ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Effect of air bubbles localization and migration after embryo transfer on assisted reproductive technology outcome

Cem Fıçıcıoğlu, M.D., Ph.D.,[a] Pınar Özcan, M.D.,[b] Melis G. Koçer, M.D.,[a] Mert Yeşiladalı, M.D.,[a] Oya Alagöz, M.D.,[c] Gülçin Özkara, M.D.,[c] Ahter T. Tayyar, M.D.,[e] and Çiğdem Altunok, M.D.[d]

[a] Department of Obstetrics and Gynecology, [c] Department of Embryology, and [d] Department of Medical Informatics, Faculty of Medicine, Yeditepe University; [b] Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Acıbadem University Faculty of Medicine; and [e] Department of Obstetrics and Gynecology, Zeynep Kamil Gynecologic and Pediatric Training and Research Hospital, İstanbul, Turkey

Objective: To evaluate the effect of embryo flash position and movement of the air bubbles at 1 and 60 minutes after ET on clinical pregnancy rates (PRs).
Design: Prospective clinical trial.
Setting: University fertility clinic.
Patient(s): A total of 230 fresh ultrasound-guided ETs performed by a single physician (C.F.) at the IVF center of Yeditepe University Hospital between September 2016 and February 2017 were included.
Intervention(s): Transabdominal ultrasonographic guidance at ET.
Main Outcome Measure(s): Clinical PRs.
Result(s): There was no significant difference in terms of clinical PRs between women with embryo flash located >15 mm and <15 mm from the fundus at 1 or 60 minutes ($P=.6$ and $P=.7$, respectively). The PRs in women with embryo flash located <15 mm and >15 mm from the fundus were 47% and 60%, respectively ($P=.6$). The clinical intrauterine PRs were 69.5%, 38.5%, and 19.1% in fundal, static, and cervical, respectively. The highest PR was in fundal when compared with others ($P<.01$). The clinical PR appears to be associated with the embryo flash movement/migration and the PR was dramatically reduced when the embryo migrated from its original position toward the cervix at 60 minutes.
Conclusion(s): We concluded that clinical PR appears to be associated with the embryo flash movement/migration at 60 minutes after ET and embryo flash movement toward the fundus is associated with higher clinical PRs. Further well-designed randomized controlled trials are required to optimize ET technique in the future. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Embryo transfer, in vitro fertilization, air bubble, embryo flash position, assisted reproductive technology

There are many factors including female age, ovarian reserve, ET technique, embryo quality, and endometrial receptivity to influence the success of assisted reproductive technology (ART) and predictors of pregnancy outcome (1). The ET is the final and crucial step of ART. Despite high rate of success of ART with great advances in several factors, there is no consensus on the optimal ET technique. Therefore, studies recently focused on the importance of ET to achieve higher pregnancy rates (PRs).

After the introduction of ultrasound guidance for ET, publications recently moved on to assess the effect of various parameters related to ET on PR that are able to determine ART success and failure. Studies evaluated these technical parameters, such as transfer catheter type, catheter-loading technique, catheter placement, blood or mucus effects injection speed, catheter withdrawal, and ultrasonographic parameters, such as ET depth, fundal level of the uterine cavity, the

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Reprint requests: Pınar Özcan, M.D., Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Acıbadem University Faculty of Medicine, İstanbul, Fatih 34093, Turkey (E-mail: drpinarozcan@hotmail.com).

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optimal location for embryo deposition within the uterus, exact position of the catheter tip, and air bubble (2–9).

Monitoring the final position of air bubble at ET could be associated with PR. In our previous study (7), we demonstrated that the optimal position of embryos, as shown by the location of air bubbles at ET, is a distance of <10 mm from the fundal endometrial surface and placing air bubbles closer to the fundus is associated with higher PRs. But the position of the air bubble in the uterine cavity may change after ET. Therefore, after the initial assessment of the air bubbles at ET, the embryo can migrate toward the fundus or toward the cervix, or it may remain static. We then hypothesized that the change of the embryo flash position at 60 minutes after ET may have either a positive or negative influence for PR. The purpose of our current study is to evaluate the effect of embryo flash position and movement of the air bubbles at 1 and 60 minutes after ET on clinical PRs.

MATERIALS AND METHODS

Participants

A total of 230 fresh ultrasound-guided ETs, performed by a single physician (C.F.), at the IVF center of Yeditepe University Hospital between September 2016 and February 2017 were included. The prospective study protocol was approved by the Ethical Committee of the Medical Faculty of Yeditepe University. Written informed consent was obtained from all patients. Inclusion criterias were patients programmed for IVF, body mass index (BMI) $\leq$25 kg/m^2, between 18 and 41 years old, and with FSH levels on cycle day 3 of $\leq$12 mIU/mL. Exclusion criterias were patients with congenital or acquired uterine anomalies, repeated implantation failure, with blood present on the catheter during the transfer procedure, with a difficult transfer or with a suspicion of touching the fundus, presence of hydrosalpinx, and cycle cancelation.

Data collected included age, duration of infertility, type of infertility, BMI, serum FSH, E_2, and antimüllerian hormone (AMH) levels on cycle day 3, maximum E_2 levels, total number of oocytes retrieved, number of mature oocytes retrieved, number of embryos transferred, endometrial thickness on day of ET (in millimeters), and clinical PR. All ETs were classified into three groups according to the embryo flash movement/migration. It was evaluated by measuring the change of the embryo flash position at 60 minutes after ET. If it had remained within $\pm$15 mm from its original position, it was classified as static; if it had migrated <15 mm toward the fundus or >15 mm toward the cervix, it was classified as fundal and cervical, respectively (Supplemental Fig. 1, available on-line). The evaluation and management of the patients and ET are performed by one operator (C.F.).

Assisted Reproduction Procedures

A controlled ovarian stimulation protocol was used: antagonist (Cetrotide; Serono) protocol and stimulation with recombinant FSH (Gonal F; Serono) as previously described (7). A single dose of recombinant hCG (Ovitrelle, 250 mg; Serono) was administered to trigger when at least two follicles reached a mean diameter of 17 mm. Transvaginal uktrasound-guided oocyte retrieval was carried out 36 hours after recombinant hCG administration under general anesthesia. Fertilization of the oocytes was performed 4–6 hours after retrieval by using standard intracytoplasmic sperm injection (ICSI) techniques. According to maternal age, indication for IVF, and number and quality of embryos available, one or two embryos were transferred on day 5. As luteal phase support, vaginal crinone gel (Crinone 8%, 90 mg; Merck Serono, Central Pharma Ltd.) daily was started on the day of retrieval. Serum quantitative beta-hCG levels were obtained at 12 days after ET. A clinical pregnancy was defined as the presence of a fetal sac visualized by transvaginal ultrasound examination at 6–8 weeks of amenorrhea.

Embryo Selection and ET

All ETs were performed by one experienced operator (C.F.) with the Wallace catheter (Smiths Medical International Ltd.) using after-load transfer technique under transabdominal ultrasound guidance without any anesthesia or sedation. The highest quality embryos according to morphology and cleavage criteria were selected for transfer. After the women, with moderately full bladder, were placed in a lithotomy position, the cervix was exposed with a bivalve speculum. The mucus in the cervical canal was cleaned by using a sterile cotton swab soaked in culture medium. Embryos were loaded into a Wallace catheter (Smiths Medical International Ltd.) by using a "three-drop technique." First, an air bubble was loaded into the catheter. Then, 20 μL of medium was drawn up into the catheter, followed by the embryos in the smallest possible volume of medium. A second air bubble was then loaded into the catheter. Finally, enough medium was drawn up to bring the total volume to 30 μL. The outer catheter was first inserted into the cervical canal. Once the guide was positioned before or after the internal os, the inner catheter was placed through the outer catheter. The tip of the inner catheter was placed 1.5–2 cm from the fundal endometrial surface. The medium containing the embryos was gently released into the uterine cavity. The catheter was slowly withdrawn and examined by the same embryologist under a stereomicroscope to be sure that there were no retained embryos. After the procedure, the patient was kept supine for approximately 60 minutes. Ultrasonography were carried out at 1 and 60 minutes after ET. The embryo flash position at 1 and 60 minutes after ET and the embryo flash movement/migration were recorded for future analysis. The embryo flash position at 1 and 60 minutes after ET was assessed by measuring the distance between the air bubble and the uterine fundus in the coronal image. The embryo flash movement/migration was assessed by measuring the change of the embryo flash position at 60 minutes after ET. If embryo had migrated >15 mm toward the fundus, it was classified as fundal, or >15 mm toward the cervix, it was classified as cervical, and if the embryo flash had remained within $\pm$15 mm from its original position, it was classified as static (Supplemental Fig. 1). When more than one air bubble was seen, the closest one to uterine fundus was used for the measurements. We measured the distance from the lead portion of the air bubble to the uterine fundus.