Optimizing the embryo transfer technique
Abou-Setta, A.M.

Citation for published version (APA):
Chapter 7

Soft versus firm embryo transfer catheters for assisted reproduction: a systematic review and meta-analysis.

Ahmed M. Abou-Setta, Hesham G. Al-Inany, Ragaa T. Mansour, Gamal I. Serour, Mohamed A. Aboulghar.

Abstract

Background: The true impact of the embryo transfer catheter choice on an IVF programme has not been fully examined. We therefore decided to systematically review the evidence provided in the literature so that we may evaluate a single variable in relation to a successful transfer, the firmness of the embryo transfer catheter.

Methods: An extensive computerized search was conducted for all relevant articles published as full text, or abstracts, and critically appraised. In addition, a hand search was undertaken to locate any further trials.

Results: A total of 23 randomized controlled trials (RCT) evaluating the types of embryo transfer catheters were identified. Only ten of these trials, including 4141 embryo transfers, compared soft versus firm embryo catheters. Pooling of the results demonstrated a statistically significantly increased chance of clinical pregnancy following embryo transfer using the soft (643/2109) versus firm (488/2032) catheters [P = 0.01; odds ratio (OR) = 1.39, 95% confidence interval (CI) = 1.08–1.79]. When only the truly RCT were analysed, the results were again still in favour of using the soft embryo transfer catheters [soft (432/1403) versus firm (330/1402)], but with a greater significance (P < 0.00001; OR = 1.49, 95% CI = 1.26–1.77).

Conclusion: Using soft embryo transfer catheters for embryo transfer results in a significantly higher pregnancy rate as compared to firm catheters.

Key words: catheter/ embryo transfer/ ICSI/ IVF/ meta-analysis/ randomized controlled trial
**Background**

Embryo transfer is the final and most crucial step in IVF. About 80% of patients undergoing IVF reach the embryo transfer stage, but only a small proportion of them achieve pregnancy. The pregnancy rate after embryo transfer is dependent upon multiple factors including embryo quality, endometrial receptivity and the technique of the embryo transfer itself (1).

Recently, several surveys have shown that the embryo transfer catheter ranks high as an important, independent factor in the success of an IVF programme. A survey of Australian clinicians rated the type of catheter used as the third most important variable in embryo transfer (2). In addition, a postal survey in the UK found that the type of catheter used was believed to be the fourth most important variable (3).

The ideal embryo transfer catheter should avoid any trauma to the endocervix and/or endometrium as it finds its way into the uterine cavity. Several studies have compared different kinds of catheters for embryo transfer but most of these studies are either observational, retrospective, or are prospective but non-randomized. Even in the few prospective, randomized trials published, the majority had small sample sizes; sizes too small to reach a definite conclusion with statistical soundness. Therefore, the impact of the embryo transfer catheter choice on an IVF programme has been investigated in relatively small samples, albeit the examination of a single factor in reproductive medicine is more reliable when large groups are involved (4, 5). We therefore decided to systematically review the evidence provided in the literature so that we may evaluate a single variable in relation to a successful transfer, the firmness of the embryo transfer catheter.
Materials and methods

Criteria for considering studies for this review
All published, unpublished and ongoing randomized trials reporting data that compares outcomes for women undergoing embryo transfer through the cervical route following IVF, or ICSI using soft compared with firm embryo transfer catheters, were sought in all languages.

Types of outcome measures
The primary outcome measures used for this systematic review were implantation rate (IR), clinical pregnancy rate (CPR) and ongoing/take-home baby rate. The secondary outcomes were ease of transfer (catheter failure rate) and simultaneous occurrence of traumatic events (e.g. use of a tenaculum, stylette, sounding, and/or dilatation). In addition, the presence of blood, mucus and/or retained embryos on the tip of the catheter was evaluated.

Search strategy for identification of studies
A computerized search was conducted using MEDLINE (1978 to present), EMBASE (1980 to present), the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 2, 2005, and the National Research Register [a register of ongoing and recently completed research projects funded by, or of interest to, the UK’s National Health Service (NHS)] as well as entries from the Medical Research Council’s Clinical Trials Register, and details on reviews in progress collected by the NHS Centre for Reviews and Dissemination. The following Medical Subject Headings and text words were used: embryo transfer, embryo transfer technique, embryo transfer catheter, Cook, Erlangen, Frydman DT, Frydman, Gynetics, Rocket, TDT, Tom Cat, Wallace, and randomised controlled trial(s), randomized controlled trial(s) (RCTs).
Furthermore, the reference lists of all known primary studies and review articles were also examined to identify additional relevant citations. In addition, a hand search of the citation lists of relevant publications, review articles, abstracts of major scientific meetings and included studies were searched for trials. Moreover, the reviewers sought ongoing and unpublished trials by contacting experts in the field, and commercial entities.
**Methods of the review**
A standardized data extraction form was developed and piloted for consistency and completeness. Two reviewers (A.M.A.S. and H.G.A.I.) considered trials for inclusion, evaluated methodological quality and extracted trial data independently. Differences in interpretation were resolved by discussion and mutual agreement and refereeing by a third reviewer (R.T.M.). Data management and analysis was then conducted using the Review Manager (RevMan) 4.2 statistical software package. Individual outcome data were included in the analysis if they met the pre-stated criteria. Where possible, data were extracted to allow an intention-to-treat analysis. If data from the trial reports were insufficient or missing, the authors contacted the investigators of individual trials for additional information, in order to perform analyses on an intention-to-treat basis.

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Heterogeneity by visual inspection of the outcome tables and by using the $X^2$-test for heterogeneity with a 10% level of statistical significance was utilized. Where statistical heterogeneity was found, the reviewers looked for an explanation. If studies with heterogeneous results were thought to be comparable, statistical synthesis of the results using a random effects model was undertaken. Furthermore, a meta-regression analysis (subgroup analyses) was undertaken to determine, if possible, the source behind the heterogeneity. In addition, the $I^2$ test was used to attempt at quantifying any apparent inconsistency. An $I^2$ value greater than 50% may be considered substantial hererogeneity.

In the absence of heterogeneity, results were pooled using a fixed effect model, the relative risk and risk difference [and 95% confidence intervals (CI)].

**Description of studies**
During the course of this review, we came across several commercially available embryo transfer catheters. They were divided into two groups: soft or firm, according to the available literature and the experience of the authors.
**Soft embryo transfer catheters**

The Frydman® embryo transfer catheter has a soft 23 cm long inner polyurethane catheter with an external diameter of 1.53 mm with an open end.

The Edwards–Wallace® embryo transfer catheter system set is open-ended and made of polyethylene, and has a firm outer Teflon introducer. It has an 18 or 23 cm long inner silicon catheter with an external diameter of 1.6 mm and an open end.

The Cook® Soft-Pass embryo transfer catheter system consisted of two parts fitted coaxially. The outer sheath of the catheter was 6.8 French size (FR) with an overall length of 17 cm and an inner catheter of 4.4 FR, measuring 23.5 cm. The tip of the inner sheath incorporates an echogenic stainless-steel band embedded circumferentially within a polyethylene sheath to enable its imaging at the time of transabdominal ultrasonogram.

The Cook® Soft-Trans embryo transfer catheter system set consists of a single lumen cannula with a 12.5 cm firm proximal part and a 4.0 cm soft distal part. The transfer catheter is made of an undisclosed soft polyurethane material.

The Cook® Sydney IVF® catheter system set consists of a double lumen catheter set. The guiding (outer) catheter is 19 cm long, has a polycarbonate hub, a bulb tip and the distal end is angled. The transfer (inner) catheter is 23 cm long and the tip is 2.8 French size.

The Gynetics® Delphin embryo transfer catheter is single lumen catheter set, 21 cm in length. It uses a combination of a soft, flexible intrauterine catheter and a solid cervix catheter, but is softer than Gynetics® Emtrac-A embryo transfer catheter.

**Firm embryo transfer catheters**

The Erlangen® embryo transfer catheter consists of an introducing metal cannula (fitted with an obturator) and an insertion catheter. The cannula has an external diameter of 2 mm, and its tip is olive-shaped with a diameter of 3 mm. The silicon movable collar is usually placed 2–3 cm from the tip. The instrument has a length of 25 cm. To facilitate handling, the proximal end of the instrument is provided with a ring to accommodate the operator’s finger. The quality of the steel used for the instrument permits the cannula to be bent to match the individual ‘angle of kink’ between the uterine corpus and the cervix.
The Tom Cat® embryo transfer catheter was initially used for draining the bladder of male cats; hence its name. It is 11.5 mm long and is made of polyethylene. The external and internal diameters of the tip are 1 mm and 0.3 mm respectively. The base is 6 mm in diameter and fits onto a 1 ml disposable syringe.

The TDT® (Tight Difficult Transfer) embryo transfer catheter consists of a single lumen 18 cm long polyethylene/polyprene cannula (Frydman 4.5) and a partly polyethylene, partly metal transfer catheter. The cannula is standard equipped with a malleable metal obturator, allowing bending it into the required curve necessary for passage through the cervical canal.

The Rocket® Embryon embryo transfer catheter is 18 cm in length. The inner transfer catheter is made of polyurethane and the outer sheath is made of white polythene.

The Gynetics® Emtrac-A embryo transfer catheter is a single lumen catheter set 21 cm in length. It uses a combination of a soft, flexible intrauterine catheter and a solid cervix catheter.

A total of 23 prospective RCT evaluating the types of embryo transfer catheters were identified (10 full-text papers, 12 conference abstracts and one unpublished trial comparing different types of embryo transfer catheters). Of these studies, one was excluded because it compared a soft embryo transfer catheter to surgical placement of the embryos in the uterine cavity using a hysteroscope (6). In the remaining studies, only ten trials compared soft versus firm embryo catheters including 4141 embryo transfers (7-16) (Table I). The remaining studies either compared soft versus soft transfer catheters (17-25) or firm versus firm transfer catheters (26-28) (See Figure 1a).

Methodological quality of included studies

The methodological quality of each trial was assessed in terms of randomization, blinding of the patients, sample size, the absence of confounders and the extent of follow-up. Each trial was judged, and given a quality rating as adequate or inadequate: A = adequate, B = unclear, C = inadequate, D = not used. Furthermore, validity scores were given to each item: A = 4, B = 3, C = 2, D = 1 and the total was tabulated (Table II). High quality trials were defined as those receiving >15 points. Moderate quality trials were defined as receiving 10–15 points. Poor quality trials were defined as receiving <10 points.
Furthermore, a funnel plot assessed publication bias, quality and heterogeneity (Figures 2a, b).

Randomization was considered to be proper when computer generated number tables or sealed envelopes were used. Quasi-randomization was considered to be an inadequate form of randomization. As one study used alternate randomization (10) and the randomization was not clear from the manuscript in five studies (8, 9, 12, 14, 16), only four studies described a proper method of randomization (7, 11, 13, 15).

Furthermore, blinding was examined with regards to who was blinded in the trials. All levels were sought and categorized as follows: (i) single blind (the investigator only knew of the allocation), (ii) no blinding (both investigator and participant knew the allocated treatment), (iii) unclear. It is important to note that double blind was not sought since it would be impossible to blind the operator from knowing the type of catheter being used. In all the studies, the exact level of blindness could not be extracted, therefore they were stated as unclear.

Sample size calculations were considered to be proper when the authors of the studies pre-calculated the number needed in each arm prior to starting the trial. This prevents the occurrence of Type II errors. Only two studies (13, 15) undertook sample size calculations.

As for the presence of confounders, for the purpose of this systematic review, confounders included any factors that might have helped to alter the results. These included more than one operator (as pregnancy rates are often operator dependent), testing several factors at the same time (e.g. soft versus firm catheters combined with ultrasound-guided versus clinical touch), unequal characteristics in the two groups (e.g. statistically significant differences in patient age), the transfer of fresh IVF, cryo embryos and/or donor oocytes in the same trial. Four studies (7, 8, 10, 13) showed obvious presence of confounders. Furthermore, the remainder of the studies could not be considered free from confounders since either they were only published as abstracts in conference proceedings and/or the authors did not provide enough information in the text of the published manuscripts.

Finally, quality scores were assigned to each trial for completeness of follow-up. Only three studies (8, 11, 15) completed follow-up until delivery, while the remaining studies were discontinued before follow-up could occur.
Results

Primary outcome measures

Implantation rate
For the implantation rate, data were only available from two studies (8, 14). Using the fixed effect model, there was no statistically significant difference in the chance of embryo implantation following embryo transfer using the soft (103/573) versus firm (60/360) catheters [P = 0.34, odds ratio (OR) = 1.18, 95% CI = 0.84–1.67]. However, there was statistical heterogeneity between the studies (P = 0.0003, I² = 92.5%). Therefore, the random effects model was used for the meta-analysis, but this did not alter the results: soft (103/573) versus firm (60/360) catheters (P = 0.71, OR = 1.28, 95% CI = 0.35–4.72).

In addition, meta-regression analyses were undertaken to determine the source of the heterogeneity. Subgroup analyses were undertaken by excluding the moderate quality study (8) to determine if the heterogeneity was caused by this factor. When Grunert et al. (8) was removed and the results were re-analysed using the fixed effect model, this did alter the overall statistical outcome of the results in favour of the soft catheters: soft (53/170) versus firm (23/154) catheters (P = 0.001, OR = 2.51, 95% CI = 1.45–4.35).

Clinical pregnancy rate
For the clinical pregnancy rate, data were available from all ten studies. Using the fixed effect model, pooling of the results demonstrated a statistically increased chance of clinical pregnancy following embryo transfer using the soft (643/2109) versus firm (488/2032) catheters (P < 0.00001, OR = 1.39, 95% CI = 1.20–1.59). Nevertheless, there was significant statistical heterogeneity between the studies (P = 0.003, I² = 63.4%).

In order to nullify this heterogeneity, the random effects model was utilized. Pooling of the results still demonstrated a significantly increased chance of clinical pregnancy following embryo transfer using the soft versus firm catheters (P = 0.01, OR = 1.39, 95% CI = 1.08–1.79).

In addition, meta-regression (subgroup analyses) was undertaken to determine the source of the heterogeneity. Subgroup analyses were undertaken by excluding one study at a time to determine if the heterogeneity was caused by one factor, or if multiple factors were involved. When Ghazzawi et al. (10) was removed and the results were
re-analysed using the fixed effect model, the heterogeneity was nullified 
(P = 0.15, I² = 32.9%). However, this did not alter the overall statistical 
outcome of the results: soft (612/1949) versus firm (440/1872) 
catheters, but on the contrary it increased the statistical gap between 
the two groups (P < 0.00001, OR = 1.49, 95% CI = 1.49–1.73). 
Furthermore, when only the fresh IVF procedure (i.e. excluding frozen 
replacement and donor cycles) were analysed, using the random effect 
model, the results were still in favour of using the soft embryo transfer 
catheters [soft (613/1964) versus firm (466/1882) catheters] (P = 0.02, 
OR = 1.38, 95% CI = 1.07–1.79). 
In addition, when only the true RCT were analysed, using the fixed 
effect model, the results were again still in favour of using the soft 
embryo transfer catheters [soft (432/1403) versus firm (330/1402) 
catheters] (P < 0.00001, OR = 1.49, 95% CI = 1.26–1.77).

_Ongoing pregnancy/take-home baby rate_
For the ongoing pregnancy/take-home baby rate, data were available 
from three studies (8, 11, 15). Using the fixed effect model, pooling of 
the results demonstrated a significantly increased ongoing pregnancy/
take-home baby rate following embryo transfer using the soft (290/978) 
versus firm (240/948) catheters (P = 0.03, OR = 1.25, 95% CI = 1.02–
1.53).

**Secondary outcome measures**

_Catheter failure_
For the failure rate using the assigned catheter, data were available 
from five studies (7, 11, 12, 13, 15). Using the random effect model, 
pooling of the results demonstrated a trend towards statistical 
significance, but this increased chance of failure following embryo 
transfer using the soft (100/1563) versus firm (11/1571) catheters did 
not reach statistical significance (P = 0.06, OR = 7.51, 95% CI = 0.94–
60.11).

_Traumatic events_
Data pertaining to traumatic events during the embryo transfer, use of a 
tenaculum, stylette, sounding and/or dilatation, were recorded in three 
studies (7, 10, 13). Using the random effects model, pooling of the 
overall results demonstrated a significantly increased chance of
traumatic events during embryo transfer using the soft (229/684) versus firm (104/686) catheters (P < 0.0001, OR = 5.40, 95% CI = 1.28–222.84).

For the rate of using a tenaculum, data were available from two studies (7, 13). Using the fixed effect model, pooling of the results demonstrated a statistically increased chance of tenaculum use following embryo transfer using the soft (84/524) versus firm (62/526) catheters (P = 0.02, OR = 1.61, 95% CI = 1.07–2.43).

For the rate of using a stylette in corporation with the embryo transfer, data were available from only one study (13), which did not use a stylette in any of the cases.

For the rate of using sounding, data were available from two studies (10, 13). Using the fixed effect model, pooling of the results demonstrated a significantly increased chance of need for sounding during embryo transfer using the soft (36/484) versus firm catheters (6/486) (P < 0.0001, OR = 7.45, 95% CI = 3.04–18.26).

For the rate of using dilatation, data were available from three studies (7, 10, 13). Using the fixed effect model, pooling of the results demonstrated a significantly increased chance of need for dilatation during embryo transfer using the soft (45/684) versus firm catheters (16/686) (P = 0.0002, OR = 3.07, 95% CI = 1.70–5.54).

**Catheter tip**

Data pertaining to another important aspect of embryo transfer is the catheter tip. Blood, mucus, and the retention of embryos at the tip of the embryo transfer catheters were described in four studies (7, 10, 12, 13). Using the random effects model, pooling of the overall results demonstrated a significantly increased chance of these events during embryo transfer using the soft (163/1328) versus firm (55/1320) catheters (P < 0.02, OR = 5.63, 95% CI = 1.32–24.02).

Blood on the tip of the catheter was described in two studies (7, 13). Using the fixed effect model, there was no significant difference between the two groups: soft (42/524) versus firm (39/526) (P = 0.37, OR = 1.10, 95% CI = 0.67–1.79).

Mucus on the tip of the catheter was described in one study (10). There was a significantly increased chance of finding mucus on tip of the catheter in the soft catheter group (65/160) when compared with the firm catheter group (0/160) (P = 0.0002).
Retained embryos were described in three studies (10, 12, 13). Using the random effects model, there was a trend towards increased likelihood of retained embryos using the soft catheters (56/644) versus firm catheters (16/634), but this did not reach statistical significance (P = 0.05, OR = 4.52, 95% CI = 1.01–20.28).
Discussion
Although most patients who undergo assisted procreation, via IVF or ICSI, reach the embryo transfer stage and have embryos of good quality available for transfer, embryo implantation remains the rate-limiting step in the success of this form of therapy. The main factors that affect embryo implantation are uterine receptivity, embryo quality, and efficiency of the embryo transfer procedure. The aim must be to transfer the embryos with a high degree of reliability atraumatically.

There have been many publications over the years discussing ways of improving embryo transfer and hopefully pregnancy rates. Multiple factors may affect the success of uterine embryo transfer including the experience of the physician (29), the use of ultrasound guidance (30, 31), the ease of the procedure (32), the presence or absence of blood on the catheter (33) and bacterial contamination of the catheter (34). In addition, other factors concerning embryo transfer that might affect the chance for an ongoing pregnancy have been identified, such as the use of cervical introducers or obturators (10), the value of resting after transfer (35), the position of embryo insertion in the uterus (36, 37), flushing of the cervical canal to remove mucus (38), microbiological factors in terms of the local flora (39) and retention of embryos in the catheter (40, 41). Since it would be difficult to compare several factors at the same time, we decided to concentrate on one factor, the firmness of the embryo transfer catheter, as a possible cause of limiting the success of the embryo transfer.

One crucial factor that has not gained enough attention and scrutiny as a deciding factor is catheter technology. There is no conclusive evidence for the preferred use of any particular catheter and previous randomized trials have been too small to show significant differences in pregnancy rates. Moreover, some authors have concluded that the success rate of embryo transfers is not even influenced by the choice of the embryo transfer catheter used (42). Therefore the catheter choice has been mainly left to personal choice, availability and implied cost-effectiveness.

Several embryo transfer catheters are commercially available. All are mainly composed of non-toxic plastics and/or metal, but vary in length, calibre, location of the distal port (end- or side-loading), and degree of stiffness and malleability. These catheters can be subdivided by the material they are made of (i.e. metal, hard or soft plastics) and whether
they are equipped with, or without, an introducing cannula that facilitates the transfer procedure.

In this systematic review, soft embryo transfer catheters overall performed better compared with the firm embryo transfer catheters. Even though the implantation rate seemed to be questionable in favour of the soft catheters, there is definitely a strong statistical trend for clinical pregnancies using the soft catheters. This was apparent in the clinical pregnancy and ongoing pregnancy/take-home baby rate.

One theory why the softer catheters produce better results is built on decreasing the trauma to the endometrium. The softer the materials used, the lesser the chance for damage to the endometrium and the lesser the chance for uterine contractions. The soft transfer catheters follow the natural curvature of the uterine cavity better than the firmer catheters, possibly reducing the risk of burrowing into the posterior endometrium in the anteflexed uterus, or stimulating uterine junctional zone contractions. This is supported by the ultrasound-detected endometrial changes following intrauterine insemination, which differ between firm and soft catheters (43). The Tom Cat catheter was shown to cause significantly more trauma to the endometrium than did the Edwards–Wallace catheter. In addition, a retrospective analysis of 518 embryo transfers, comparing five catheters [firm (Tefcat, Tom Cat, Norfolk) and soft (Frydman, Wallace)] found that a soft catheter was associated with higher pregnancy rates than a firm catheter (44). The results of this meta-analysis confirm that this increased pregnancy rate is both statistically and clinically significant.

In contrast, the soft catheters were also associated with a higher degree of failure to negotiate the cervix and therefore the simultaneous occurrence of traumatic events (use of tenaculum, stylette, sounding and/or dilatation). In addition, they had a higher rate of blood, mucus and retained embryos at the tip of the embryo transfer catheter, but overall these events did not seem to alter the pregnancy rates.

Passing soft catheters through the cervical canal is often difficult and even sometimes impossible. In a series of 876 embryo transfer procedures by Wood et al. (45), 1.3% were impossible, 3.2% were very difficult (requiring manipulation for >5 min or cervical dilatation) and 5.6% were difficult (requiring manipulation) to perform. In another study by Mansour et al. (46), soft catheters resulted in the highest rate (37.6%) of difficult embryo transfer with the consequences of lowering
the pregnancy rate. Furthermore, difficult transfers have been associated with lower pregnancy rates (46, 47). Our review supports the theory that softer catheters are associated with a higher incidence of difficult transfers, but not negatively affecting the pregnancy rates. Since difficult transfers have been associated with a poorer outcome than easy transfer, it would be useful to directly examine the uterine cavity for any lesions post-transfer. Unfortunately, this would not be possible without ultimately affecting the pregnancy rate. Therefore indirect measures of the degree of difficulty are utilized. These include patient discomfort during the procedure, the need for use of a tenaculum, stylette, sounding and/or cervical dilatation, and the presence of blood on the catheter post-transfer.

Different approaches have been described in cases of difficult embryo transfers with varying success rates (46, 48-50). A commonly used initial approach is to negotiate the cervix using the outer sheath of the catheter, with its inner noodle withdrawn (51). Once the uterine cavity is entered, the inner noodle is used to deposit the embryos, taking care to avoid the fundus. Even though this technique works efficiently in certain situations, in others it is not sufficient. Therefore more invasive and potentially traumatic events are sometimes undertaken by clinicians to overcome the problematic cervix. These include the use of a tenaculum, stylette, sounding and/or cervical dilatation. Overall these events have been associated with increased uterine junctional zone contractions and a decreased pregnancy rate (32, 47, 49, 52). Alternatively, the cervical route may be bypassed and the embryos may be transferred transmyometrially into the uterine cavity using the ‘Towako method’ (48).

Another tell-tale sign of a difficult transfer is the post-transfer presence of blood on the transfer catheter. Amongst clinicians, the absence of blood on the catheter or cannula is ranked high as an important factor towards success (2). This opinion is supported by literature reports in which the presence of blood on the transfer catheter has been associated with lower pregnancy rates (52, 33). In addition, Perin et al. (26) found that contamination of the catheter with blood and mucus accounted for significantly lower implantation and clinical pregnancy rates. In our review, even though these events were present more
frequently with the softer catheters, it did not seem to drastically alter the outcome. Finally, the incidence of retained embryos was shown in this review to be higher with the softer embryo catheters. The role of retained embryos in decreasing the pregnancy rate is controversial with some studies claiming a negative effect (52) and other claiming no such effect (53, 33). Again, we could not confirm that the increased incidence of retained embryos with the soft catheters had any great influence on the overall outcome.

In conclusion, the results of this study clearly indicate that the type of embryo transfer catheter contributes significantly to the success rate of an IVF programme. Soft catheters rather than firm catheters are associated with better pregnancy rate, even though a soft catheter is also associated with more traumatic events. More adequately powered, high quality RCT are needed to support the development of an ideal soft catheter that finds its way to the cavity with minimal failure rate.
Acknowledgements
The authors would like to thank all the corresponding authors that were contacted for more information and provided us with assistance. Special thanks to Dr Janelle McDonald, Dr Robert Norman and Dr Raja Karaki, whose direct assistance has helped to increase the accuracy of this systematic review by providing us with missing information.
References


Table I. Review table of the prospective, randomized, controlled studies analysed, comparing soft (SC) versus firm (FC) embryo transfer catheters

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Catheter type and firmness</th>
<th>Sample size</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edwards–Wallace catheter (SC)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frydman catheter (SC)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tight Difficult Transfer (TDT) catheter (FC)</td>
<td>100</td>
<td>Random number table</td>
</tr>
<tr>
<td></td>
<td>Tight Difficult Transfer (TDT) catheter (FC) + ultrasound-guided</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Wisanto et al., 1989</td>
<td>Edwards–Wallace catheter (SC)</td>
<td>49</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>Cook catheter (SC)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frydman DT catheter (FC)</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Grunert et al., 1998</td>
<td>Gynetics Delphin catheter (SC)</td>
<td>113</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>Gynetics Emtrac-A catheter (FC)</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Amorocho et al., 1999</td>
<td>Edwards–Wallace catheter (SC)</td>
<td>160</td>
<td>Alternative randomization</td>
</tr>
<tr>
<td></td>
<td>Erlangen metal catheter (FC)</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Ghazzawi et al., 1999</td>
<td>Edwards–Wallace catheter (SC)</td>
<td>240</td>
<td>Dark sealed envelopes</td>
</tr>
<tr>
<td></td>
<td>Tight Difficult Transfer (TDT) catheter (FC)</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>Catheter type and firmness</td>
<td>Included studies</td>
<td>Randomization</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>160</td>
<td>Edwards–Wallace catheter (SC)</td>
<td>Lavery et al., 2001</td>
<td>Not determined</td>
</tr>
<tr>
<td>148</td>
<td>Rocket embryo transfer catheter (FC)</td>
<td></td>
<td>Computer-generated</td>
</tr>
<tr>
<td>326</td>
<td>Cook catheter (SC)</td>
<td>McDonald and Norman, 2002</td>
<td>Not determined</td>
</tr>
<tr>
<td>324</td>
<td>Tom Cat catheter (FC)</td>
<td></td>
<td>Random number table</td>
</tr>
<tr>
<td>58</td>
<td>Cook SIVF 6019 catheter (SC)</td>
<td>Mortimer et al., 2002</td>
<td>Not determined</td>
</tr>
<tr>
<td>60</td>
<td>Tom Cat catheter (FC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>639</td>
<td>Tight Difficult Transfer (TDT) catheter (FC)</td>
<td>Van Weering et al., 2002</td>
<td></td>
</tr>
<tr>
<td>657</td>
<td>Cook K-soft 5000 ‘soft trans universal’ set (SC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>Edwards–Wallace catheter (SC)</td>
<td>Foutouh et al., 2003</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>Rocket embryo transfer catheter (FC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Randomization (4)</td>
<td>Sample size (4)</td>
<td>Blinding (4)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Wisanto et al., 1989</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Grunert et al., 1998</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Amorocho et al., 1999</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ghazzawi et al., 1999</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Curfs et al., 2001</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lavery et al., 2001</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>McDonald and Norman, 2002</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Study</td>
<td>Total score (20)</td>
<td>Follow-up (4)</td>
<td>Confounders (4)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Mortimer et al., 2002</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Van Weering et al., 2002</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Foutouh et al., 2003</td>
<td></td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 1. Quorum flow diagram.

Potentially relevant RCTs identified and screened for retrieval (n=21)

RCTs excluded, with reasons (n=1)

RCTs retrieved for more detailed evaluation (n=20)

RCTs excluded, with reasons (n=10)

Potentially appropriate RCTs to be included in the meta-analysis (n=10)

RCTs excluded from meta-analysis, with reasons (n=0)

RCTs included in meta-analysis (n=10)

RCTs withdrawn, by outcome, with reasons (n=0)

RCTs with usable information, by outcome (n=10)
Figure 2. Funnel plots comparing soft vs firm ET catheters for all RCTs (a) and for the truly RCTs (b).
Figure 3. Meta-analysis of clinical pregnancy rates for all RCTs (random effects model), Truly RCTs (fixed effect model) and fresh IVF cycles only (random effects model.)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Soft Embryo Catheter n/N</th>
<th>Firm Embryo Catheter n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisanto 1989</td>
<td>50/200</td>
<td>20/200</td>
<td>3.93 [1.23, 3.42]</td>
<td></td>
<td>2.05 [1.70, 2.42]</td>
</tr>
<tr>
<td>Grunert 1998</td>
<td>35/99</td>
<td>20/51</td>
<td>2.71 [0.42, 2.42]</td>
<td></td>
<td>1.81 [1.12, 2.42]</td>
</tr>
<tr>
<td>Amorcho 1999</td>
<td>45/113</td>
<td>27/101</td>
<td>3.42 [1.02, 3.24]</td>
<td></td>
<td>3.89 [0.33, 0.94]</td>
</tr>
<tr>
<td>Ghazzawi 1999</td>
<td>31/160</td>
<td>48/160</td>
<td>3.89 [0.56, 0.94]</td>
<td></td>
<td>1.25 [0.87, 1.79]</td>
</tr>
<tr>
<td>Curfs 2001</td>
<td>113/240</td>
<td>100/240</td>
<td>3.89 [0.56, 0.94]</td>
<td></td>
<td>1.25 [0.87, 1.79]</td>
</tr>
<tr>
<td>Lavery 2001</td>
<td>77/160</td>
<td>34/148</td>
<td>3.78 [0.59, 1.71]</td>
<td></td>
<td>1.63 [1.14, 2.33]</td>
</tr>
<tr>
<td>McDonald 2002</td>
<td>96/324</td>
<td>67/326</td>
<td>5.97 [0.87, 1.79]</td>
<td></td>
<td>2.38 [1.30, 4.04]</td>
</tr>
<tr>
<td>Mortimer 2002</td>
<td>31/60</td>
<td>16/58</td>
<td>3.53 [0.87, 1.79]</td>
<td></td>
<td>2.11 [1.30, 4.04]</td>
</tr>
<tr>
<td>Van Weering 2002</td>
<td>173/639</td>
<td>135/657</td>
<td>6.49 [1.11, 1.86]</td>
<td></td>
<td>2.34 [1.15, 4.79]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2109</td>
<td>2032</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 643 (Soft Embryo Catheter), 488 (Firm Embryo Catheter)</td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 2.56 (P = 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

02 Subgroup Analysis (only Truly RCTs)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Soft Embryo Catheter n/N</th>
<th>Firm Embryo Catheter n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Truly RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curfs 2001</td>
<td>113/240</td>
<td>100/240</td>
<td>2.41 [1.25, 1.79]</td>
<td></td>
<td>1.25 [0.87, 1.79]</td>
</tr>
<tr>
<td>Van Weering 2002</td>
<td>173/639</td>
<td>135/657</td>
<td>6.87 [1.11, 1.86]</td>
<td></td>
<td>2.34 [1.15, 4.79]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1403</td>
<td>1423</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 432 (Soft Embryo Catheter), 330 (Firm Embryo Catheter)</td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 4.39 (P = 0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

03 Clinical PR (fresh IVF only)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Soft Embryo Catheter n/N</th>
<th>Firm Embryo Catheter n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Clinical PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grunert 1998</td>
<td>35/99</td>
<td>20/51</td>
<td>2.71 [0.42, 2.42]</td>
<td></td>
<td>1.81 [1.12, 2.42]</td>
</tr>
<tr>
<td>Amorcho 1999</td>
<td>45/113</td>
<td>27/101</td>
<td>3.42 [1.02, 3.24]</td>
<td></td>
<td>3.89 [0.33, 0.94]</td>
</tr>
<tr>
<td>Ghazzawi 1999</td>
<td>31/160</td>
<td>48/160</td>
<td>3.89 [0.56, 0.94]</td>
<td></td>
<td>1.25 [0.87, 1.79]</td>
</tr>
<tr>
<td>Curfs 2001</td>
<td>113/240</td>
<td>100/240</td>
<td>3.89 [0.56, 0.94]</td>
<td></td>
<td>1.25 [0.87, 1.79]</td>
</tr>
<tr>
<td>Lavery 2001</td>
<td>77/160</td>
<td>34/148</td>
<td>3.78 [0.59, 1.71]</td>
<td></td>
<td>1.63 [1.14, 2.33]</td>
</tr>
<tr>
<td>McDonald 2002</td>
<td>96/324</td>
<td>67/326</td>
<td>5.97 [0.87, 1.79]</td>
<td></td>
<td>2.38 [1.30, 4.04]</td>
</tr>
<tr>
<td>Mortimer 2002</td>
<td>31/60</td>
<td>16/58</td>
<td>3.53 [0.87, 1.79]</td>
<td></td>
<td>2.11 [1.30, 4.04]</td>
</tr>
<tr>
<td>Van Weering 2002</td>
<td>173/639</td>
<td>135/657</td>
<td>6.49 [1.11, 1.86]</td>
<td></td>
<td>2.34 [1.15, 4.79]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1964</td>
<td>1882</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 613 (Soft Embryo Catheter), 466 (Firm Embryo Catheter)</td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 2.48 (P = 0.01)</td>
<td></td>
</tr>
</tbody>
</table>