Impact of Transabdominal Ultrasound Guidance on Performance and Outcome of Transcervical Uterine Embryo Transfer

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Purpose: To determine the impact of transabdominal ultrasound guidance on embryo transfer during IVF therapy.

Methods: Retrospective analysis of 823 consecutive embryo transfers. Three hundred and sixty-seven procedures performed with transabdominal ultrasound guidance were compared to 456 cases performed with the "clinical touch" method.

Results: Ultrasound-guided embryo transfer yielded higher, but not statistically significant, clinical pregnancy (48% vs. 44%) and implantation rates (22% vs. 20%). The incidence of multiple pregnancies, ectopic and multiple pregnancy rates were similar. The frequency of negative factors typically associated with difficult transfers, such as requirement of use of tenaculum, and presence of blood or mucus in the catheter tip, were significantly lower in the ultrasound-guided group in comparison with the clinical touch group. Ultrasound-guided embryo transfer was associated with a significantly increased easiness of transfer performance; 95% of the transfers were rated as very easy in the ultrasound-guidance group compared to 87% in the clinical touch group. The use of a soft pass catheter was the only variable independently and significantly associated with pregnancy success (odds ratio = 2.74).

Conclusion(s): Ultrasound-guidance facilitates embryo transfer and in combination with the use of a soft catheter should be implemented to optimize embryo transfer results.

KEY WORDS: Catheter; embryo transfer; IVF; pregnancy rate; ultrasound guidance.

INTRODUCTION

Embryo transfer is the final and most crucial step in IVF. About 80% of patients undergoing IVF reach the embryo transfer stage but only a variable proportion of them achieve a pregnancy (1). It has been estimated that poor embryo transfer technique may account for as much as 30% of all failures in assisted reproduction (2). The importance of the technique by

which the embryos are transferred to the uterine cavity is reflected in the difference in the pregnancy rates associated with different individuals performing the embryo transfer within the same program (3,4).

Strickler *et al.*, were the first to demonstrate a possible improvement in pregnancy rate with ultrasound-guided embryo transfer (5). One year later Leong *et al.*, reached the same conclusion (6). More recently, through observational trials, some authors have demonstrated benefits with ultrasound-guided embryo transfer (7,8). However, while a few prospective and randomized trials have reported an improvement in outcome with ultrasound guidance (9,10), others have not shown a significant difference (11–14).

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Other authors have demonstrated an improvement in pregnancy rate with ultrasound-guided embryo transfer but only in patients who had previously failed to conceive when embryos were transferred by the clinical touch method (15). On the other hand, Prapas *et al.*, have reported a significant higher pregnancy rate in ultrasound-guided procedures with embryos transferred 3 or 4 days after retrieval, but not for embryos transferred on day 5 (9).

In view of the controversies found in the literature and the significance of the topic, we conducted a retrospective controlled study to examine the impact of the use of transabdominal ultrasound-guidance during embryo transfer in our IVF program. The objective was to determine if there was an improvement in pregnancy and implantation rates when compared to the "clinical touch" method. Furthermore, we analyzed whether ultrasound-guided embryo transfer had an impact on the rates of transfer difficulties and complications.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at Eastern Virginia Medical School. All consecutive embryo transfer procedures performed in our program from January 1, 2000 through December 31, 2001 were analyzed. All cycles were included irrespective of the age of the woman, diagnosis of infertility, ovarian stimulation protocol used, or performance of standard IVF or ICSI (16). The clinical touch method was used for all transfers (n : 456) performed between January 2000 and December 2000, whereas ultrasound-guided embryo transfers (n : 367) were carried between January 2001 and December 2001.

All embryo transfers were performed on day 3. Patients were placed in the dorsal lithotomy position and no anesthesia was used. In all cases, the clinicians started the embryo transfer by placing a bivalve speculum in order to expose the cervix. The exocervix was cleansed of cervical mucus using a cotton swab embedded with culture medium. Concurrently in the adjacent embryology laboratory, cleavage status and the morphological appearance of the embryos was evaluated to select the best embryos before loading them into the transfer catheter. Embryo quality was estimated using the scoring system of Veeck (17).

In all cases the embryo transfer catheter was loaded in the following way: under visual guidance on the dissection microscope, the tip of the catheter was placed into the center well (away from the embryos

for transfer) and approximately 30 μ L of the culture medium were drawn up. Then without drawing up any air, the catheter tip was placed next to the embryos and the embryos were drawn up into approximately 10 μ L of medium, keeping the embryos at the very bottom of the fluid column.

A mock transfer was performed in all cases immediately prior to the embryo transfer procedure. The Cook soft pass, flexible tip catheter (Softpass Embryo Transfer Catheter, Cook Ob/Gyn, Spencer, Indiana, USA) was selected as first choice or elective catheter. If there was impossibility to use such catheter, the Cook blue styled catheter (SMS Embryo Transfer Catheter, Cook Ob/Gyn) or the Marrs catheter (Marrs Set, Cook Ob/Gyn) were used as a second or third choice, respectively. This policy allowed us to find out the best catheter to use in every case.

In the "clinical touch" method, the catheter was introduced into the cervical os and advanced into the uterus. If any resistance occurred, the outer sheath of the soft catheter was separated and advanced up to or through the internal cervical os. Once the catheter was felt to reach the upper uterine cavity (without touching the fundus) it was retracted about 0.5–1 cm and the embryos were gently expelled followed by gentle withdrawal of the catheter.

For ultrasound-guided transfers, the uterus and endometrial cavity were visualized in a sagittal plane through a full bladder window using the convex probe (3.5 MHz) of a real time ultrasound (Hitachi EUB-405, Tokyo, Japan). Efforts were made to visualize the catheter as it traversed the cervix. The catheter was then threaded through the internal cervix os under direct visualization. Then the catheter was advanced under real-time ultrasound guidance to a point approaching but not touching the fundus (0.5–1 cm). We arbitrarily selected this position, as our goal was to avoid touching the fundus since it was previously demonstrated that touching the fundus reduced the chances of pregnancy (18). Then the embryos were gently expelled and the droplet visualized moving through the catheter and being deposited in the uterine fundus. Gentle removal of the catheter was also followed via ultrasound. In both groups, the catheter was then checked under the microscope for retained embryos, and/or presence of mucus or blood.

The clinician was required to rate the embryo transfer in terms of ease of transfer before he/she left the embryo transfer room. The rating system guidelines were very easy: transfer catheter was introduced without any difficulty through the cervix;

easy: transfer required some manipulation including either the separation of the transfer catheter to advance the more rigid sheath and/or the use of a tenaculum to straighten the cervical canal; and difficult: use of second or third choice catheter and/or requirement for cervical dilatation using a rigid instrument.

The primary outcome measures were clinical pregnancy rate and implantation rate. Clinical pregnancy was defined as the presence of a gestational sac by ultrasound at 6–7 weeks. Implantation rate was defined as the total number of gestational sacs in relation to the total number of embryos replaced. Secondary outcomes were easiness of transfer and proportion of cases with retained embryos, and presence of mucus or blood. Results were analyzed by Chi-square analysis, logistic regression adjusted for clustered observations, and negative binomial regressions adjusted for clustered observations as appropriate. Statistical analysis was performed blindly and independently by a statistician (see acknowledgement). Results are presented as mean $\pm$ standard deviation. P values < 0.05 were considered statistically significant.

RESULTS

There were a total of 1420 embryos transferred by clinical touch and 1115 embryos by ultrasound guidance. The mean number of embryos transferred were, 3.1 and 3.04 respectively (not significant). There were no significant differences in cleavage status or morphology scores among the groups and there were no significant differences between groups in regard to the mean age of the female patients, mean number of mature oocytes retrieved, mean number of oocytes fertilized, or proportion of IVF and ICSI cases (data not shown).

The clinical pregnancy rate was 48% when ultrasound guidance was used and 44% when the clinical touch method was implemented ($P = 0.4$). Similarly there was no significant difference in the implantation rate (22% vs. 20%; $P = 0.2$). There were four cases of ectopic pregnancies in the clinical touch group and two in the ultrasound-guided group ($P > 0.1$). There was no difference in the incidence of multiple pregnancies and miscarriage between the two groups ($P > 0.1$) (Table I). The clinical pregnancy rate was similar in both groups when one, two, three or four embryos were transferred (data not shown).

There were no significant differences among clinicians or assisting embryologists performing the embryo transfers among groups or within individuals

Table I. Outcome of Embryo Transfers Performed with and Without Ultrasound Guidance

	Clinical touch	Ultrasound guided	P
Pregnancy rate	44%	48%	ns
Implantation rate	20 %	22%	ns
Ectopic pregnancy	0.9%	0.6%	ns
Multiple pregnancy	29%	28%	ns
Miscarriage rate	14%	16%	ns

Note. ns: Not significant.

(data not shown). While in the clinical touch transfer, 87% of transfers were rated as very easy, 6% were easy, and 6% difficult, in the ultrasound-guided transfer group, 95% of the transfers were scored as very easy, 3% were easy, and 2% difficult ($P = 0.01$).

The assessment of the frequency of potential negative factors typically associated with difficult transfers revealed that the requirement for the use of tenaculum was lower in the ultrasound-guided group in comparison with the clinical touch group (4% vs. 9%, $P = 0.01$). The proportion of cases with presence of blood in the tip of the catheter was 10% in the ultrasound-guided group and 19% in the clinical touch group ($P = 0.01$). Cervical mucus in the tip of the catheter was less observed in the ultrasound-guided group (10% vs. 14%, $P = 0.04$) (Table II). In addition, the use of the elective catheter (flexible soft pass) was statically higher in the ultrasound-guided group than in the clinical touch group (98% vs. 95%, respectively, $P = 0.02$).

By logistic regression, there was no significant association between the implementation of ultrasound guidance and pregnancy or implantation. Factor potentially affecting implantation and pregnancy rates were analyzed also by logistic regression with adjustment for dependant observations. Blood or mucus in the catheter tip were not influencing pregnancy or implantation rate ($P < 0.1$). On the other hand, the use of the elective catheter was the only variable

Table II. Easiness of Transfer and Rates of Tenaculum Use, Presence of Blood and Mucus in the Catheter Tip, and Use of Soft Catheter

	Clinical touch	Ultrasound guided
Easiness of transfer	87%	95%*
Tenaculum use	9%	4%*
Blood in catheter tip	19%	10%*
Mucus in catheter tip	14%	10% $\pm$
Use of soft catheter	95%	98% $\S$

* $P = 0.01$; $\pm P = 0.04$; $\S P = 0.02$.

independently, significantly, and positively associated with pregnancy success (odds ratio = 2.74, $P = 0.04$).

DISCUSSION

The establishment of a clinical pregnancy in IVF is influenced by many factors including the quality of the gametes, laboratory conditions, the technique of embryo transfer, and endometrial receptivity. Despite numerous improvements in hormonal preparations and optimized embryo culture methods, a large number of transferred embryos fail to implant. Recent attention has focused on the technique of transcervical embryo transfer and the use of transabdominal ultrasound to monitor catheter introduction and deposition of embryos.

The present study, although retrospective in its nature, is one of the largest series published comparing ultrasound-guided embryo transfer and clinical touch embryo transfers. It is important to note that no major changes in terms of stimulation protocols and laboratory conditions took place in the IVF procedures during the study period. We are conscious of the inherent bias associated with retrospective studies; however, it has been documented that well-designed and carefully performed retrospective studies can provide useful and reliable results (19).

Ultrasonographic guidance has several potential advantages in comparison with the clinical touch transfer. It may facilitate the introduction of the catheter through the cervix and therefore the use of more flexible, soft catheters; it may avoid touching the fundus (thought to be a triggering of uterine contractility) (20), and it may be used to confirm that the catheter is beyond the os in cases of elongated cervical canal allowing direction of the catheter along the contour of the endometrial cavity (21). On the other hand, the technique may pose the disadvantage of the need for a full bladder leading to increased transient patients' discomfort.

Our study showed a nonsignificant improvement of pregnancy and implantation rates when comparing ultrasound-guidance with the clinical touch method. As with any technique there is a learning curve, which may have had some influence in the lack of positive effect observed. On the other hand, the use of ultrasound was associated with a significant improvement in the easiness of performing the procedure and also with a significant reduction in the presence of factors typically associated with a poorer outcome, such as presence of blood/mucus and use of a tenaculum. We

consequently consider the use of transabdominal ultrasound guidance to be beneficial and facilitator of the embryo transfer procedure.

Stimulation of the cervix causes release of oxytocin, thus increasing uterine contractility (22). In a prospective clinical trial serial blood samples were collected in time intervals of 20 s during the embryo transfer procedure in order to measure serum oxytocin concentrations (23). It was concluded that the placement of tenaculum was associated with a release of oxytocin that least until the end of the embryo transfer. Our study demonstrated that ultrasound-guidance diminished the proportion of cases requiring the use of a tenaculum (24). However, no randomized controlled trial has proven the negative effect of the use of tenaculum, and again, in our series the use of tenaculum was lower in the ultrasound-guided group, but it was not reflected as a significantly increased pregnancy or implantation rate.

The difficulty of embryo transfer is subjectively influenced by various factors, including patient selection, transfer technique, type of catheter use and experience of physician (25). The rating of the embryo transfer was performed prospectively as very easy, easy, and difficult, and the clinician was required to rate and record the results immediately post transfer. Since this was not a blinded procedure, we cannot exclude inherent biases but we minimized such possibilities.

The difficulty of transfers differed widely between published series. Lindheim *et al.* (7) reported a 19% incidence of difficult transfers while others reported less than 3% (10). In our study we found less than 6% difficult embryo transfers in both ultrasound guided and clinical touch groups.

Variations in catheter design include stiff or soft materials, end or side openings, the presence of an outer sheath, malleability and quality of the materials and finish. Stiff catheters and use of rigid outer sheath make catheter placement easier but may cause more bleeding, trauma, mucus plugging, and stimulation of uterine contractions (20).

Several studies have demonstrated that soft catheters are superior in terms of pregnancy rate (1,2,26). The proportion of our cases in which the soft catheter was used was higher among embryo transfers performed under ultrasound guidance but again that was not reflected as an increment in the pregnancy rate among the groups. But overall, the use of soft catheter was the only independent variable associated with improved pregnancy outcome. It is possible that the soft catheter is not solely responsible for a

better pregnancy outcome but rather that maneuvers performed initially during the mock transfer are the factors eventually affecting pregnancy.

In conclusion, ultrasound guidance facilitated the transfer as evidenced by a significant decrease in the incidence of factors that are known to negatively influence success, such as easiness of the transfer technique, use of a tenaculum, and presence of blood and/or mucus in the transfer catheter. It is concluded that ultrasound guidance facilitates embryo transfer and in combination with the use of a soft catheter should be implemented to optimize embryo transfer results.

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