Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials

Hassan N. Sallam, M.D., Ph.D., F.R.C.O.G., and Sameh S. Sadek, M.D.
Department of Obstetrics and Gynaecology, Alexandria University, Alexandria, Egypt

Objective: To conduct a meta-analysis of randomized controlled studies to evaluate abdominal ultrasound-guided embryo transfer compared to the clinical touch method.

Design: Meta-analysis.

Setting: Four studies performed in academic research centers in Barcelona, Vizcaya, Hong Kong, and Madrid.

Patient(s): A total of 2,051 patients: 1,024 received ultrasound-guided embryo transfers and 1,027 received clinical touch method transfers.

Intervention(s): Fourteen studies were retrieved from the literature, but only four of them fitted our selection criteria. The meta-analysis was conducted using the RevMan software with the Peto-modified Mantel-Haenszel method and the fixed effect model.

Main Outcome Measure(s): The primary outcome measures were the clinical pregnancy and ongoing pregnancy rates. The secondary outcome measures were the incidences of ectopic pregnancies, miscarriage rate, multiple pregnancies, and difficult transfers.

Result(s): Compared to the clinical touch method, abdominal ultrasound-guided transfer significantly increased the clinical pregnancy rate and the ongoing pregnancy rate. There was no effect on the incidence of ectopic pregnancy, multiple pregnancy, or miscarriage rate.

Conclusion(s): Ultrasound-guided embryo transfer increases the clinical pregnancy and ongoing pregnancy rates significantly compared to the clinical touch method. (Fertil Steril 2003;80:1042–6. ©2003 by American Society for Reproductive Medicine.)

Key Words: Embryo transfer, ICSI, IVF, meta-analysis, randomized controlled trial, ultrasound

Despite numerous developments in assisted reproduction, the clinical pregnancy rate (CPR) in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) remains low. It has been estimated that up to 85% of the embryos replaced into the uterine cavity fail to implant (1). The cause of this low CPR may reside in the technique of embryo transfer (ET), the endometrial receptivity, or the capacity of the embryo to properly invade the endometrium.

In an attempt to improve the ET technique, Strickler et al. (2) suggested the use of abdominal ultrasound guidance in a small number of patients undergoing IVF and reported encouraging results. Subsequently, some investigators reported that ultrasound-guided ET improves the CPR and implantation rate (3, 4), but others reported no improvement in their results (5, 6). Vaginal ultrasound-guided ET was also reported (7, 8), as well as the use of three-dimensional ultrasound during ET (9).

In view of these conflicting results, the aim of this work was to conduct a meta-analysis of randomized controlled studies to evaluate the technique of abdominal ultrasound-guided ET in patients undergoing IVF and ICSI.

METHODS

A meticulous search of the literature was conducted for studies reporting the use of abdominal ultrasound-guided ET. This consisted of searching the MEDLINE database, the EMBASE database, the Cochrane Library, as well as hand-searching relevant publications and proceedings of international congresses. A combination of the following key words were used in the search: embryo transfer,
Fourteen relevant studies were retrieved from the literature (2–6, 10–19). The articles were scrutinized independently by both reviewers and evaluated for inclusion in the meta-analysis using predetermined criteria and a predetermined scoring system. To be included in the analysis, the studies had to be properly randomized using computer-generated tables or similar methods. Moreover, the intervention and control groups had to be similar, the patients had to be analyzed in the same group, and the follow-up had to be complete. Analysis of agreement between both reviewers was performed using kappa statistics.

Out of the 14 studies, four fulfilled our predetermined criteria (3, 4, 15, 19). Investigators from the four studies were contacted by e-mail to clarify any missing information. A meta-analysis of the four selected studies was then conducted. The primary outcome measures were the CPR and the ongoing pregnancy rate (OPR). The secondary outcome measures were the incidence of ectopic pregnancies, the miscarriage rate, and the incidence of difficult transfers. Sensitivity analysis was also performed to determine the effect of the number of embryos transferred on the CPR.

The CPR was defined as the presence of a positive pregnancy test together with the ultrasound visualization of at least one intrauterine and/or extrauterine gestation sac at 6 to 8 weeks after ET. The OPR was defined as the ultrasound visualization of a living fetus with a pulsating heart beyond 10 weeks of gestation.

The χ² test was used to compare qualitative variables, and Student’s t-test to compare quantitative variables, using the Microstat statistical software. The significance level was set at P=.05. The meta analysis was conducted using the RevMan software with the Peto-modified Mantel-Haenszel method and the fixed effect model (20). Homogeneity was tested by performing the Breslow-Day test (21). Institutional review board approval was not sought because only previously published data were used.

RESULTS

Clinical Pregnancy Rate

The four studies reported their CPR. A total of 374 clinical pregnancies occurred in 1,024 ultrasound-guided transfer cycles (36.5%) compared with 301 out of 1,027 clinical touch transfer cycles (29.3%) (P<.001). The odds ratio (±95% CI) for the CPR was 1.42 (1.17–1.73) in favor of the ultrasound-guided transfers (Fig. 1).

Ongoing Pregnancy Rate

The four studies reported their OPR. A total of 336 ongoing pregnancies resulted from 1,024 ultrasound-guided transfer cycles (32.8%) compared with 259 out of 1,027 clinical touch transfer cycles (25.2%) (P<.0001). The odds ratio (±95% CI) for the OPR was 1.49 (1.22–1.82) in favor of the ultrasound-guided transfers (Fig. 2).

Ectopic Pregnancy Rate

The four studies reported their ectopic pregnancy rate. A total of five among the 449 pregnancies resulting from ultrasound-guided transfer cycles were ectopic pregnancies (1.1%) compared with 11 out of 385 pregnancies in the clinical touch transfer cycles (2.9%) (P=.115). The odds ratio (±95% CI) for the ectopic pregnancy rate was 0.39 (0.14–1.10).
Multiple Pregnancy Rate

Only three studies reported their multiple pregnancy rate (4, 15, 19). A total of 77 among the 283 pregnancies that resulted from ultrasound-guided transfer cycles were multiple pregnancies (27.2%), compared with 57 out of 240 pregnancies in the clinical touch transfer cycles (23.8%) ($P = .422$). The odds ratio ($\pm 95\%$ CI) for the multiple pregnancy rate was 1.18 (0.79–1.75).

Miscarriage Rate

Only three studies reported their miscarriage rate (4, 15, 19). A total of 30 among the 283 pregnancies with ultrasound-guided transfer cycles were multiple pregnancies (10.6%), compared with 29 out of 240 pregnancies in the clinical touch transfer cycles (12.1%) ($P = .693$). The odds ratio ($\pm 95\%$ CI) for the miscarriage rate was 0.83 (0.48–1.44).

Incidence of Difficult Transfers

Only three studies reported their incidence of difficult transfers. A total of 76 difficult transfers occurred among the 837 ultrasound-guided transfer cycles (9.1%) compared with 127 out of 840 in the clinical touch transfer cycles (15.1%) ($P < .0001$). The odds ratio ($\pm 95\%$ CI) for diminishing the rate of difficult transfers was 0.55 (0.41–0.75) in favor of the ultrasound-guided transfers (Fig. 3). However, the $\chi^2$ test (Breslow-Day) for homogeneity of the studies showed that this result cannot be accepted ($P = .0001$).
Effect of the Number of Embryos Transferred

The CPR relative to the number of embryos transferred was reported by two studies (3, 15). In cycles with one embryo transferred, six pregnancies out of 36 transfers occurred in the ultrasound-guided transfer cycles (16.7%) compared with four out of 39 in the clinical touch transfer cycles (10.3%) (P=.634). The odds ratio (±95% CI) for transferring one embryo was 1.79 (0.47–6.85). In cycles with two embryos transferred, 83 pregnancies out of 288 transfers occurred in the ultrasound-guided transfer cycles (28.8%) compared with 68 out of 279 in the clinical touch transfer cycles (24.4%) (P=.2704). The odds ratio (±95% CI) for transferring two embryos was 1.25 (0.86–1.82). In cycles with three embryos transferred, 88 pregnancies out of 221 transfers occurred in the ultrasound-guided transfer cycles (39.8%) compared with 70 out of 236 in the clinical touch transfer cycles (29.7%) (P<.05). The odds ratio (±95% CI) was 1.63 (1.09–2.43) in favor of the ultrasound-guided transfers.

DISCUSSION

Ultrasound-guided ET was first suggested by Strickler et al. (2) in 1985. Those investigators reported that ultrasound-guided transfers were easier and had less catheter distortion. They found that with ultrasound guidance the catheter tip could be accurately positioned in the fundus of the uterine cavity and that the ejection of the transfer bubble into the uterus could be documented. The practice was comforting to the physician and the patient. We have also reported that the use of abdominal ultrasound to measure the uterocervical angle before ET and mould the catheter accordingly increased the clinical pregnancy rate and implantation rate significantly and diminished the incidence of difficult transfers and blood during transfers (17).

However, not all studies reported a significant improvement in the CPR when ET was performed under abdominal ultrasound guidance, possibly because they lacked enough power. We have calculated that to improve the CPR from 23% to 30%, taking 5% as the significance level and accepting a 90% probability of finding a true difference, the least number needed to study was 786 patients in each arm of the study.

In the present meta-analysis, a total of 1,024 women undergoing ET under abdominal ultrasound guidance was compared with 1,027 women undergoing the transfer with the clinical touch method. Only properly randomized, controlled studies using computer-generated random tables were included. Non-randomized and quasi-randomized studies were excluded (including our own). Studies using transvaginal ultrasound and three-dimensional ultrasound were not included, as no randomized controlled studies have been found in the literature. A study on the use of abdominal ultrasound-guided ET of embryos resulting from donated oocytes was also excluded as this was done retrospectively (18).

The results of this meta-analysis show that abdominal ultrasound-guided ET significantly increases the CPR and the OPR for patients treated with IVF and ICSI. It has been suggested that this may be a result of the decrease in the incidence of difficult transfers. However, in the present meta-analysis, this fact could not be confirmed because of the heterogeneity of the studies, which may be related to the subjective nature of assessing the “difficulty” of the procedure in the included studies. In support of this finding, we have previously reported that ultrasound-guided ET increased the CPR by avoiding blood during transfers rather than by diminishing the incidence of difficult transfers (17). It may also be suggested that the increase in CPR may be biased by the inclusion of the study of Coroleu et al. (3), who routinely deposited their embryos at least 1.5 cm below the uterine fundus. However, when the study was excluded from the analysis, the CPR and the OPR were still significantly higher in the ultrasound-guided group (odds ratio = 1.28 [95% CI 1.04, 1.58] and odds ratio = 1.34 [95% CI 1.07, 1.69], respectively).

The present meta-analysis showed no effect of ultrasound-guided ET on the rates of ectopic pregnancy, multiple pregnancy, or miscarriage. This is probably a result of the low incidence of these events in relation to the numbers studied. These points may be further clarified by updating the meta-analysis with future studies involving larger numbers of patients.

Similarly, sensitivity analysis was performed on the number of embryos transferred and showed that ultrasound-guided ET increased the CPR significantly when three embryos were transferred but not when one or two embryos were transferred. This may be due to the relative distribution of the subjects receiving one, two, or three embryos in the studies analyzed.

In conclusion, ET performed under abdominal ultrasound guidance significantly improves the CPR for patients treated with IVF and ICSI and should be offered for patients treated with these modalities.

References


