Ultrasound-guided embryo transfer improves pregnancy rates and increases the frequency of easy transfers

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BACKGROUND: Recent reports have suggested that ultrasound (US) guidance during embryo transfer might improve pregnancy rates. METHODS: A prospective randomized (computer-generated random table) trial was performed to compare embryo transfer under abdominal US guidance (n = 255 women) with clinical touch embryo transfer (n = 260). RESULTS: The clinical pregnancy rate was 26.3% (67/255) in the US-guided transfer group compared with 18.1% (47/260) in the clinical touch transfer group (P < 0.05). The implantation rate was 11.1% (100/903) in the US group compared with 7.5% (66/884) in the clinical touch group (P < 0.05). US-guided transfer was associated with a decrease in the difficulty of the transfers: 97% of transfers were easy in the US-guided group compared with 81% in the clinical touch group (P < 0.05). CONCLUSIONS: US-guided embryo transfer increased pregnancy and implantation rates in IVF cycles, as well as the frequency of easy transfers. It is suggested that the decrease in cervical and uterine trauma can play a role in the increase in pregnancy rates associated with US-guided transfer. It is recommended that embryo transfer should be performed under US guidance.

Key words: embryo transfer/IVF/meta-analysis/pregnancy rate/ultrasound

Introduction

While embryo transfer is at present the most inefficient step in IVF, until recently embryo transfer technique had received little attention. A survey of embryo transfer practice in the UK showed that the factor that got the highest rating was the need for a standardized protocol for embryo transfer technique (Salha et al., 2001). It is generally accepted that an atraumatic embryo transfer is essential for successful implantation (Leeton et al., 1982; Wood et al., 1985; Diedrich et al., 1989).

Over the last few years a number of works have been directed towards the study of ultrasound (US)-guided embryo transfer. However, few of them are truly randomized and their results are controversial (Coroleu et al., 2000; Tang et al., 2001). Indeed, the mechanism by which pregnancy rates (PR) are increased, if any, is not well known.

The aim of our study was to assess whether US-guided transfer diminishes the frequency of difficult transfers and increases the per transfer PR.

Material and methods

During the period of study, a prospective randomized trial was performed with all the patients assisted at our Human Reproduction Unit in our IVF programme. Transfers of cryopreserved embryos and of embryos resulting from oocyte donation were not included. No ICSI cases were included, as at that time ICSI was not available at our unit. In all cases the age of the woman was <40 years. Randomization was made in accord with a computer-generated random table. Randomization was performed on the morning of the embryo transfer. Patients were contacted and embryo transfer was scheduled. No specific recommendations were given regarding bladder repletion in the clinical touch group, whereas cases subjected to US-guided transfer were instructed to come into our unit with a relatively full bladder.

Our IVF cycle management has been previously described (Matorras et al., 1998). Briefly, it consisted of down-regulation with gonadotrophin-releasing analogue, triptoreline acetate (Decapetyl; Laboratorios Lasa, Madrid, Spain) s.c. daily from day 20–22 of the pre-treatment cycle. Recombinant FSH (Gonal F; Serono, Madrid, Spain) injection was started on day 2 of the treatment cycle. HCG (Profasi; Serono) 10 000 IU was given i.m. when there were at least three follicles reaching 18 mm in diameter. Transvaginal US-guided oocyte retrieval was scheduled 36 h after HCG injection. The luteal phase was supplemented with micronized progesterone (Progeffik; Efiik, Spain) vaginally 200 mg/12 h.

Just prior to starting ovarian stimulation, a mock transfer was performed. Patients received no instructions concerning bladder repletion. In the mock transfer the following data were recorded: uterine position, fundal length and special characteristics of cervical canal. The information of the mock transfer was recorded and used when performing the embryo transfer. For the mock transfer as well as for the embryo transfer we always used the Frydman catheter (Laboratoire CCD, Paris, France). This catheter has a soft 23 cm long inner polyuretane catheter with an external diameter of 1.53 mm.
with an open end. It has a stiffer outer sheath that stabilizes the softer inner cannula, which carries the embryos and actually enters the endometrial cavity for embryo transfer.

Embryo transfer was carried out at 48–72 h post-oocyte retrieval in 86.8% of cases, in 3.9% at 4 days after oocyte retrieval and in 9.3% after 5–6 days. All patients were placed in the lithotomy position. A bivalve speculum was placed to expose the cervix. The exocervix was cleaned with Ham F-10 medium (Invitrogen Corporation, UK). The mucus of the cervical canal was not removed. Concurrently, in the adjacent embryo culture laboratory, the morphological appearance of the embryos was evaluated and the best embryos were selected and loaded into the Frydman catheter. Drawing up the embryos into the insertion catheter was done with the aid of a disposable tuberculin syringe using the ‘3-drop’ procedure in which the embryos are separated by a bubble of air from a preceding and a following drop of medium.

Clinical touch transfer consisted of the insertion of a Frydman catheter, gently, through the cervical canal. If after three attempts the insertion of the catheter was not possible, a Pozzi tenaculum was applied to the anterior cervical lip to place the uterus horizontally. If in spite of this, it was not possible to place the catheter, a hysterometer was used. In the very rare cases where this was painful or difficult, paracervical anaesthesia was employed. In all cases, the embryos were released according to the clinician feeling, trying to place the embryos within 1 cm of the uterine cavity fundus, following the information from the mock transfer performed before starting ovarian stimulation. After embryo transfer the catheter was checked for the presence of blood.

Cases subjected to US-guided transfer were instructed to come into our unit with a relatively full bladder (3–4 h from the last miction). The US machine we used was an Aloka SSD-1200, 3.5 MHz. The embryos were released when the US scan showed the catheter to be within 1 cm of the uterine cavity fundus. US also made possible the visualization of the ‘transfer bubble’ after the embryos had been ejected.

US-guided transfer was performed by means of the same Frydman catheter. In most cases, embryo transfer was performed only with the soft catheter, without using the outer guide. In cases where US-guided transfer as described above was not possible, US-guided transfer was performed with instrumental assistance, following the same steps as in clinical touch transfer.

In both classical and US-guided embryo transfer, the catheter was carefully removed after a period of 10 s. The catheter was then checked under the microscope and flushed for embryos retained within the lumen or adherent to the outside of the catheter. After embryo transfer, the patient was transferred to the recovery area and allowed to empty her bladder within 10–15 min of embryo transfer, and she was discharged 30 min after embryo transfer.

Our embryo transfer systematic consisted of the transfer of four embryos—when available—except in blastocyst transfers where only three were transferred. Pregnancy was defined as the presence of a gestational sac and a positive pregnancy test.

Transfers were classified as follows: (i) easy, if only the Frydman catheter was necessary; (ii) intermediate, when catheter manipulation plus a tenaculum was necessary; (iii) difficult, if a hysterometer was necessary; (iv) very difficult, if additional procedures were necessary (multiple catheter changes, cervical dilatation, paracervical anaesthesia).

For meta-analysis, Medline was searched under the key words: ‘embryo transfer’ and the limit ‘randomized controlled trial’. Additional searches were done with ‘embryo transfer’ and ‘ultrasound’ and with ‘embryo transfer’ and ‘ultrasound-guided’. Cross-references picked up were also selected. The last search was done on October 1, 2001.

### Results

#### Homogeneity of groups

Both groups proved to be comparable regarding the main demographic characteristics, as well as the main cycle parameters (Table I).

#### Pregnancy rate

The PR in the US-guided group was significantly higher than in the classical transfer (26.3 versus 18.1%; 67 out of 255 versus 47 out of 260; $\chi^2 = 4.5$, $P = 0.03$, OR = 1.6, 95% CI = 1.04–2.51; Table II). Furthermore, the implantation rate was 11.1% (100 out of 903) in the US group compared with...
7.5% (66 out of 884) in the classical group ($\chi^2 = 6.5$, $P = 0.01$, OR = 1.5, 95% CI = 1.1–2.2). The ongoing pregnancy rate was also higher in the US group (22.4%) than in the clinical touch group (14.2%; $\chi^2 = 5.1$, $P = 0.02$, OR = 1.7, 95% CI = 1.1–2.8).

The frequency of ectopic pregnancy was 3.0% (two out of 65) in the US group, compared with 2.1% (one out of 47) in the classical group (Table II). Both ectopic pregnancies in the US group occurred in patients with good visualization of the pathway of the catheter tip.

**Characteristics of transfers**

While in the clinical touch transfer 80.8% of transfers were easy, 12.3% moderately difficult, 5.8% difficult and 1.2% very difficult, in the US-guided transfer 96.9% of cases were easy transfers and 2.7% were of moderate difficulty, whereas only 0.4% were difficult and none very difficult ($\chi^2 = 34.2$, $P < 0.001$). We found good transabdominal visualization of the pathway of the catheter tip in 85% of cases.

When PRs were analysed according to the difficulty of transfer, among easy transfers there was a trend to higher PR when the transfer was performed under US guidance compared with clinical touch (26.3 versus 18.6%; $\chi^2 = 3.44$, $P = 0.06$, OR = 1.6, 95% CI = 1.0–2.5).

Among US-guided embryo transfer, when embryo transfer was performed without the outer sheath the PR was 27.0% (46 out of 170) compared with 24.7 (21 out of 85) when the outer sheath was used ($P > 0.05$). The characteristics of the transfers are shown in Table III.

**Discussion**

The possible use of US guidance to facilitate embryo transfer was first reported by Strickler et al. and shortly afterwards by Leong et al. (Strickler et al., 1985; Leong et al., 1986). In the past few years a number of groups have studied US-guided transfer. Results are controversial, both in randomized and non-randomized trials. In non-randomized trials, some authors have reported better results with US-guided transfer (Lindheim et al., 1999; Wood et al., 2000). Concerning randomized trials, significantly better results have been obtained with US-guided transfer (Prapas et al. 1995, 2001; Coroleu et al., 2000), while in other reports no differences were obtained (Hurley et al., 1991; Al-Shawaf et al., 1993; Kan et al., 1999; Tang et al., 2001). Some of the discrepancies could be due to the different methodology employed (selection of patients, method of transfer), as well as to the reduced size of some of the populations under study. Thus, it has been reported that US-guided embryo transfer increased PR when embryo transfer was performed on day 3 and 4, but not on day 5 (Prapas et al., 2001). Indeed, in one randomized trial, while no significant differences were observed in PR, a significantly increased implantation rate was reported (Tang et al., 2001). On the other hand, many of the so called ‘randomized trials’ are not truly randomized trials, since the criteria for performing the US-guided transfer was the availability of the US machine or of the gynaecologist (Hurley et al., 1991; Al-Shawaf et al., 1993; Prapas et al., 1995, 2001; Kan et al., 1999).

From our data it is evident that US-transfer significantly improved the PR (26.3 versus 18.1%) and implantation rates (11.1 versus 7.5%). If the data of our report concerning PR are analysed together with all the previous randomized reports, statistical significance persists (Table IV), both when considering only truly randomized trials and when analysing randomized and pseudo-randomized trials together. As one can see in Table IV, in both analyses very similar results were obtained, the OR being close to 1.5, with statistical significance.

We had a 3.0% ectopic pregnancy rate in the US group, including one case of ovarian pregnancy, already reported (Lure et al., 2002). This ectopic pregnancy rate was similar to that obtained in the clinical touch group, agreeing with previous reports in which US-guided embryo transfer did not decrease the rate of ectopic pregnancies (Hurley et al., 1991; Sieck et al., 1997; Coroleu et al., 2000).

In our series, there was a dramatic difference in difficult transfers between the groups. While in clinical touch transfers we had 6% of difficult transfers, only 0.4% of US-guided transfers were difficult. Furthermore, even among easy transfers there was a trend to higher PR when embryo transfer was performed under US guidance. Moreover, much of the US-guided transfers were performed without the outer sheath, suggesting that in those cases the insertion trauma was lower.

One problem when analysing the ‘difficulty’ of embryo transfers is its subjective nature. Indeed it depends on a number of variables, including patient selection, transfer technique, type of catheter and the experience of the physician. Thus the

<table>
<thead>
<tr>
<th>Table III. Difficulty of the transfer and pregnancy rates. Ultrasound (US)-guided transfer versus clinical touch transfer</th>
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<tbody>
<tr>
<td><strong>US-guided transfer</strong></td>
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<tr>
<td>Frequencya % (n/N)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Easy</td>
</tr>
<tr>
<td>Moderately difficult</td>
</tr>
<tr>
<td>Difficult</td>
</tr>
<tr>
<td>Very difficult</td>
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</tbody>
</table>

*aP < 0.001 ($\chi^2 = 34.2$) (comparing the difficulty of the embryo transfer in US-guided versus clinical touch).

*bP = 0.06 ($\chi^2 = 3.44$) (comparing pregnancy rates in easy transfers in US-guided versus easy transfers in clinical touch).
frequency of embryo transfers reported as difficult differs widely. In a series of 876 embryo transfer procedures, 1.3% were impossible, 3.2% very difficult and 5.6% difficult (Wood et al., 1985). In more recent surveys, while some authors refer to 2–3% of difficult transfers (Coroleu et al., 2000), others have reported rates of 14% (Tur-Kaspa et al., 1998) and 19% (Lindheim et al., 1999).

Coroleu et al. did not observe significant differences in the difficulty of the procedure between US-guided and clinical touch transfer, although the frequency of non-easy transfers was low in both populations (2–3%) (Coroleu et al., 2000). Kan et al. reported no differences in the difficulty of transfers, but they excluded from their study patients in whom a difficult transfer was anticipated. On the other hand, they had a relatively high frequency of difficult transfers in both populations (10–11%) (Kan et al., 1999). In a retrospective report, whereas no significant differences were found in the difficulty of embryo transfer, it was reported that when the uterus was acutely anteflexed, the subjective feeling was that US-guided embryo transfer was easier and followed a straighter course (Wood et al., 2000).

Tactile assessment of embryo transfer has been reported as unreliable (Woolcott and Stanger, 1997) and a number of suboptimal catheter placements have been reported. It has been shown that an easy, atraumatic transfer is essential for successful implantation (Wood et al., 1985; Diedrich et al., 1989; Goudas et al., 1998; Ghazzawi et al., 1999), although there are controversial reports (Tur-Kaspa et al., 1998). It is possible that minimizing endometrial trauma could decrease myometrial contractions, which could in turn enhance implantation (Fanchin et al., 1998; Lesny et al., 1998).

According to our experience, we suggest that one important mechanism of the increased PR obtained with US-guided transfer is the reduction of catheter insertion-induced trauma. Presumably the most important factor is the visualization of the endometrial cavity and also frequently the cervical canal, facilitating atraumatic penetration into the uterus. Following the pathway of the catheter by US guidance should decrease the propensity for the clinician to make catheter contact with the fundus, as has been previously suggested (Wood et al., 2000).

One could speculate that additionally, the filling of the bladder necessary to perform the abdominal US, could straighten the utero-cervical junction, thus favouring easy entry into the endometrial cavity, especially in acutely anteflexed uteri (Sundstrom et al., 1984; Wood et al., 2000). Perhaps the pressure of the US transducer in the lower abdomen could also play a role. Another factor to be considered was that the majority of US-guided embryo transfers were performed with the soft catheter, without the outer sheath. There are a number of reports stating that soft catheters are associated with higher PR than hard catheters (Wood et al., 2000).

Probably, although not analysed in our study, another factor could be the adequate placement of embryos into the uterine cavity. Indeed, US guidance can give confidence and reassurance to patients and clinicians performing the procedure (Hurley et al., 1991; Al-Shawaf et al., 1993). It is recommended that embryo transfer should be performed under US guidance.

### References


### Table IV. Meta-analysis of pregnancy rates in randomized trials. Ultrasound (US)-guided transfer versus clinical touch transfer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>US-guided transfer (%)</th>
<th>Clinical touch transfer (%)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Coroleu et al.</td>
<td>2000</td>
<td>50 (91/182)</td>
<td>33.7 (61/180)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tang et al.</td>
<td>2001</td>
<td>26.0 (115/441)</td>
<td>22.5 (81/359)</td>
<td>NS</td>
</tr>
<tr>
<td>Matorras et al. (this study)</td>
<td>2002</td>
<td>26.3 (67/255)</td>
<td>18.1 (47/260)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Quasi-randomized trials</td>
<td></td>
<td></td>
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<tr>
<td>Hurley et al.</td>
<td>1991</td>
<td>20.2 (199/94)</td>
<td>17.5 (43/246)</td>
<td>NS</td>
</tr>
<tr>
<td>Al-Shawaf et al.</td>
<td>1993</td>
<td>28.9 (44/152)</td>
<td>30.3 (27/89)</td>
<td>NS</td>
</tr>
<tr>
<td>Prapas et al.</td>
<td>1995</td>
<td>36.1 (22/61)</td>
<td>22.5 (16/71)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Kan et al.</td>
<td>1999</td>
<td>37.8 (37/98)</td>
<td>29.8 (28/97)</td>
<td>NS</td>
</tr>
<tr>
<td>Prapas et al.</td>
<td>2001</td>
<td>47.6 (206/433)</td>
<td>36.0 (229/636)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Global meta-analysis</td>
<td>2002</td>
<td>35.0 (601/1716)</td>
<td>27.5 (532/1938)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Meta-analysis including only truly randomized trials</td>
<td>2002</td>
<td>31.4 (273/870)</td>
<td>23.7 (189/799)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\( \chi^2 = 20; \text{ odds ratio (OR)} = 1.4; 95\% \text{ confidence interval (CI) } = 1.23–1.64. \\
\( \chi^2 = 12; \text{ OR } = 1.5; 95\% \text{ CI } = 1.18–1.85. \\
NS = \text{ not significant.} \)


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