Ultrasound guided embryo transfer does not offer any benefit in clinical outcome: a randomized controlled study

Sir,

We read the article by Kosmas et al. (2007) with great interest. Several trials and one meta-analysis reported higher pregnancy rates with ultrasound guided embryo transfer (USET) compared with non-ultrasound guided embryo transfers (NUSET) (Buckett, 2003). These authors conducted a large single center randomized controlled trial and concluded that transabdominal ultrasound guidance during embryo transfer did not improve clinical pregnancy and implantation rates provided that the transfer was performed by an experienced operator. We concur that large randomized trials can yield contradictory results to previously published meta-analyses that include smaller studies (LeLorier et al., 1997). However, we have several concerns regarding the design of the present study and reporting and conclusions drawn from the results.

First, trials included in the meta-analysis by Buckett have demonstrated consistently higher absolute pregnancy rates after USET performed with a full or at least a moderately full bladder, compared with NUSET. Trials, in which these differences did not reach statistical significance, did not have adequate statistical power to demonstrate significance between the actually observed values (Kan et al., 1999; Garcia-Velasco et al., 2002), and this is why meta-analyses are done. A full bladder was required for USET in all included studies; therefore, the conclusion of the meta-analysis may be better stated as ‘ultrasound guided embryo transfer with a full bladder significantly increases the chance of clinical pregnancy and the embryo implantation rate’. We believe that USET with and without a full bladder are different entities. In Kosmas et al.’s trial a full bladder was not required for USET and the authors justified this by referring to an inadequately powered ‘pilot’ study that compared outcome of embryo transfers performed under US guidance with or without a full bladder and embryo transfers performed with the ‘clinical touch’ method (Lorusso et al., 2005). We do not think that the results of a single pilot study are sufficient to justify a USET protocol with an empty bladder.

A full bladder during transabdominal ultrasound guidance not only facilitates visualization of the cervical canal and the endometrial strip, but also renders the negotiation of the cervico-uterine junction easier by decreasing anteflexion of the uterus in women with an anteverted uterus. Sallam et al. (2002) demonstrated that pregnancy rate after embryo transfer was inversely associated with the degree of uterine anteflexion. Transabdominal ultrasound even performed with a full bladder may not be of sufficient guidance in 10% of patients undergoing embryo transfer (Garcia-Velasco et al., 2002). This figure can be expected to be higher when the bladder is empty, and in Kosmas et al.’s trial, a substantial number of subjects may have emptied their bladder before ET as the decision was left to the patient. The results of the present study may have been better evaluated had the authors reported (i) the proportion of women who had an empty or full bladder at the time of embryo transfer in both groups, (ii) the proportion of the procedures where the ultrasonographic view was satisfactory, i.e. they were able to follow the catheter tip throughout the procedure and (iii) whether having a full bladder or not affected the visualization of the embryo transfer procedure. If a substantial number of women undergoing USET had not had a full bladder during embryo transfer procedures, then this trial should be regarded as evaluating a different situation from previous trials evaluating USET.

Another point of concern is the outer cervical os–catheter tip distance being significantly different between the study groups in Kosmas et al.’s study. Although the authors have reported the mean distances and standard deviations, they have not reported the ranges for these measurements. In some women, the depth of the endometrial cavity may be at the lower or upper extreme of the ranges reported as normal. We have been measuring lengths of the cervical canal and the endometrial cavity during embryo transfer in the context of an ongoing trial, and according to our preliminary data in over 200 women, the external cervical os–uterine fundus distance (CFD) ranges between 48 and 110 mm; 25% of women having a CFD of <6 cm and 10% having a CFD of >8 cm (unpublished data). Therefore, if embryos are routinely transferred at the 6th cm from the external cervical os without ultrasound guidance, the catheter will touch the fundus in the first group, and embryos will be dislodged at >2 cm distance to the fundus in the latter group. Regarding these facts one can conclude that even if USET does not benefit the majority of women, it may be of great benefit in women who do not comply with the population average. Unfortunately a trial with adequate power to demonstrate this benefit would require a substantially large number of subjects.

In conclusion, embryo transfer is a crucial step of assisted reproduction treatment, USET is a noninvasive procedure, and most IVF units, if not all, already have ultrasound equipments that may be utilized for embryo transfer. Therefore, we believe avoidance of using ultrasound to guide embryo transfer is not to the best interest of patients.

Letters to the Editor
References


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Reply: Ultrasound guided embryo transfer does not offer any benefit in clinical outcome: a randomized controlled study

Sir

We thank Drs Ata and Urman for their interest in our study (Kosmas et al., 2007). For the study design, trial committee had to consider two major aspects. Embryo transfer performance is linked with the clinician (Hearns-Stokes et al., 2000), and a certain number of embryo transfers is required for achieving competence equal to experienced providers (Papageorgiou et al., 2001). Therefore, we limited our study to one experienced clinician who performed all embryo transfer.

Decreased uterine contractility during embryo transfer (Fanchin et al., 2001), day of embryo transfer and number of embryos transferred are all factors that play an important role for successful embryo transfers.

Pseudo-randomization methods were the randomization choice in those studies that show a significant positive effect (Buckett, 2003). Pseudo-randomization included randomization based on availability of the ultrasound machine (Prapas et al., 2001), the transfer room (Prapas et al., 2001), ultrasonographer availability (Kan et al., 1999) and randomization done by alternative allocation of patients to each group (Sallam et al., 2002). It is important to understand that pseudo-randomization can introduce significant bias into statistical analysis and this bias can be incorporated in the pooled results. A study that used a true randomization (Garcia-Velasco et al., 2002) did not report significant difference in the outcome after embryo transfer with or without ultrasound guidance. Other studies (Prapas et al., 2001) found no significant difference in pregnancy rates for Day 5 embryo transfers with or without ultrasound guidance.

The corresponding author assumes that embryo transfer with full bladder is a different entity than embryo transfer with empty bladder. A recent meta-analysis of three studies (Abou-Setta, 2007) shows significantly higher likelihood of clinical pregnancy [OR 1.55 (95% CI = 1.16–2.08)] and ongoing pregnancy [OR = 1.44 (95% CI = 1.04–2.04)] with a full bladder. From these three, the two randomized studies included, showed no significant difference in clinical pregnancy rates [OR 1.02 (95% CI = 0.59–1.77)] and only adding the third pseudo-randomized study, makes the difference significant in favor a full bladder embryo transfer. Pooled results incorporate the bias of the single study. Under current evidence, full bladder during embryo transfer is not a different entity from empty bladder, regarding pregnancy rates.

All patients in the ultrasound-guided (US) embryo transfer group had embryo transfer under ultrasound guidance. Sixty patients were excluded because of poor or no visibility during embryo transfer (study flowchart).

Anatomical variability was minimal. In 21 patients, the outer cervical os–uterine fundus distance (as measured, in the US embryo transfer group) was <6 cm. Thirteen of them became pregnant. Most of these measurements were between 5 and 6 cm.

A very neat meta-analysis (Abou-Setta et al., 2007) compared US versus clinical touch method. This meta-analysis states that ultrasound guidance improves clinical pregnancy rates [OR 1.50 (95% CI = 1.34–1.67)]. By excluding the trials (n = 12) with unclear method of randomization or pseudo-randomization, the previous significant difference in clinical pregnancy is lower [OR 1.43 (95% CI = 1.21–1.68)] (Random effects model). Also in this meta-analysis, heterogeneity is significant. The number of patients needed to treat to obtain one additional clinical pregnancy with use of ultrasound guidance need to be calculated. On the basis of these facts, results are debatable.

As a conclusion, all randomized controlled trials have to be uniformly designed, performed by a single clinician and transfer an equal amount of embryos the same day (Day 3 or 5).

References


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