

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

Ahmed M.Abou-Setta^{1,3}, Hesham G.Al-Inany^{1,2}, Ragaa T.Mansour¹, Gamal I.Serour¹
and Mohamed A.Aboulghar^{1,2}

¹The Egyptian IVF–ET Center, 3, Street 161, Hadayek El Maadi, Cairo 11431 and ²The Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt

³To whom correspondence should be addressed: E-Mail: abousetta_md@hotmail.com; ivf@link.net

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

Introduction

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 (Mansour and Aboulghar, 2002).

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 (Kovacs, 1999). In addition, a postal survey in the UK found that the type of catheter used was believed to be the fourth most important variable (Salha *et al.*, 2001).

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 (Templeton *et al.*, 1996; Ramsay, 1999). 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

*Part of this manuscript was presented orally during the European Society of Human Reproduction and Endocrinology's 2005 Annual Meeting (Copenhagen, Denmark).

(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 χ^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 heterogeneity.

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/polyprrene 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 (Sweet *et al.*, 1998). In the remaining studies, only ten trials compared soft versus firm embryo catheters including 4141 embryo transfers (Wisanto *et al.*, 1989; Grunert *et al.*, 1998; Amorcho *et al.*, 1999; Ghazzawi *et al.*, 1999; Curfs *et al.*, 2001; Lavery *et al.*, 2001; McDonald

and Norman, 2002; Mortimer *et al.*, 2002; Van Weering *et al.*, 2002; Foutouh *et al.*, 2003) (Table I). The remaining studies either compared soft versus soft transfer catheters (al-Shawaf *et al.*, 1993; Mayer *et al.*, 1999; Boone *et al.*, 2001; Karande *et al.*, 2002; Levi-Setti *et al.*, 2002; Saldeen *et al.*, 2003; McIlveen *et al.*, 2004; Taylor *et al.*, 2005; Lashen, unpublished data) or firm versus firm transfer catheters (Perin, 1999; Meriano *et al.*, 2000; Schiewe *et al.*, 2001). (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 (Ghazzawi *et al.*, 1999) and the randomization was not clear from the manuscript in five studies (Grunert *et al.*, 1998; Amorcho *et al.*, 1999; Lavery *et al.*, 2001; Mortimer *et al.*, 2002; Foutouh *et al.*, 2003), only four studies described a proper method of randomization (Wisanto *et al.*, 1989; Curfs *et al.*, 2001; McDonald and Norman, 2002; Van Weering *et al.*, 2002).

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 (McDonald and Norman, 2002; van Weering *et al.*, 2002) 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

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

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

Table II. Review table of the validity scores for the included studies

Study	Randomization (4)	Sample size (4)	Blinding (4)	Confounders (4)	Follow-up (4)	Total score (20)
Wisanto <i>et al.</i> , 1989	4	1	3	1	1	10
Grunert <i>et al.</i> , 1998	3	1	3	1	4	12
Amorcho <i>et al.</i> , 1999	3	1	3	4	1	12
Ghazzawi <i>et al.</i> , 1999	2	1	3	1	1	8
Curfs <i>et al.</i> , 2001	4	1	3	4	4	16
Lavery <i>et al.</i> , 2001	3	1	3	4	1	12
McDonald and Norman, 2002	4	4	3	1	1	13
Mortimer <i>et al.</i> , 2002	3	1	3	4	1	12
Van Weering <i>et al.</i> , 2002	4	4	3	4	4	19
Foutouh <i>et al.</i> , 2003	3	1	3	4	1	12

Quality rating of included studies. A = adequate (4), B = unclear (3), C = inadequate (2), D = not used (1).

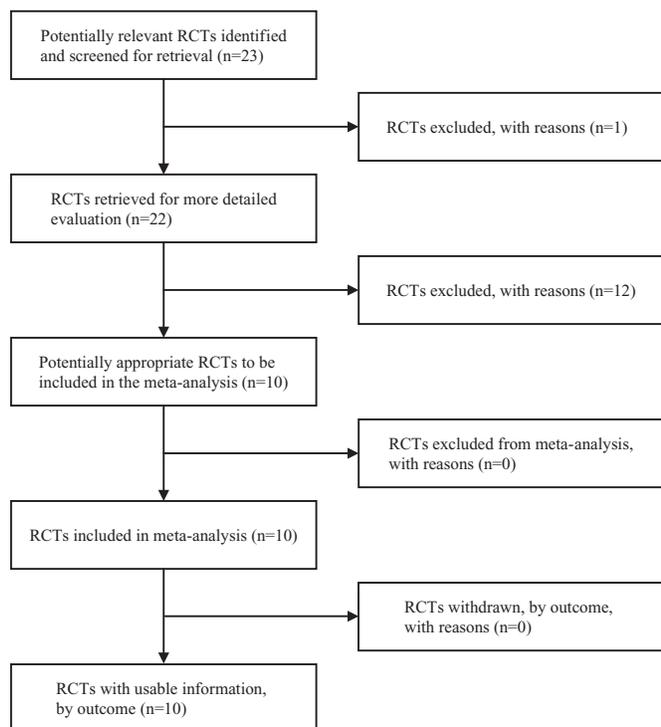


Figure 1. Quorum flow diagram.

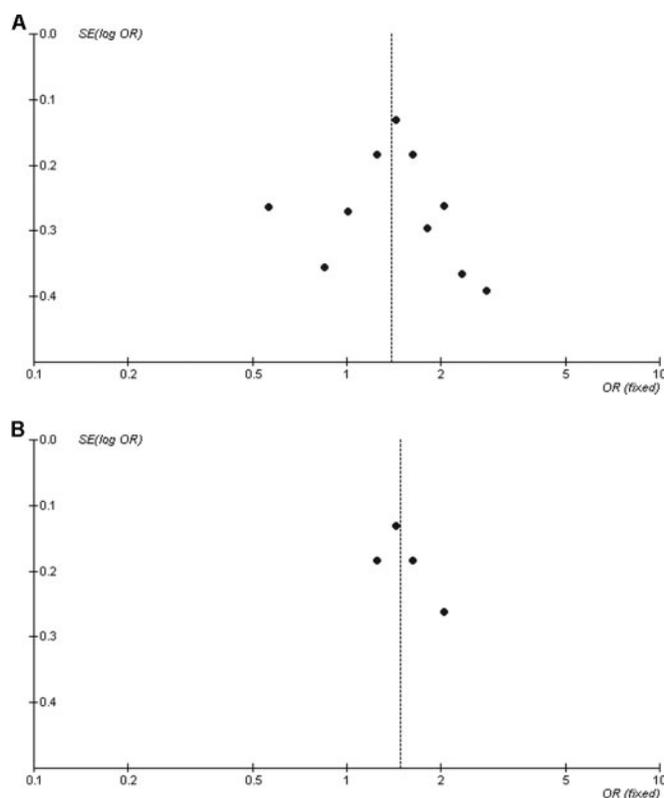


Figure 2. Funnel plots comparing soft vs firm ET catheters for all RCTs (a) and for the truly RCTs (b).

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 (Wisanto *et al.*, 1989; Grunert *et al.*, 1998; Ghazzawi *et al.*, 1999; McDonald and Norman, 2002) 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 (Grunert *et al.*, 1998; Curfs *et al.*, 2001; van Weering *et al.*, 2002) 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 (Grunert *et al.*, 1998; Mortimer *et al.*, 2002). 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 ($P = 0.0003$; $I^2 = 92.5\%$). 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 (Grunert *et al.*, 1998) to determine if the heterogeneity was caused by this factor. When Grunert *et al.* (1998) 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 ($P = 0.003$; $I^2 = 63.4\%$).

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.* (1999) was removed and the results were re-analysed using the fixed effect model, the heterogeneity was nullified ($P = 0.15$; $I^2 = 32.9\%$). However, this did not alter the overall statistical outcome of the results: soft (612/1949) versus firm (440/1872) catheters, but on

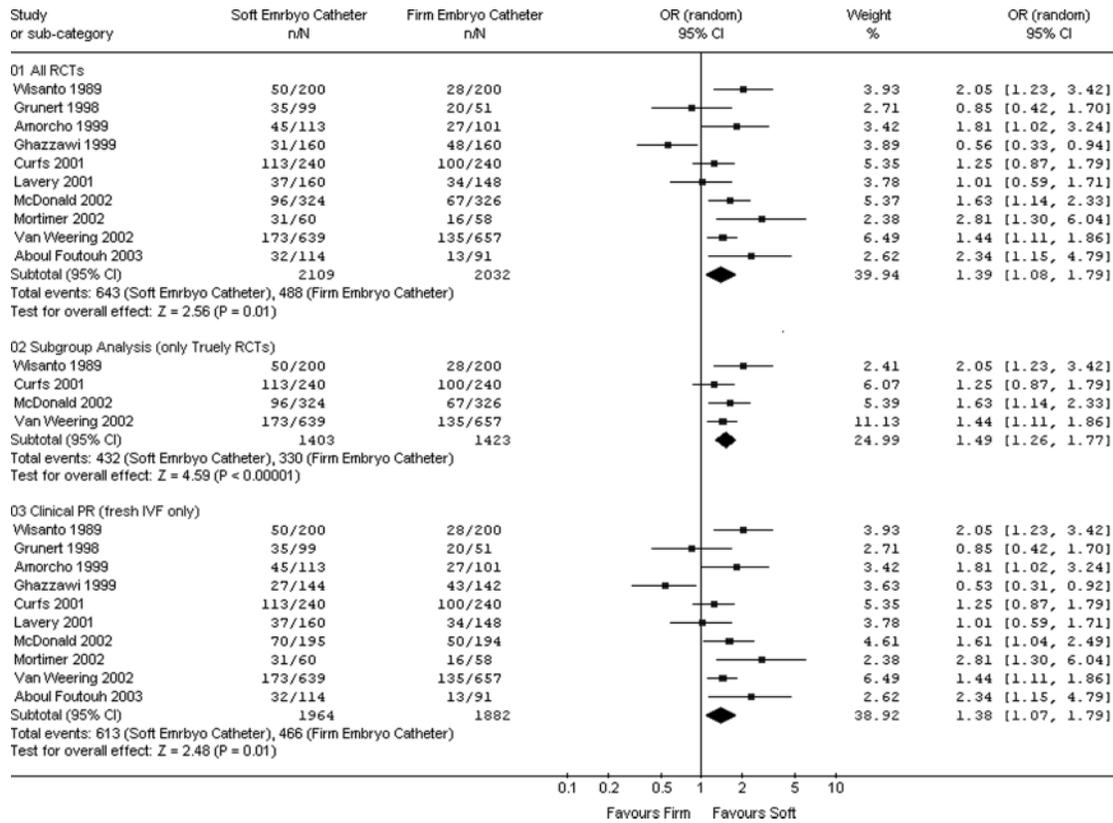


Figure 3. Meta-analysis of clinical pregnancy rates for all RCTs (random effects model), Truly RCTs (fixed effect model) and fresh IVF cycles only (random effects model.)

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 (Grunert *et al.*, 1998; Curfs *et al.*, 2001; Van Weering *et al.*, 2002). 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 (Wisanto *et al.*, 1989; Curfs *et al.*, 2001; Lavery *et al.*, 2001; McDonald and Norman, 2002; Van Weering *et al.*,

2002). 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 (Wisanto *et al.*, 1989; Ghazzawi *et al.*, 1999; McDonald and Norman, 2002). 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 (Wisanto *et al.*, 1989; McDonald and Norman, 2002). 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 (McDonald and Norman, 2002), which did not use a stylette in any of the cases.

For the rate of using sounding, data were available from two studies (Ghazzawi *et al.*, 1999; McDonald and Norman, 2002). 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 (Wisanto *et al.*, 1989; Ghazzawi *et al.*, 1999; McDonald and Norman, 2002). 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 (Wisanto *et al.*, 1989; Ghazzawi *et al.*, 1999; Lavery *et al.*, 2001; McDonald and Norman, 2002). 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 (Wisanto *et al.*, 1989; McDonald and Norman, 2002). 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 (Ghazzawi *et al.*, 1989). 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 (Ghazzawi *et al.*, 1999; Lavery *et al.*, 2001; McDonald and Norman, 2002). 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 (Lu, 1999), the use of ultrasound guidance (Buckett, 2003; Sallam and Sadeek, 2003), the ease of the procedure (Lesny *et al.*, 1998), the presence or absence of blood on the catheter (Goudas *et al.*, 1998) and bacterial contamination of the catheter (Egbase *et al.*, 1996). 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 (Ghazzawi *et al.*, 1999), the value of resting after transfer (Woolcott and Stanger, 1997), the position of embryo insertion in the uterus (Yovich *et al.*, 1985; Waterstone *et al.*, 1991), flushing of the cervical canal to remove mucus (Sallam *et al.*, 2000), microbiological factors in terms of the local flora (Ralph *et al.*, 1999) and retention of embryos in the catheter (Friedler *et al.*, 1993; Moore *et al.*, 2000). 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 (Diedrich *et al.*, 1989). 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 ante-flexed 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 (Lavie *et al.*, 1997). 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 (Wood *et al.*, 2000). 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.* (1985), 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.* (1990), 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 (Mansour *et al.*, 1990; Lesny *et al.*, 1998). 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 (Mansour *et al.*, 1990; Kato *et al.*, 1993; Groutz *et al.*, 1997; Tur-Kaspa *et al.*, 1998). A commonly used initial approach is to negotiate the cervix using the outer sheath of the catheter, with its inner noodle withdrawn (Glass *et al.*, 2000). 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 (Visser *et al.*, 1993; Groutz *et al.*, 1997; Lesny *et al.*, 1998, 1999). Alternatively, the cervical route may be bypassed and the embryos may be transferred transmyometrially into the uterine cavity using the 'Towako method' (Kato *et al.*, 1993).

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 (Kovacs, 1999). This opinion is supported by literature reports in which the presence of blood on the transfer catheter has been associated with lower pregnancy rates (Visser *et al.*, 1993; Goudas *et al.*, 1998). In addition, Perin *et al.* (1999) 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 (Visser *et al.*, 1993) and other claiming no such effect (Nabi *et al.*, 1997; Goudas *et al.*, 1998). 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

- al-Shawaf T, Dave R, Harper J, Linehan D, Riley P and Craft I (1993) Transfer of embryos into the uterus: how much do technical factors affect pregnancy rates? *J Assist Reprod Genet* 10,31–36.
- Amorcho B, Gomez E, Pontes L, Campos I and Landeras J (1999) Does the selection of catheter for embryo transfer affect the success rate of an ART unit? [abstract] 15th Annual Meeting of the ESHRE (Tours, France), 1999. *Hum Reprod* 14(Suppl 1)205.
- Boone WR, Johnson JE, Blackhurst DM and Crane MM 4th (2001) Cook versus Edwards–Wallace: are there differences in flexible catheters? *J Assist Reprod Genet* 18,15–17.
- Buckett WM (2003) A meta-analysis of ultrasound-guided versus clinical touch embryo transfer. *Fertil Steril* 80, 1037–1041.
- Curfs MHJM, Cleine JH, van Kamp AA, Kruse-Blankestijn ME, Hondelink MN and Leerentveld RA (2001) Comparison of the Wallace versus TDT embryo-transfer catheter: a prospective, randomized study. Third Biennial Alpha Conference, September 8–11, 2001, New York, New York, USA. *Reprod Biomed Online* : 3(Suppl 1).
- Diedrich K, Van der ven H, Al-Hasani S and Krebs D (1989) Establishment of pregnancy related to embryo transfer techniques after in-vitro fertilization. *Hum Reprod* 4(Suppl 1),111–114.
- Egbase PE, al-Sharhan M, al-Othman S, al-Mutawa M, Udo EE and Grudzinskas JG (1996) Incidence of microbial growth from the tip of the embryo transfer catheter after embryo transfer in relation to clinical pregnancy rate following in-vitro fertilization and embryo transfer. *Hum Reprod* 11,1687–1689.
- Foutouh IA, Youssef M, Tolba M, Rushdi M, Nakieb A and Meguid WA (2003) Does embryo transfer catheter type affect pregnancy rate? *Middle East Fertil Soc J* 8,154–158.
- Friedler S, Lewin A and Schenker JG (1993) Methodology of human embryo transfer following assisted reproduction. *J Assist Reprod Genet* 10,393–404.
- Ghazzawi IM, Al-Hasani S, Karaki R and Sousa S (1999) Transfer technique and catheter choice influence the incidence of transcervical embryo expulsion and the outcome of IVF. *Hum Reprod* 14,677–682.
- Glass KB, Green CA, Fluker MR, Schoolcraft WB, McNamee PI, Meldrum DR (2000) Multicenter randomized controlled trial of cervical irrigation at the time of embryo transfer. (abstract no. O-085) *Fertil Steril* 74 (Suppl 1) S31.
- Goudas VT, Hammit DG and Damario MA (1998) Blood on the embryo transfer catheter is associated with decreased rates of embryo implantation and clinical pregnancy with the use of in vitro fertilization–embryo transfer. *Fertil Steril* 70,878–882.
- Groutz A, Lessing JB, Wolf Y, Yovel I, Azem F and Amit A (1997) Cervical dilation during ovum pick-up in patients with cervical stenosis: effect on

- pregnancy outcome in an in vitro fertilization-embryo transfer program. *Fertil Steril* 67,909-911.
- Grunert GM, Dunn RC, Valdes CT, Wun CC and Wun WSA (1998) Comparison of Wallace, Frydman DT and Cook embryo transfer catheter for IVF: a prospective randomised study [abstract]. Annual Meeting of the American Society of Reproductive Medicine, 1998. *Fertil Steril* 70, S120.
- Karande V, Hazlett D, Vietzke M and Gleicher N (2002) A prospective randomized comparison of the Wallace catheter and the Cook Echo-Tip catheter for ultrasound-guided embryo transfer. *Fertil Steril* 77,826-830.
- Kato O, Takatsuka R and Asch R (1993) Transvaginal-transmyometrial embryo transfer: the Towako method; experience of 104 cases. *Fertil Steril* 59,51-53.
- Kovacs GT (1999) What factors are important for successful embryo transfer after in-vitro fertilization? *Hum Reprod* 14,590-592.
- Lashen H (unpublished data) A prospective randomised trial comparing two embryo transfer catheters. National Research Register (NRR): <http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0059115928>
- Lavery S, Ravhon A, Skull J, Ellenbogen A, Taylor J, Dawson K, Trew G, Margara R and Winston R (2001) A prospective randomized controlled trial of Wallace and Rocket embryo transfer catheters in an IVF-embryo transfer programme [abstract]. *Hum Reprod* 16(Suppl 1),124.
- Lavie O, Margalioth EJ, Geva-Eldar T and Ben-Chetrit A (1997) Ultrasonographic endometrial changes after intrauterine insemination: a comparison of two catheters. *Fertil Steril* 68,731-734.
- Lesny P, Killick SR, Tetlow RL, Robinson J and Maguiness SD (1998) Embryo transfer: can we learn anything new from the observation of junctional zone contractions? *Hum Reprod* 13,1540-1546.
- Lesny P, Killick SR, Tetlow RL, Robinson J and Maguiness SD (1999) Embryo transfer and uterine junctional zone contractions. *Hum Reprod Update* 5,87-88.
- Levi-Setti PE, Albani E, Baggiani AM, Zannoni E, Colombo G, Liprandi V (2002) Prospective randomized study comparing two soft catheters for embryo transfer. *Fertil Steril* 78;3(Suppl 1)S234.
- Lu MC (1999) Impact of 'non-physician factors' on the 'physician factor' of in vitro fertilization success: is it the broth, the cooks, or the statistics? *Fertil Steril* 71,998-1000.
- Mansour R and Aboulghar M (2002) Optimizing the embryo transfer technique. *Hum Reprod* 17,1149-1153.
- Mansour R, Aboulghar M and Serour G (1990) Dummy embryo transfer: a technique that minimizes the problems of embryo transfer and improves the pregnancy rate in human in vitro fertilization. *Fertil Steril* 54,678-681.
- Mayer JF, Nechiri F, Jones EL, Weedon VM, Kalin HL, Lanzendorf SE, Oehinger SC, Toner JP and Muasher SJ (1999) Prospective randomized analysis of the impact of two different transfer catheters on clinical pregnancy rates [abstract]. ASRM/CFAS Conjoint Annual Meeting September 25-30, 1999 (Toronto, Canada). *Fertil Steril* (Suppl 1), S144-145.
- McDonald JA and Norman RJ (2002) A randomized controlled trial of a soft double lumen embryo transfer catheter versus a firm single lumen catheter: significant improvements in pregnancy rates. *Hum Reprod* 17,1502-1506.
- McIlveen M, Lok D, Pritchard J and Lashen H (2004) A randomised controlled trial comparing two embryo transfer catheters. *Hum Reprod* 19,127S.
- Meriano J, Weissman A, Greenblatt EM, Ward S and Casper RF (2000) The choice of embryo transfer catheter affects embryo implantation after IVF. *Fertil Steril* 74,678-682.
- Moore DE, Soules MR, Klein NA, Fujimoto VY, Agnew KJ and Eschenbach DA (2000) Bacteria in the transfer catheter tip influence the live-birth rate after in vitro fertilization. *Fertil Steril* 74,1118-1124.
- Mortimer S, Fluker M and Yuzpe A (2002) Effect of embryo transfer catheter on implantation rates [abstract]. 58th Annual Meeting of the American Society for Reproductive Medicine. *Fertil Steril* 78(3), S17-18.
- Nabi A, Awonuga A, Birch H, Barlow S, Stewart B (1997) Multiple attempts at embryo transfer: does this affect in-vitro fertilization treatment outcome? *Hum Reprod* 12,1188-1190.
- Perin PM (1999) The influence of two different transfer catheters on the pregnancy rate in a human in vitro fertilization program. *Reprod Clim* 14,81-88.
- Ralph SG, Rutherford AJ and Wilson JD (1999) Influence of bacterial vaginosis on conception and miscarriage in the first trimester: cohort study. *Br Med J* 319,220-223.
- Ramsay S (1999) Experts give practical advice in reproductive medicine. *Lancet* 354,51.
- Saldeen P, Bergh T, Sundstrom P and Holte J (2003) A prospective randomized controlled trial comparing two embryo transfer catheters in an ART programme [abstract]. 19th Annual Meeting of the European Society of Human Reproduction and Embryology. *Hum Reprod* 18(Suppl 1),130-131.
- Salha OH, Lamb VK and Balen AH (2001) A postal survey of embryo transfer practice in the UK. *Hum Reprod* 16,686-690.
- Sallam HN and Sadek SS (2003) Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials. *Fertil Steril* 80,1042-1046.
- Sallam HN, Farrag F, Ezzeldin A, Agameya A, Sallam AN (2000) Vigorous flushing of the cervical canal prior to embryo transfer, a prospective randomised study. *Fertil Steril* 74;3(Suppl 1)S203.
- Schiewe M (2001) IVF-ICSI pregnancy outcomes in a randomized embryo transfer catheter trial comparing the cook soft-pass catheter to the Edward-Wallace catheter [abstract] (2001) 51st Annual Meeting of the American Society of Reproductive Medicine, *Fertil Steril* 76;3(Suppl 1),181.
- Sweet CR, Hamidi J, El Mansari El, Guttieri T and Harrington T (1998) Hysteroscopic vs. catheter embryo transfer: a randomized prospective pilot study. American Society Reproductive Medicine (San Francisco, USA). *Fertil Steril* 70,(Suppl 1)S331.
- Taylor TH, Colturato LF, Jones AE, Wright G, Elsner CW, Kort HI and Nagy ZP (2005) Prospective comparison of three soft ET catheters. *Hum Reprod* 20(Suppl 1), i130.
- Templeton A, Morris JK and Parslow W (1996) Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 348,1402-1406.
- Tur-Kaspa I, Yuval Y, Bider D, Levron J, Shulman A and Dor J (1998) Difficult or repeated sequential embryo transfers do not adversely affect in-vitro fertilization pregnancy rates or outcome. *Hum Reprod* 13,2452-2455.
- van Weering HG, Schats R, McDonnell J, Vink JM, Vermeiden JP and Hompes PG (2002) The impact of the embryo transfer catheter on the pregnancy rate in IVF. *Hum Reprod* 17,666-670.
- Visser DS, Fourie FL and Kruger HF (1993) Multiple attempts at embryo transfer: effect on pregnancy outcome in an in vitro fertilization and embryo transfer program. *J Assist Reprod Genet* 10,37-43.
- Waterstone J, Curson R and Parsons J (1991) Embryo transfer to low uterine cavity. *Lancet* 337,1413.
- Wisanto A, Janssens R, Deschacht J, Camus M, Devroey P and Van Steirteghem AC (1989) Performance of different embryo transfer catheters in a human in vitro fertilization program. *Fertil Steril* 52,79-84.
- Wood C, McMaster R, Rennie G, Trounson A and Leeton J (1985) Factors influencing pregnancy rates following in vitro fertilization and embryo transfer. *Fertil Steril* 43,245-250.
- Wood EG, Batzer FR, Go KJ, Gutmann JN and Corson SL (2000) Ultrasound-guided soft catheter embryo transfers will improve pregnancy rates in in-vitro fertilization. *Hum Reprod* 15,107-112.
- Woolcott R and Stanger J (1997) Potentially important variables identified by transvaginal ultrasound-guided embryo transfer. *Hum Reprod* 12,963-966.
- Yovich JL, Turner SR and Murphy AJ (1985) Embryo transfer technique as a cause of ectopic pregnancies in in vitro fertilization. *Fertil Steril* 44,318-321.

Submitted on April 21, 2005; resubmitted on June 12, 2005; accepted June 16, 2005