Optimizing the embryo transfer technique
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Chapter 5

A prospective randomized controlled trial comparing two embryo transfer catheters in an ART program.

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Abstract
Objective: To compare the performance of the Cook Sydney IVF (SIVF) embryo transfer (ET) catheter and the Edwards-Wallace (EW) ET catheter.
Design: Prospective randomized controlled clinical trial with an intention-to-treat analysis.
Setting: Two-center study.
Patient(s): Four hundred consecutive women <40 years undergoing ET with two fresh embryos.
Intervention(s): Women were randomly allocated to undergo ET with either the EW or the SIVF catheter, with possible catheter change in case of insertion difficulties.
Main Outcome Measure(s): Live birth and clinical pregnancy rates.
Result(s): Two hundred two women were allocated to the SIVF catheter and 198 to the EW catheter. No significant differences in the clinical pregnancy rates (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.66–1.47) and live-birth rates (OR 1.09, 95% CI 0.72–1.65) were found. The EW catheter had to be changed more often than the SIVF catheter (OR 9.5, 95% CI 3.3–27.5) because of catheter insertion problems.
Conclusion(s): The pregnancy and live birth rates were not significantly different with the two catheters, but catheter insertion failure was significantly more common with the EW catheter than with the SIVF catheter.
Introduction
Assisted reproductive technology (ART) is a fast-paced and ever-changing field in medicine. All parts of IVF/ICSI treatment are evolving toward more evidence-based procedures, resulting in increasing success rates. Although older reports suggested that many clinicians were little aware of the great importance of transfer technique skills, numerous published trials now document that the embryo transfer (ET) procedure has a huge impact on pregnancy and delivery rates (1–3). Clearly, the aim of the ET technique must be to minimize the risk of misplacing the embryo, and to minimize the risk of cervical and endometrial trauma. Attempts at optimizing the ET procedure include the use of dummy ET (4), softer ET catheters (5–6), and ultrasound guidance (7–10). The literature now includes numerous randomized trials and systematic reviews assessing different ET catheters (5–6, 11). In the majority of these studies, the Wallace Classic catheter was used as the standard. Its popularity has only been shadowed by its relatively higher rate of difficult transfers, and in some cases failure to navigate the unrelenting cervix, compared with its firmer rivals.

Today, a new generation of competitor catheters have entered the market. They share the softness of the Wallace catheter and incorporate newer technologic advances in their design. Even so, there is limited evidence in the literature on the success of these new rivals compared with the time-tested Wallace catheter. Therefore, in the present study we wished to compare the standard Edwards-Wallace (EW) catheter to the Cook Sydney IVF (SIVF) catheter in a clinical setting in Sweden to determine if a change in policy should be implemented. Before the study, we had routinely used the EW catheter for ET. Our aim was to compare the pregnancy rates, live birth rates, and ease of use (defined as the rate of successful insertion) of the two catheters in IVF treatments.
Materials and methods
This two-center prospective randomized controlled clinical trial was performed to determine if the Cook SIVF catheter performed as well as the standard EW catheter in our IVF programs. The protocol was approved by the Medical Faculty Research Ethics Committees at Lund University and Uppsala University, and all of the women gave their oral and written consent to participate.

Participants
Four hundred consecutive women undergoing IVF/ICSI were recruited from IVF-Kliniken CURA, Malmo, and Carl von Linne Kliniken, Uppsala, Sweden. The study was performed from August 2001 to February 2002. Inclusion criteria were age <40 years and at least two embryos generated from a fresh IVF cycle on the day of ET. Randomization was performed on the day of ET using a computer-generated randomization table with a 1:1 ratio into two groups: Cook SIVF and EW. Operator blinding was deemed unnecessary, because patients were randomized immediately before the transfer, and there is no feasible way of blinding the clinicians to the type of catheter allocation. Even so, clinicians were discouraged from discussing the group allocation with the patients. All patients signing the consent form participated in the study.

Cook Sydney IVF Catheter
The SIVF catheter (K-Jets-7019-SIVF; Cook IVF, Eight Miles Plains, Queensland, Australia) consists of an outer firm and an inner ultrasoft catheter. The outer guiding catheter (17 cm long) is slightly stiff, with a preshaped curve and a rounded bulb tip to help negotiate the cervical canal. It has a depth marker at 4 cm from the tip, which can be pulled back to a second marker at 5 cm. The inner catheter (23 cm long) is made of a soft material with a rounded bullet tip. In general, the inner catheter does not negotiate the cervical canal directly but rather is introduced into the uterine cavity through the outer catheter.

Edwards-Wallace Embryo Replacement Catheter
The Edwards-Wallace catheter (Classic Embryo Replacement Catheter; Smiths Medical, Hythe, Kent, U.K.) design also consists of an outer firm and inner soft catheter. The outer guiding catheter (18 cm long) is straight and made of rigid Teflon. The inner catheter (23 cm long) is
made of a soft polyethylene. In contrast to the Sydney IVF catheter, generally the inner catheter of the Edwards-Wallace is introduced directly through the cervix.

**Ovarian Stimulation Protocol**

Our standard ovarian stimulation protocol has previously been described in detail (12). In brief, the majority of patients were down-regulated with the long GnRH agonist protocol, although a minority of the women were treated with a GnRH antagonist. For ovarian stimulation, recombinant FSH (Gonal F; Laboratories Serono, Geneva, Switzerland; or Puregon; Organon, The Netherlands) was used in daily doses ranging from 75 IU to 450 IU SC depending on individual patient response. Final oocyte maturation was induced with urinary hCG (10,000 IU Profasi SC; Laboratories Serono) when the leading follicles were 18–20 mm in diameter, and ovum pick-up was scheduled 36 hours later.

**Embryo Transfer and Luteal Phase Support**

Embryo transfer was performed 48–72 hours after ovum pick-up by one of four experienced clinicians. A bivalve speculum was inserted into the vagina to expose the cervix. Endovaginal secretions and excess mucus was wiped off with a sterile cotton swab.

The embryo transfers with SIVF were performed in two steps. First, the guiding SIVF catheter was passed through the cervical canal until the bulb tip of the catheter was located just past the internal os. Then the transfer (inner) catheter was loaded with the two best quality embryos available in a continuous column of 20–30 mL culture medium (i.e., no air) and passed through the outer catheter and gently advanced into the uterine cavity. The embryos were expelled at a level of 6–6.5 cm from the external os. The SIVF catheter was withdrawn directly after deposition of embryos and without moving the inner catheter back inside the outer catheter.

In ETs with the EW catheter, the inner catheter of the EW was introduced directly through the cervix and retracted into the outer one for negotiation of the cervical canal only if difficulties were encountered. The outer catheter was used only for gentle manipulation and for stabilization of the inner catheter, when needed, and was advanced just beyond the external os. The embryos were expelled at 6–6.5 cm from the external os.
If the study catheter could not be inserted through the internal os, the cervical canal was straightened with a forceps or tenaculum. If it still was not possible to insert the catheter, a change of catheter was made. Dilatation of the cervical canal was not performed in any case. Obturators for the EW catheter was not used. Ultrasound guidance was not used. In case of insertion failure despite manipulations as stated above, primarily the other study catheter was used, and only if neither of the study catheters could be inserted a complete switch of catheter, to the Frydman Tight-Difficult-Transfer (TDT) catheter, was made. After embryo injection, the catheter was flushed and checked under a stereomicroscope to ascertain that there were no retained embryos. Patients were allowed to ambulate immediately following the transfer procedure. For luteal phase support, natural micronized progesterone pessaries (Apoteksbolaget, Stockholm, Sweden), 400 mg tid, were prescribed for 18 days.

Outcome Measures
The primary outcomes were the rates of clinical pregnancies and live births. Immediately after the transfer, all events that had occurred were recorded, including catheter insertion difficulties. Clinical pregnancy was defined as the presence of a gestational sac on ultrasound at 7 weeks of gestation. Live birth was defined as delivery of a living baby after at least 28 weeks of gestation.

Statistical Analysis
Statistical analysis was performed according to the intention-to-treat principle. All analyses were two sided, and values of \( P<.05 \) were considered to be significant. Continuous variables were compared using the t test or Mann-Whitney U test for parametric and nonparametric data, respectively. Qualitative variables were compared with the chi-squared test or Fisher exact test, accordingly, and the 95% confidence intervals (CI). Odds ratios (ORs) and 95% CIs were calculated to examine the odds of improving clinical outcomes. Clinical and demographic data are also presented as mean ± SD or as frequency distribution for simplicity. Statistical analyses were performed with the aid of StatView (SAS Institute, Cary, NC) and MedCalc (Mariakerke, Belgium) software.
Results

Of all basic variables, only maternal parity differed between the two groups, with more nulliparas in the SIVF group (Table 1). There was no significant difference in number of oocytes retrieved and preembryo quality between the EW and SIVF groups. There was no significant interclinician difference in pregnancy rate (P=.5).

For the primary outcomes there were no significant differences between the clinical pregnancy rate (OR 0.99, 95% CI 0.66–1.47), or live birth rates (OR 1.09, 95% CI 0.72–1.65) between the two catheters (Table 2). The implantation rate (number of gestational sacs divided by number of embryos transferred) was 103/404 (25.5%) with the SIVF catheter and 101/396 (25.5%) with the EW catheter.

Failure to negotiate the cervix, requiring changing the catheter to a either the other study catheter or a firmer alternative (TDT catheter) was more frequently seen with the EW catheter (32/198) than with the Cook catheter (4/202; OR 9.5, 95% CI 3.84–31.55). There was no difference in pregnancy and delivery rate for the actual catheter used, as shown in Table 3.

When comparing failure rates for the EW catheter in relationship to physician, one physician had a statistically significantly higher failure rate (P=.002). However, when excluding this physician from the analysis of insertion failure, the failure rate for the EW catheter was still significantly higher 25/184 (13.6%) compared with the SIVF catheter 4/202 (2%; Fisher exact test P<.0001; OR 7.8, 95% CI 2.6–22.8).

Because the pregnancy rate was lower with the rigid TDT catheter, a sensitivity analysis was performed in easy transfers not requiring the use of the TDT catheter. The clinical pregnancy rates in the groups randomized to SIVF and EW (excluding TDT) were then 40% and 41%, respectively (P=.8).

According to the study protocol, a switch to the other study catheter was performed in the cases of failed catheter insertion, followed by an attempt with the TDT catheter if the second catheter also failed. Among the 32 catheter changes made in women randomized to the EW catheter, the switch to the SIVF catheter was successful in 26 cases, and in the remaining six cases a second switch to the TDT catheter had to be done. The clinical pregnancy rate in women randomized to the EW catheter but successfully changed to SIVF was 11/26 (42%), and in the further switch to the TDT catheter it was 1/6 (17%). In the four cases of
failed transfer in patients randomized to the SIVF catheter, a switch to the EW catheter was successful in one case, whereas a second switch to the TDT catheter had to be performed in the remaining three patients. The pregnancy rate was 1/3 (33%) in patients switched to TDT.
Discussion
This prospective randomized study showed no difference in pregnancy or delivery rate between the EW and SIVF catheters according to an intention-to-treat analysis. The pregnancy rates were 40.4% and 40.1%, respectively, and the delivery rates 31.8% and 33.7%. As a secondary outcome, the rate of insertion failure was studied. The SIVF catheter was successfully inserted through the cervix at first attempt in 98% of cases, whereas the first EW catheter insertion failed in 32 women (16%). All of these 32 women had a second attempt with a SIVF catheter, which was successful in 26 cases, and in the remaining six cases a stiff TDT catheter was successfully inserted. Thus, in the EW group an SIVF catheter was successfully used as a “rescue” catheter in 26/198 (13%) of the women, and this switch did not affect the outcome negatively according to the intention-to-treat analysis.
Although the pregnancy and delivery rates with the actual catheter used (randomized catheter results added with the secondary alternative) were similar in the EW and SIVF groups, it should be emphasized that this result in the SIVF group was accomplished in spite of a higher proportion of difficult transfers. Transfers with the TDT catheter, i.e., the third catheter choice in both groups, resulted in a delivery rate of 2/9 (22%).
Because it is well known that, compared with stiff catheters, a soft catheter performs better in terms of pregnancy rate (5, 6), we thought it was unethical to change directly from a soft to a stiff catheter (e.g., a TDT catheter) in case of insertion failure with the EW or SIVF catheters, when an alternative soft catheter was available. We believe the higher percentage of successful transfers with the SIVF catheter is related to its semifirm design with a bulb-shaped tip with maintained stability and tactile transmission. The EW catheter works very well in easy transfers but had a higher insertion failure rate in the present study. If a stiff obturator had been used for the EW catheter, the insertion failure rate might have been lower. However, for the SIVF catheter no obturator was available on the Scandinavian market at the time of the study, and using an obturator for only one of the catheters would have biased the results.
All clinicians participating in the present trial each had experience with several thousand embryo transfers. Moreover, before the trial, the EW catheter was used routinely, and all of the four clinicians had very
limited experience with the SIVF catheter. Our previous insertion failure rate in the two clinics with the EW catheter was 9% and 10%, respectively, lower than in the current study. An enthusiasm for a new soft catheter might have made us more liberal to replace the EW with SIVF in case of difficulties. After the study period when the SIVF catheter was accepted, the overall insertion failure rate with SIVF has stabilized at approximately 1%, confirming the results from the study.

The present study is the second ever randomized trial comparing the EW and SIVF catheters. McIlveen et al. (13) randomized 150 women undergoing a fresh ET to the EW or SIVF catheters and found no significant difference in pregnancy rates (risk ratio 0.96, 95% CI 0.58–1.58; Fig. 1), but the SIVF was, as in our study, associated with a significantly lower frequency of catheter change or change to an obturator. This is remarkable, because women with a history of difficult embryo transfers were excluded from the study by McIlveen et al. A meta-analysis of the two studies showed similar homogenous results (Fig. 1).

The SIVF catheter was compared with the Tom Cat catheter in a randomized trial by McDonald and Norman (14). In contrast to the two studies comparing SIVF and EW catheters, the SIVF catheter was superior to the Tom Cat catheter regarding pregnancy rate: 29.6% versus 20.5% (OR 1.63, 95% CI 1.14–2.3). The authors speculate that the reasons are the protection of the tip of the inner transfer catheter inside the guiding catheter when inserted through the cervical canal, and the softer tip of the inner catheter causing less trauma to the endometrium. Despite differences in operator experience in favor of the EW catheter in the present study, we accomplished more successful transfers with the SIVF catheter, indicating that the SIVF catheter is user friendly with a short learning curve.

Despite the soft tip of the SIVF catheter, McIlveen et al. (13) noticed that the SIVF catheter tip was blood stained in 37% of cases. We also noticed a high incidence of bloodstained tips in the SIVF catheters, but the rate was not consistently registered. However, blood on the catheter tip did not endanger the chance of pregnancy, according to both studies, and it is possible that contamination of blood on the SIVF catheter is related more to cervical than endometrial trauma.


**Conclusion**

According to the intention-to-treat protocol, there is no significant difference in clinical pregnancy or live birth rates between the EW catheter and the Cook SIVF catheter. Even so, catheter insertion failure was significantly more common with the EW catheter than with the SIVF catheter.
References

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sydney IVF</th>
<th>Edwards Wallace</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>202</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>32.7 ± 3.8</td>
<td>33.4 ± 3.5</td>
<td>P = 0.06</td>
</tr>
<tr>
<td><strong>Primigravida</strong></td>
<td>163</td>
<td>139</td>
<td>P = 0.01</td>
</tr>
<tr>
<td><strong>Rank of cycle</strong></td>
<td>0.7</td>
<td>0.7</td>
<td>P = 0.9</td>
</tr>
<tr>
<td><strong>BMI (mean)</strong></td>
<td>23.8</td>
<td>23.8</td>
<td>P = 0.9</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>31</td>
<td>29</td>
<td>P = 0.8</td>
</tr>
</tbody>
</table>

Table 2: Outcome measures- intention to treat analysis

<table>
<thead>
<tr>
<th></th>
<th>Sydney IVF</th>
<th>Edwards Wallace</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td>202</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical pregnancy rate</strong></td>
<td>81 (40.1%)</td>
<td>80 (40.4%)</td>
<td>O.R = 0.99; 95% CI = 0.66 to 1.47</td>
</tr>
<tr>
<td><strong>Live-birth rate</strong></td>
<td>68 (33.7%)</td>
<td>63 (31.8%)</td>
<td>O.R = 1.09; 95% CI = 0.72 to 1.65</td>
</tr>
</tbody>
</table>

Table 3: Outcome measures- actual catheter used

<table>
<thead>
<tr>
<th></th>
<th>Sydney IVF</th>
<th>Edwards Wallace</th>
<th>TDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td>228</td>
<td>163</td>
<td>9</td>
</tr>
<tr>
<td><strong>Clinical pregnancy rate</strong></td>
<td>91 (40.0%)</td>
<td>68 (41.2%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td><strong>Live-birth rate</strong></td>
<td>76 (33.3%)</td>
<td>53 (32.5 %)</td>
<td>2 (22.2%)</td>
</tr>
</tbody>
</table>
Figure 1: Meta-analysis forest plot comparing the clinical pregnancy and catheter failure rates between the Edwards-Wallace and Cook Sydney IVF catheters.

### 01 Clinical Pregnancy Rate

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>74.62</td>
<td>1.01</td>
<td>[0.68, 1.51]</td>
</tr>
<tr>
<td>Mcilveen 2005</td>
<td>25.38</td>
<td>0.94</td>
<td>[0.47, 1.89]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.00, 0.99 [0.70, 1.41]

Total events: 102 (Wallace Catheters), 104 (Cook Catheters)

Test for heterogeneity: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%

Test for overall effect: Z = 0.03 (P = 0.97)

### 02 Catheter Failure Rate

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>63.36</td>
<td>9.54</td>
<td>[3.31, 27.53]</td>
</tr>
<tr>
<td>Mcilveen 2005</td>
<td>36.64</td>
<td>1.52</td>
<td>[0.25, 9.37]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.00, 6.60 [2.75, 15.88]

Total events: 35 (Wallace Catheters), 6 (Cook Catheters)

Test for heterogeneity: Chi² = 2.97, df = 1 (P = 0.08), I² = 66.3%

Test for overall effect: Z = 4.22 (P < 0.0001)