctors does not increase the fertility rate in ART cycles compared to using the traditional and blind method in Iran. At the same time, it is necessary to examine other advantages of using this method.

Key Words: ART freeze cycles, Conventional experimental method, Embryo transfer, Length of the uterus, Pregnancy, Transvaginal ultrasound.

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1- INTRODUCTION

Infertility is a reproductive disorder defined as failure to achieve a clinical pregnancy after, at least, 12 months of regular unprotected intercourse (1). One of the major scientific advances in the management of infertile couples is the progression of Assisted Reproductive Techniques (ART) especially In Vitro Fertilization (IVF) (2, 3). Embryo Transfer (ET) is the last and most important step in ART cycles (4-6) which is considered one of the most inefficient steps in IVF (7).

Factors affecting the success of embryo transfer include the age of the woman, the medical history of the patient, the quality of the embryo, endometrial receptivity, uterine contractions, use of tenaculum, the degree of difficulty of embryo transfer, the volume of the transfer medium, the depth of uterine transfer and the method of embryo transfer (4, 8-10). Evidence shows that the method of ET and the skill of the doctors performing the embryo transfer can affect the implantation rate (7, 11). ET is usually performed in one of these three approaches: Traditional method and blind transfer (with or without clinical touch) (12), ultrasound-guided ET (13), and ET based on previously measured uterine length (14, 15).

Due to the blind nature and reliance solely on clinical 'feel' for the location of the embryo catheter tip at the time of embryo placement, traditional ET has been suggested as a major cause of failure in assisted reproductive cycles (2, 8). Some studies have stated that determining the place of implantation of the embryo and the length of the uterus in advance may reduce the rate of ectopic pregnancies (7). Transvaginal ultrasound-guided ET has also been reported to be attributed to successful IVF cycles with increased implantation rates in patients who had previously failed to conceive during clinical touch embryo transfer (2). Using measurement of uterine length during the

treatment cycle in order to place the fetus at a depth of 1-1.5 cm in the fundus, while increasing the clinical pregnancy and implantation rate, also reduces the miscarriage rate (5).

However, the results of other studies revealed that in patients who undergo ET by an experienced operator, ultrasound guidance does not increase the overall clinical pregnancy rate and the embryo implantation rate (6, 7).

Therefore, according to the challenges regarding the effectiveness of ultrasound guidance in the pregnancy rate in the IVF treatment cycle, as well as the use of blind ET technique in many IVF centers in Iran, this study aims to compare the results of the conventional ET method (blind) with the ET that was performed based on the prior measurement of uterine length using vaginal ultrasound.

2- METHODS AND MATERIALS

2-1. Design and I population

This prospective cohort study included patients who completed either IVF cycle using one of the conventional experimental methods or with ET based on measuring the length of the uterus with transvaginal ultrasound before transfer in freeze cycles in the IVF unit of Shariati Hospital, Tehran, Iran from 2018 to 2019.

2-2. Participants

Patients were included in the study with the aim of comparing the results of ET using the conventional experimental method with ET based on patient selection. 100 patients were included in the study; 52 people in the ET group based on measuring the length of the uterus with transvaginal ultrasound before transfer in freeze cycles, 48 participants in the transfer group using conventional and traditional methods.

2-2-1. Inclusion and exclusion criteria

The patients could be included in the study, in case,

- Their age was between 18 and 45 years,
- GnRH antagonist protocol was used during ovarian stimulation,
- A hormone replacement protocol was used in preparation for the FET cycle, and
- There was at least one high-quality frozen embryo, and planned transfer of 1-3 high-quality embryos in this cycle.

Exclusion criteria included:

- Patients with abnormal liver and kidney function, abnormal thyroid function, immune disorders, or blood disorders.
- Patients with repeated implantation failure
- Patients with mixed fibroids, endometrial polyps, endometriosis or uterine abnormalities
- Patients with hysteroscopy examination of uterine adhesions or endometrial lesions
- Patients with body mass index ≥ 30 kg/m²
- Chromosomal abnormalities in couples
- Presence of an abnormal uterine cavity due to endometrial polyps, subcutaneous or intrauterine myomas that distort the uterine cavity, Müllerian anomalies
- Presence of any systemic disease that potentially reduces the rate of implantation (such as autoimmune diseases)
- Ovarian stimulation (COH) with any protocol other than the GnRH antagonist protocol
- The presence of endometrial thickness ≤ 6 mm at the time of ET
- Patients who needed to change the catheter and use a more rigid catheter for cervical stenosis
- Difficult transfer

2-3. Procedure

All eligible patients underwent ovulation stimulation cycle according to the antagonist protocol and after oocyte recovery, the embryos were frozen. In the next cycles, if they were ready, the endometrial preparation cycle was done with estradiol protocol. Consequently, if there were one to three embryos with good quality, based on the patient's option, they were placed in one of the ET groups, in the conventional way (clinical touch) or transferred after measuring the length of the uterus. The fetuses were placed, and then all patients were treated with vaginal progesterone and oral estradiol. Two weeks later, a pregnancy test was performed, and if positive, they were followed up for pregnancy results and ultrasound.

2-4. Embryo transfer

All women were placed in a lithotomy position (with an empty bladder) and a sterile metal speculum was inserted to expose the cervix. The cervical mucus was cleaned using sterile gauze. Cook catheter (COOK Medical, USA) was used in all cases. First, the external catheter and then the internal catheter which were loaded with embryos were placed. In the traditional transfer method (clinical touch), the embryos were placed blindly in the middle part of the uterine cavity, approximately 5-6 cm away from the external canal based on the doctor's experience.

In the other method, embryo transfer after measuring the length of the uterus by transvaginal ultrasound, the embryos were placed at a distance of 1-1.5 cm from the uterine fundus based on the previously measured uterine length (without touching the fundus and without using ultrasound during the procedure).

Consequently, the catheter and speculum removed gently, and all women rested for one hour. The severity of ET was

determined by the physician. It is considered 'easy' when the catheter passes easily through the cervical canal, whereas any resistance to catheter placement, need for a tenaculum, or time-to-future manipulations is indicated as 'difficult ET' (excluded from the study). To support the luteal phase, all patients received vaginal suppository Cyclogest (400 mg BID) (Actover, Alpharma, UK), ampoules of progesterone (50 mg daily), and estradiol tablets (with the same preparation amounts).

2-5. Measurement of uterine length by transvaginal ultrasound

TVS measurement was performed by the same infertility specialist using the same ultrasound device (Mindray, America). Uterine depth was measured by adding several smaller measurements extending from the upper end of the endometrial cavity to the external opening of the cervix.

2-6. Outcome measurement and Data collection

Fourteen days after oocyte retrieval, beta-HCG (β -hCG) levels were measured to determine pregnancy status. Ultrasound was performed if the β -hCG was positive.

The data was collected through a researcher-made questionnaire. This questionnaire included demographic information of the patients including age, duration of infertility, as well as Anti Mullerian Hormone (AMH), Follicle-Stimulating Hormone (FSH) Levels, Endometrial Thickness (ET), uterine length and height, number of embryos transferred / type of embryo transfer method (traditional or transvaginal ultrasound measurement), BHCG level (two weeks after embryo transfer), and number of transfer (first or second).

2-7. Data analysis

Continuous variables were described with mean and standard deviation; and

categorical variables were described as numbers with percentages. Statistical analyses were performed using Student's t-test and Chi-square or Fisher's exact test, by the use of SPSS 16 software.

3- RESULTS

A total of 100 frozen ETs were performed. The conventional blind method was performed on 48 cases and the previously measured method using vaginal ultrasound was performed on 52 cases.

Mean age in ET with measuring the length of the uterus group was 31.29 ± 4.86 and in ET with clinical touch group was 31.10 ± 4.81 ; and mean BMI was 25.58 ± 3.89 and 26.40 ± 3.67 , respectively. Details of demographic information and basic clinical information of patients are presented in **Table 1**. There were no statistically significant differences between the two groups in variables such as the type of stimulation, the type of gonadotropin used, the number of retrieved eggs, the number of transferred embryos, the thickness of the endometrium, the length of the uterus, and easy or difficult transfer.

According to the results, although the pregnancy rate was higher in the ET with measuring the length of the uterus group (38.5% versus 34.0%), this difference was not statistically significant ($p=0.648$) (**Table 2**).

4- DISCUSSION

In this study, the overall pregnancy rate in embryo transfer using conventional experimental methods was compared with embryo transfer based on uterine length measurement with transvaginal ultrasound before transfer in freeze cycles. The results of the study did not reveal a significant difference in the overall rate of pregnancy, clinical pregnancy or embryo implantation between the two methods of transvaginal ultrasound guidance and blind embryo transfer.

Table-1: Comparing the demographic information and clinical characteristics between the groups

Variable	ET with measuring the length of the uterus group (No=52)	ET with clinical touch group (No= 48)	P-Value*
Age (mean \pm SD)	31.29 \pm 4.86	31.10 \pm 4.81	0.840
BMI (kg/m ²)	25.58 \pm 3.89	26.40 \pm 3.67	0.281
AMH (ng/ml)	5.15 \pm 4.78	4.35 \pm 4.17	0.380
FSH (mIU/ml)	5.15 \pm 2.25	5.95 \pm 2.17	0.074
years of infertility	5.13 \pm 3.04	5.07 \pm 2.62	0.914
No. of oocytes	4.35 \pm 4.17	5.15 \pm 4.78	0.380
Transfers number	1.44 \pm 0.65	1.48 \pm 0.67	0.043
No. of embryos	2.13 \pm 0.64	2.37 \pm 0.63	0.240
Endometrial thickness	9.88 \pm 1.14	10.22 \pm 1.27	0.168
Uterine length	43.15 \pm 10.60	45.45 \pm 4.17	0.422
Uterine height	14.69 \pm 4.80	15.48 \pm 4.17	0.207

* Independent Samples Test

Table-2: Comparing pregnancy results between the groups

Variable	ET with measuring the length of the uterus group (No=52)	ET with clinical touch group (No= 48)	p-value*
β -HCG positive	20 (38.5%)	16 (33.3%)	0.594
β -HCG negative	32 (61.5%)	32 (66.7%)	

* Chi-Square Tests

However, many studies have reported an increase in the rate of implantation and pregnancy in the presence of ultrasound and by determining the point of implantation of the fetus based on the length of the uterus (2, 3, 5, 14, 15).

Therefore, this result challenges the possibility of increasing the pregnancy rate in the ultrasound-guided embryo transfer method compared to the experimental and blind transfer method for experienced doctors. Because in this center embryo transfer was performed by a gynecologist and an experienced sonographer, and the place of embryo deposition was determined in advance, the bias caused by the difference in the operator's skill was controlled.

Nonetheless, the results of the present study are consistent with the results of two randomized clinical trials conducted by

Tang et al. (2001) (13) and Kosmas et al. (2007) (6). In these studies, no significant difference was observed between the overall pregnancy rate in the traditional embryo transfer method and the ultrasound-guided embryo transfer. In addition, the optimal depth of embryo implantation is suggested to be 10 to 20 mm from the fundus (16-18).

In our study, the average number of transferred embryos in the ET with measuring the length of the uterus and ET with clinical touch groups was 1.44 and 1.48, respectively; and no significant difference was observed between the groups. Considering that one of the effective factors in increasing pregnancy in ART cycles is the number of deposited embryos, the high number of embryos in some studies may cause overestimation in the results (7).

Moreover, some studies have claimed that bladder fullness, by straightening the uterine angle in line with the vagina, may facilitate the transfer of the embryo through the cervix after IVF and increase the overall pregnancy rate (19). While other studies have stated that embryo transfer with a full bladder makes embryo transfer difficult. Therefore, in this study, embryo transfer was performed with an empty bladder (5, 20, 21). Furthermore, a meta-analysis by Cozzolino et al. (2018) demonstrated that the quality of evidence supporting the transvaginal versus transabdominal approach in clinical pregnancy and live birth or ongoing pregnancy rates is low (22).

In general, considering that the aim of this study was to evaluate the advantage of using the embryo transfer method through transvaginal ultrasound and determine the point of implantation of the embryo in advance, it should be stated that despite using this method was seemingly more effective than the traditional method, the difference was not statistically significant in an experienced medical team. However the advantages of using this method in embryo transfer cannot be ignored. One of the most important advantages of using this method is its benefits in clinical training. Among its other merits, we can point out the diagnosis of intrauterine pathology and decision-making in the field of cancellation of ET, embryo freezing, or keeping on treatment (6).

In addition, most of the cases of embryo transfer in Iran have been performed in the traditional way and the use of 3D/4D ultrasound devices is limited mainly due to high costs they impose on the patients. In general, the transvaginal ultrasound method improves doctors' concentration, and so can be an appropriate method, especially for new centers and less experienced doctors.

Eventually, it is suggested that further randomized clinical trials should be

conducted to evaluate the true effects of this method on increasing the fertility rate using the transfer method guided by vaginal ultrasound in freezing cycles and to investigate the consequences of ART including ectopic pregnancy, continued pregnancy and abortion in Iran.

5- CONCLUSION

Applying the embryo transfer method using transfer guidelines by transvaginal ultrasound guidance and determining the location of the embryo deposition by experienced doctors does not increase the fertility rate in ART cycles compared to using the traditional and blind method in Iran. Furthermore, it is necessary to examine other advantages of using this method.

6- ETHICAL CONSIDERATIONS

This study has been approved by the Ethics Committee of Birjand University of Medical Sciences with code of IR.BUMS.REC.1399.354. Written consent was obtained from all patients to participate in the study.

7- CONFLICT OF INTEREST

None.

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