Ultrasound-guided trial transfer may be beneficial in preparation for an IVF cycle

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BACKGROUND: The objective of this study is to determine if ultrasound-guided trial transfer (UTT) in the office in preparation for an IVF cycle can be utilized as an alternative and/or adjunct to ultrasound-guided embryo transfer (UGET). METHODS: Patients planning to undergo an IVF cycle at an academic centre were included. Each patient underwent an UTT in the office by the same practitioner. The difference in length (DL), if any, was measured from the perceived top of the uterine cavity (catheter tip) to the actual cavity apex as visualized by ultrasound. RESULTS: Of the 64 patients enrolled, 19 patients (29.7%) had a measurable DL, of which 14 (21.9%) had a DL < 0.5 cm, and nine (14.1%) had a DL ≥ 1.0 cm. Significant differences were noted between patients when comparing DL to previous pregnancy status and the total cavity depth (sounding depth + DL) (P < 0.05). CONCLUSION: UTT in the office setting appears to be beneficial in preparation for an IVF cycle with embryo transfer.

Key words: embryo transfer/IVF/trial transfer/ultrasound/uterus

Introduction

Ultrasound-guided embryo transfer (UGET) during an IVF cycle was initially reported during the mid-1980s (Strickler et al., 1985; Leong et al., 1986) and has gradually become an integral part of the embryo transfer technique for many IVF clinics. The potential advantages of this technique compared with standard embryo transfer (performed by clinical feel) include the ability to visualize the uterocervical angle which may aid with difficult transfers, reliably determine the catheter distance from the fundus at the time of embryo transfer, and visualize any unforeseen uterine abnormalities before the transfer. Some studies have demonstrated a benefit in favour of UGET when compared to embryo transfer without ultrasound guidance (Coroleu et al., 2000; Prapas et al., 2001; Tang et al., 2001; Matorras et al., 2002; Sallam et al., 2002) although others have not (Al-Shawaf et al., 1993; Kan et al., 1999; Garcia-Velasco et al., 2002). Careful examination of the data from four properly randomized clinical trials (Coroleu et al., 2000; Tang et al., 2001; Garcia-Velasco et al., 2002; Matorras et al., 2002) showed a significant advantage to UGET with regard to implantation, clinical pregnancy, and ongoing pregnancy rates (Buckett, 2003; Sallam and Sadek, 2003).

The benefit of UGET can be due to the reduction in incidence of difficult transfers (Leeton et al., 1982; Nabi et al., 1997; Hearns-Stokes et al., 2000; Sallam et al., 2002), endometrial trauma (Woolcott and Stanger, 1997; Letterie et al., 1999) and bleeding (Nabi et al., 1997; Goudas et al., 1998; Sallam et al., 2002) that can cause strong fundo-uterine contractions (Lesny et al., 1999). Ultrasound can ensure catheter placement into the endometrial cavity (Woolcott and Stanger, 1997), or decrease the chance of improper embryo placement (Rosenlund et al., 1996; Woolcott and Stanger, 1997; Coroleu et al., 2002; Pope et al., 2004; Shamoni et al., 2005). Two recent studies demonstrated that cavity depth as noted by ultrasound at the time of embryo transfer differed from the cavity depth via office trial transfer by ≥1.0 cm in ≥30% of cases (Pope et al., 2004; Shamoni et al., 2005). Therefore, a significant proportion of patients would have had embryos transferred to a location that was not intended. The main risk factor predicting a discrepancy between the perceived and actual uterine cavity length was a history of pregnancy, especially if the patient had a delivery (Shamonki et al., 2005).

UGET may also have significant drawbacks that present obstacles for some practitioners, and may result in lower than expected pregnancy rates. In particular, the main disadvantages of using ultrasound guidance during embryo transfer may be the additional time and personnel required, as well as patient discomfort due to a full bladder and the urge to urinate (Buckett, 2003). We propose that ultrasound-guided trial transfer (UTT) in the office can be performed as an alternative to UGET for most patients. UTT can theoretically identify those patients with a discrepancy between perceived and actual uterine cavity length in an office setting where logistical issues are of less importance, and in some cases may be more beneficial than UGET.
Ultrasound-guided trial transfer and accuracy

concern, and thus save UGET for only a select minority of patients where the trial transfer was challenging.

The objective of this study was to determine if office UTT in preparation for an IVF cycle is more accurate than blind trial transfer and can be utilized as an alternative to UGET. We attempt to identify any discrepancies between perceived trial transfer depth and actual uterine cavity depth, and to describe which characteristics, if any, predispose patients to these differences.

Materials and methods

Patients

Patients planning an IVF cycle underwent an office trial transfer under abdominal ultrasound guidance for this prospective observational study. Sixty-four consecutive patients underwent UTT from November 2002 to April 2004. None of the patients had a prior trial transfer performed at our centre. All patients underwent successful UTT in the office without complications. Trial transfer techniques are described below. Patient characteristics and transfer characteristics analysed included age, height, weight, body mass index (BMI), pregnancy history, reason for infertility, menstrual cycle day at UTT, ease of trial transfer (easy versus difficult), ultrasound visualization at trial transfer (adequate versus poor), initial trial transfer depth, distance of the catheter tip from the peak of the uterine cavity by ultrasound, and total trial transfer depth. Outcome measures were differences between the actual versus perceived trial transfer depth and patient characteristics accounting for these differences.

Typical office trial transfer at the study centre

As described previously (Shamonki et al., 2005), patients at our centre usually undergo an office trial transfer ~1–6 months prior to the actual embryo transfer. The trial transfer is performed prior to mid-cycle, typically on or prior to cycle day 12. Each patient is placed in the dorsal lithotomy position and a bivalve speculum is used to visualize the cervix. The cervix is cleansed with betadine-soaked gauze. An Insemi-Cath® semi-rigid catheter (Cook Ob/Gyn, Spencer, IN, USA; Figure 1) is used to navigate the cervical canal into the uterine cavity until the tip is perceived to touch the uterine fundus in order to ascertain the depth and direction of the uterine cavity. The catheter is then removed and the length of the catheter that was within the uterine cavity is measured from the external os. At the time of an eventual IVF cycle, embryo placement, either on day 3 or day 5, will be performed at 1–2 cm lower than the distance measured at trial transfer, using a soft non-tapered Wallace® embryo transfer catheter (SIMS Portex Ltd, Hythe, Kent, UK). Therefore, embryos are placed at a distance of 1–2 cm below the top of the uterine cavity.

Ultrasound-guided trial transfer technique

The UTT in the study was performed in a manner identical to the typical office blind trial transfer with the addition of abdominal ultrasound guidance using a 5 MHz probe (GE Logiq 400 Pro Series; General Electric Company, Pewaukee, Wisconsin, USA). All UTTs were performed in the office on or prior to cycle day 12 of a natural menstrual cycle. Each patient was instructed to have a full bladder at the time of UTT. The same physician (G.S.) performed the trial transfer using a Cook Insemi-Cath® catheter while another physician (M.S.) performed the abdominal ultrasound. Once the physician performing the trial transfer believed the catheter was touching the top of the uterine cavity, the ultrasonographer measured the distance, if any, from the top of the cavity to the tip of the catheter [difference in length (DL); Figures 2 and 3]. At no point during the procedure did the physician performing the trial transfer observe, or have feedback regarding, the ultrasound so as not to bias the results. At the end of the UTT, ease and visualization of the procedure were assessed.

Measurements

The blind trial transfer depth was determined by measuring the length of the trial transfer catheter that was within the uterine cavity from the perceived fundal peak to the level of the external cervical os in cm. This was done by direct visualization of the cervix and catheter through the vagina. The measured depth of the transfer catheter was not done by ultrasound, but directly with a tape measure once the

Figure 1. Cook Insemi-Cath® used for trial transfer.

Figure 2. Transabdominal ultrasound showing an accurate trial transfer, with the trial transfer catheter tip touching the top of the uterine cavity (arrow).

Figure 3. Transabdominal ultrasound showing a discrepancy with perceived and actual cavity depth (trial transfer catheter outlined, arrow at uterine fundus).
catheter was removed and its depth within the uterus and cervix was marked. The DL (difference in length) was the distance from the tip of the trial transfer catheter at the perceived fundus to the actual top of the uterine cavity in centimetres as measured by abdominal ultrasound. The total cavity length was established by combining the length of the catheter within the uterus during trial transfer and the DL. Patients were grouped as having any DL versus none, a DL ≥0.5 versus <0.5 cm, or a DL ≥1.0 versus <1.0 cm.

**Statistics**

Statistical analysis was performed utilizing the SPSS for Windows, version 11.0.1 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were evaluated using the independent t-test, and qualitative variables were analysed using the χ² and Fisher’s exact tests. Correlations were performed using the Pearson and Spearman correlations. Statistical significance was set at \( P \leq 0.05 \).

**Results**

Of the 64 patients studied consecutively, 19 patients (29.7%) had a DL, of which 14 patients (21.9%) had a DL ≥0.5 cm, and nine patients (14.1%) had a DL ≥1.0 cm. When comparing patients with any DL versus none, there was no significant difference with respect to age, BMI, type of infertility, initial trial transfer catheter depth, poor versus adequate visualization, easy versus difficult sounding, and menstrual cycle day during the procedure. Similar findings were noted between patients with a DL of ≥0.5 versus <0.5 cm, and ≥1 versus <1 cm. When comparing patients with any DL versus none, significant differences in the means were noted with gravidity (2.3 versus 1.2, \( P = 0.032 \)), parity (0.7 versus 0.2, \( P = 0.013 \)), and the total cavity depth in cm (8.9 versus 7.8, \( P < 0.001 \)) respectively (Table I). The longer the true cavity length, the more likely there would be a discrepancy between perceived and measured depth. Similar findings were noted between patients with a DL of ≥0.5 cm versus <0.5 cm, and ≥1 cm versus <1 cm (Tables II and III). There was a high degree of positive correlation when comparing the DL with uterine length (\( P < 0.001 \)). DL was also significantly positively correlated with gravidity (\( P = 0.004 \)), and parity (\( P = 0.012 \)) (Table IV).

| Table I. Comparison of patient and study characteristics of difference in length (DL) versus none |
|---|---|---|
| DL: any difference | DL: no difference | \( P \) |
| Age (years) | 37.4 ± 4.0 | 35.6 ± 4.9 | NS |
| Gravida | 2.3 ± 2.4 | 1.2 ± 1.6 | 0.032 |
| Parity | 0.7 ± 0.8 | 0.2 ± 0.5 | 0.013 |
| Body mass index (kg/m²) | 23.1 ± 3.0 | 23.0 ± 4.4 | NS |
| Initial depth (cm) | 8.0 ± 0.9 | 7.8 ± 0.8 | NS |
| Total depth (cm) | 8.9 ± 1.1 | 7.8 ± 0.8 | < 0.001 |
| Cycle day of UTT | 10.1 ± 2.9 | 9.4 ± 2.3 | NS |
| Poor visualization (%) | 10.5 (2/19) | 2.2 (1/45) | NS |
| Tricky UTT (%) | 5.3 (1/19) | 4.4 (2/45) | NS |

Data are means are ±SD unless otherwise specified. Fisher’s exact test was used for percentages and the independent t-test was used for means. Significance is set at \( P \leq 0.05 \).

**Discussion**

Typically trial transfers, done by clinical feel in the office, are used as the guide for transferring embryos. Ultrasound guidance performed only at the time of embryo transfer may discover true discrepancies with the trial transfer when it may be too late; embryos may be exposed to the ambient environment longer than necessary which may have detrimental effects. The data from this study demonstrate that UTT can be a useful method in identifying patients who will otherwise have an inaccurate trial transfer if the procedure were done blindly. Two previous studies examining the accuracy of trial transfer...
demonstrated that a significant percentage of patients had inaccurate uterine cavity measurements (Pope et al., 2004; Shamonki et al., 2005). However, the discovery of an inaccurate trial transfer was made at the time of embryo transfer. This study presents a decision tree regarding the utilization of UTT, which may be especially useful for practices where UGET is not routine or practical (Figure 4).

UTT may be particularly beneficial in a practice where ultrasound is not readily available during embryo transfer, either due to a lack of equipment or qualified personnel present to perform the ultrasound. The use of ultrasound guidance during embryo transfer also adds time to each procedure, which may present a problem for practices that perform several embryo transfers per day. Furthermore, patient discomfort related to the full bladder that is required for UGET may add greater anxiety to a procedure that is already stressful for many patients. Discovery of an inaccurate trial transfer in the office setting by using simultaneous abdominal ultrasound guidance can ameliorate these issues by eliminating the need for UGET in the vast majority of patients, thus saving UGET solely for specific indications, such as a history of a difficult embryo or trial transfer, an inaccurate trial transfer, or a history of an ectopic pregnancy after IVF. Interestingly, the use of ultrasound during an embryo transfer does not eliminate ectopic pregnancies, cervical or otherwise (Sieck et al., 1997a,b). The most important risk factor for ectopic pregnancy appears to be a history of tubal disease and is not related to location of embryo deposition within the uterine cavity.

The placement of the embryos at a specific depth within the uterus has been demonstrated to correlate with successful outcome. Studies have shown that the pregnancy rate is higher when embryos are placed lower in the uterine cavity and therefore farther from the fundus (Waterstone et al., 1991; Frankfurter et al., 2003, 2004). One study retrospectively demonstrated that for every additional millimetre embryos are deposited away from the fundus, as noted by abdominal ultrasound, the odds of clinical pregnancy increased by 11% (Pope et al., 2004). The same study deemed that ectopic pregnancies occurred significantly less frequently the farther the embryos were placed from the fundus. Coroleu et al. (2002) demonstrated in a prospective randomized trial of women undergoing UGET that the pregnancy rate was significantly higher when the embryos were transferred at 1.5–2.0 cm instead of at 1.0 cm from the uterine fundus. It is not fully understood why the pregnancy rate is higher with the transfer of embryos lower in the uterine cavity. One theory suggests that catheter contact with the uterine fundus may be avoided when embryos are transferred to the lower part of the uterine cavity. Strong fundo-uterine contractions can result from fundal contact (Fanchin et al., 1998; Lesny et al., 1998), which may have a negative impact on pregnancy rates (Lesny et al., 1999). However, not all studies show an association between embryo transfer location and outcome (Rosenlund et al., 1996). In addition, others demonstrate that the best site for embryo transfer is the centre of the uterine cavity, and that the relative site of embryo deposition is more important than the actual distance from the fundus (Franco et al., 2004; Oliveira et al., 2004). Furthermore, the use of a soft catheter instead of a rigid one may cause less endometrial trauma and has been shown to improve outcome (Wood et al., 2000).

Women are more likely to have an inaccurate trial transfer if their uterine cavity is longer. The data from this study confirm findings from our previous work, where ~30% of patients were noted to have an inaccurate trial transfer by ≥1 cm at the time of UGET (Shamonki et al., 2005). The strong association between uterine length and trial transfer inaccuracy may be due to the design of the catheter utilized for the trial transfer. The Cook catheter is a semi-rigid tapered catheter which is far less expensive and easier to handle than the soft, non-tapered, sheathed embryo transfer catheters, thus making it an appropriate tool for an office trial transfer. However, because of its tapered design, the Cook catheter may become wedged at the external cervical os, giving the impression of resistance prior to reaching the uterine fundus, thus giving the practitioner a false sense of cavity length. Using a soft embryo transfer catheter for trial transfers is much more expensive and may not allow adequate tactile perception due to bending at the top of the uterine cavity.

This study, along with data from our previous research (Shamonki et al., 2005), demonstrates an association between prior pregnancy and trial transfer inaccuracy, and more directly, a link between prior pregnancy and increased uterine cavity length. Previous studies utilizing abdominal ultrasound guidance during embryo transfer demonstrate that ~30% of patients have perceived and actual uterine cavity lengths that differ by ≥1 cm (Pope et al. 2004; Shamonki et al., 2005). However, only 14% of patients in this study showed this finding. There may be numerous explanations for this discrepancy, either solely or in combination. The most likely reason is variation between practitioners. In this study, the same physician performed every office trial transfer as opposed to our previous study, where six different physicians performed the office trial transfers. Additionally, as mentioned previously, a history of pregnancy showed a positive correlation with increased uterine length and trial transfer inaccuracy. The percentage of multigravid and

Figure 4. Decision tree regarding the utilization of ultrasound-guided trial and embryo transfer.
multiparous patients in our current and previous studies differs, in that there is a higher percentage of each of these patients in our previous study. Analysis shows that 60.9% (39/64) had prior pregnancies and 29.7% (19/64) were multiparous in this study, as opposed to the 65.7% (44/67) that had prior pregnancies and the 34.3% (23/67) that were multiparous in our previous study (Shamonki et al., 2005). Another far less likely theory explaining the discrepancy is that uterus length may be increased with exposure to estradiol. The patients in the current study underwent abdominal ultrasound and trial transfer during the late follicular phase of a natural menstrual cycle where estradiol levels are typically <300 pg/ml. The patients in the two studies previously mentioned (Pope et al., 2004; Shamonki et al., 2005) underwent abdominal ultrasound at the time of their embryo transfers during the luteal phase of a stimulated cycle where estradiol levels can be significantly higher. Research has demonstrated a positive correlation between estradiol exposure and uterine size (Adams et al., 1984; Gull et al., 2001). However, if ~2 weeks of high estradiol exposure significantly lengthened the uterus during an IVF cycle, one would expect a more uniform discrepancy between trial transfer and actual uterine cavity lengths in the majority of IVF patients, which is not the case.

Physicians may argue that UGET has additional benefits over UTT other than the diagnosis of a trial transfer inaccuracy. The utilization of UGET has been associated with a decrease in the incidence of difficult transfers (Matorras et al., 2002; Sallam et al., 2002), and easier embryo transfers have been related with an improvement in IVF outcome (Leeton et al., 1982; Wood et al., 1985; Englert et al., 1986; Diedrich et al., 1989; Goudas et al., 1998; Ghazzawi et al., 1999; Hearns-Stokes et al., 2000). At our study centre, >90% of blind embryo transfers with the Wallace catheter are rated as easy, and this as well as our previous study do not show a discrepancy with trial transfer and ease of the procedure, implying that routine use of UGET to reduce the incidence of difficult transfers may not be of much benefit at a centre performing many embryo transfer procedures. However, not all prospective trials examining UGET demonstrate a reduction in difficult transfers (Tang et al., 2001), and the reduction of difficult transfers with the use of abdominal ultrasound guidance does not always lead to a better outcome (Sallam et al., 2002). Furthermore, some studies show no difference in pregnancy rates when comparing difficult and easy embryo transfers (Tur-Kaspa et al., 1998; Burke et al., 2000). Some authors claim that a full bladder, required for UGET, can make the embryo transfer easier because this reduces the angle at the cervico-uterine junction and straightens the uterine cavity in relation to the cervical canal (Sundstrom et al., 1984; Sharif et al., 1995; Wood et al., 2000). When comparing a full bladder without the use of ultrasound during embryo transfer, some data have shown a benefit (Lewin et al., 1997) while others have not (Mitchell et al., 1989). But studies that utilize transvaginal ultrasound, requiring an empty bladder during embryo transfer, show an improvement in the pregnancy rate (Lindheim et al., 1999; Koijima et al., 2001; Anderson et al., 2002) suggesting that a full bladder required for UGET is not a confounder for improving outcome. In addition, some authors have argued that the use of a mock transfer prior to IVF, which has been shown to improve pregnancy rates (Mansour et al., 1990), lessens the benefit of UGET (Tang et al., 2001). The evidence from this study would imply that the addition of ultrasound guidance during trial transfer would further reduce the benefit of UGET when used routinely.

Ultrasound-guided trial transfer in the office setting appears to be of benefit in preparation for an IVF cycle. The main risk factor for having an inaccurate trial transfer is the presence of a longer uterus which is associated with prior pregnancy. Ultrasound-guided trial transfer may therefore greatly reduce the need for ultrasound-guided embryo transfer with its associated drawbacks by diagnosing and correcting inaccuracies of the trial transfer and detecting potentially difficult embryo transfers, in time to adjust the transfer technique, long before the patient will undergo an IVF cycle.

References


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