Intrauterine insemination catheters for assisted reproduction: a systematic review and meta-analysis

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BACKGROUND: Intrauterine insemination (IUI) is the oldest and most practised form of assisted reproduction worldwide. We systematically reviewed the literature so that we could evaluate the use of soft versus firm catheters in subfertile women undergoing IUI. METHODS: Extensive searches were conducted for full-text manuscripts, conference abstracts, ongoing and unpublished trials. Primary outcomes were clinical pregnancy (CPR) and ongoing pregnancy (OPR)/live birth rates (LBRs) per woman. Secondary outcomes were multiple pregnancy rate (MPR) per clinical pregnancy, difficulty cannulating the cervix, bleeding and patient discomfort. Meta-analysis was performed using the Peto-modified Mantel-Haenszel fixed-effect model. RESULTS: Seven randomized trials were identified, and four were excluded. No significant differences were noted for CPR and LBR per woman [OR = 0.96, 95% CI = 0.70–1.32 and OR = 0.82, 95% CI = 0.43–1.58, respectively]. As for the secondary outcomes, MPRs per cycle were also not significantly different. More difficulty was noted with soft catheters and more patient discomfort with firm catheters. Bleeding following the procedure was similar between the two groups. CONCLUSIONS: Catheter choice during IUI does not seem to be a detrimental factor for success, as in other assisted reproduction techniques (ART). More studies are warranted to draw definitive conclusions and support the results of this systematic review.

Key words: assisted reproduction/catheters/Intrauterine insemination/meta-analysis

Introduction

With the advent of modern assisted reproduction techniques (ART), intrauterine insemination (IUI), or artificial insemination (AI), has been a mainstay of therapy for couples suffering from various forms of infertility. Even today, after the proven success of IVF and ICSI, IUI continues to be utilized worldwide as a cost-effective, and in many cases, successful first line of therapy (Mansour et al., 1989; Aboulghar et al., 2003; Hughes, 2003).

The basis behind the IUI procedure is to use a catheter to deliver washed spermatozoa past the cervical mucus barrier into the uterine cavity and thereby increase the sperm concentration at the site of fertilization. Even so, the pregnancy rate per IUI cycle has shown to vary markedly (Hughes, 1997). Therefore, traditionally, couples have been advised to undertake three to six IUI cycles before considering failure to become pregnant using AI (Aboulghar et al., 2001).

Several factors have been accepted as being prognostic to the success of IUI treatments. These include the woman’s age, cause of infertility, sperm volume and quality, and controlled ovarian stimulation (Sahakyan et al., 1999; Duran et al., 2002).

One aspect of assisted reproduction that has gained importance over the past few years is catheter technology. In a recently published systematic review and meta-analysis performed by our team, the softness of the embryo transfer catheter was found to be a determining factor in the success of embryo transfer procedures (Abou-Setta et al., 2005a). The explanation for this difference is still unclear, but it is theorized to be associated with either the traumatic effects of the catheter during introduction into the uterine cavity or junctional zone contractions with the firmer catheters (Kovacs, 1999). No matter the aetiology, the type of embryo transfer catheter has proved to have a considerable effect on treatment outcome.

In contrast to embryo transfer catheters, the impact of the AI catheter choice on an ART programme has been poorly investigated, and data comparing different types of IUI catheters are limited. Several studies have compared different catheters for IUI, but most of these studies are observational, retrospective or prospective, but non-randomized. We therefore decided to systematically review the literature so that we could evaluate the use of soft versus firm catheters in subfertile women undergoing IUI.

Materials and methods

Criteria for considering studies for this review

All published, unpublished and ongoing prospective, randomized controlled trials reporting data comparing outcomes for women...
undergoing IUI through the cervical route, using soft versus firm catheters, were sought in all languages. Trials comparing soft versus soft, or firm versus firm, catheters were excluded.

Types of outcome measures
The primary outcome measures used for this systematic review were the clinical pregnancy rate (CPR) per randomized woman and the ongoing pregnancy rate (OPR)/live birth rate (LBR) per randomized woman. The secondary outcomes were the multiple pregnancy rate (MPR) per clinical pregnancy, ease of introduction (difficulty in cannulating the cervix), simultaneous occurrence of traumatic events (e.g. the presence of blood on the catheter or bleeding per cervix) and patient discomfort (e.g. cramping during or immediately after the procedure).

Search strategy for identification of studies
Identification of studies according to the inclusion criteria was performed independently by two reviewers (A.M.A.S. and H.G.A.I.) with conflicts being resolved by mutual agreement and by discussion with the other reviewers (R.T.M., M.M.A., A.K., G.I.S. and M.A.A.). Computerized searches (February 2006) were conducted using MEDLINE (1966 to present), the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 1, 2006, the National Research Register, the Medical Research Council’s Clinical Trials Register and the NHS Centre for Reviews and Dissemination. The following medical subject headings and text words were used: artificial insemination, intrauterine insemination, intrauterine insemination technique, intrauterine insemination catheter and randomized controlled trial(s). Furthermore, the reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (e.g. ESHRE and ASRM) and included studies were examined to identify additional relevant citations. Finally, 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. Trials were considered for inclusion, and trial data were extracted. Data extraction was performed independently by two reviewers (A.M.A.S. and H.G.A.I.) with conflicts being resolved by the other reviewers (R.T.M., M.M.A., A.K., G.I.S. and M.A.A.). Data management and analysis was conducted using the Review Manager (RevMan) 4.2 and the Meta-analysis with Interactive Explanations (MIX) 1.0 statistical software packages.

Individual outcome data were included in the analysis if they met the prestated criteria. Where possible, data were extracted to allow for an intention-to-treat analysis—defined as including in the denominator all randomized cycles. If data from the trial reports were insufficient or missing, the authors contacted the investigators of individual trials via e-mail for additional information, in order to perform analyses on an intention-to-treat basis. Missing data were acquired for two of the included studies (Segal et al., 1998; Fancsovits et al., 2005).

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 χ²-test for heterogeneity with a 10% level of statistical significance was utilized.

In addition, the I²-test was used to attempt at quantifying any apparent inconsistency. The I²-test is a statistical measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates, which is due to heterogeneity rather than sampling error (chance) (Higgins et al., 2003). An I²-value greater than 50% may be considered to represent substantial heterogeneity.

Comparison methods
Meta-analysis of dichotomous data was performed using the Peto-modified Mantel-Haenszel method utilizing a fixed-effect model, and the odds ratio (OR) and 95% confidence intervals (CIs) were evaluated.

The Peto-modified Mantel-Haenszel method, also known as the Peto odds ratio method or Peto’s method, uses an inverse variance approach but utilizes an approximate method of estimating the log odds ratio and uses different weights (Yusuf et al., 1985). In addition, the P-value was calculated and presented for further confirmation of the results. A P-value of <0.05 was considered to be significant.

Search results
A total of seven trials were identified [three full-text papers (Smith et al., 2002; Fancsovits et al., 2005; Miller et al., 2005) and four conference abstracts (Segal et al., 1998; Murber et al., 2002; Spiessens et al., 2003; Miller et al., 2004); Figure 1]. Of these studies, two conference abstracts were excluded because they were also published as full-text manuscripts (Murber et al., 2002; Miller et al., 2004). In addition, one conference abstract (Spiessens et al., 2003) was excluded because it compared a soft IUI catheter with a soft embryo transfer catheter. The remaining studies (n = 4) were evaluated further and included.

Catheter design
During the course of this review, we came across several commercially available IUI catheters. They were divided into two groups, soft or firm, according to the available literature and the experience of the authors.

Soft artificial insemination catheters
(i) The Wallace™ embryo transfer catheter (Smiths Medical, London, UK) is open-ended and is 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.
(ii) The Wallace™ artificial insemination catheter (Smiths Medical) is a soft, flexible, double-lumen catheter, utilizing a co-axial system.

![Figure 1. QUOROM statement flow diagram.](https://academic.oup.com/humrep/article/21/8/1961/2938645)
The inner catheter is 18 cm long, with a rounded tip, and utilizes a bilateral side dispersion design to help prevent contamination and blockage of the catheter during insertion. Its outer sheath is flexible, but with memory, which can be pre-shaped to aid insertion. (iii) The Cook™ Soft-Pass® artificial insemination catheter (Cook Women’s Health, Spencer, IN, USA) is also a soft, flexible, double-lumen, co-axial catheter system. The inner catheter is 19 cm long with a rounded tip. Its outer guide catheter is similar to the outer sheath of the Wallace artificial insemination catheter. (iv) The Gynetics™ artificial insemination catheter (Gynetics Medical Products, Hamont-Achel, Belgium) is also a soft, flexible, double-lumen, co-axial catheter system. It is 20.6 cm in length with a rounded tip. In addition, similar to the Wallace artificial insemination catheter, it uses two lateral ports at the distal end for intrauterine sperm distribution. It also comes with a solid, thicker outer catheter for bypassing the difficult cervix.

**Firm artificial insemination catheters**

(i) The Tomcat™ artificial insemination catheter (Kendall Sovereign, Mansfield, MA, USA) is a firm, semi-rigid, single-lumen catheter. It is 11.4 cm long, 3.5 French (Fr) and with an open-end design. Originally, it was designed for draining the bladders of male cats, hence its name. It is designed with a semi-rigid but flexible body which, combined with its inherent memory, enables the catheter to be moulded to the curvature of the uterus.

(ii) The Makler™ IUI Cannula and Insemination Device (Sefi-Medical Instruments, Haifa, Israel) is composed of two main parts: (i) a cannula that can be fitted to the tip of 1.0 ml tuberculin syringe and (ii) a carrier to hold the syringe. The Makler IUI catheter is a firm, semi-rigid, single-lumen catheter with a rounded tip. It has a flared-base shape, which serves to seal the cervix at the time of insemination to help prevent the backflow of the injected contents. This is accomplished by entirely obliterating the cervical external os by the flared base of the cannula. The clamp is then fixed to the outer brim of the speculum and the tension of the spring is adjusted so that the cannula is gently pressed against the cervical outlet.

**Description of included studies (Table 1)**

Segal et al. (1998) conducted a trial including 51 patients undergoing 51 cycles of IUI. The patients were randomized into three groups of 17 patients undergoing 17 insemination cycles (i.e. one cycle per patient). Insemination was performed using a Wallace IUI catheter, a Wallace embryo transfer catheter or a Tomcat catheter in each of the respective groups.

Smith et al. (2002) conducted a trial including 364 patients undergoing 747 cycles of IUI. With the use of quasi-randomization (i.e. patient’s birth date), the cycles were randomized into two groups: Tomcat catheter group (even years) and Wallace IUI catheter group (odd years). The number of patients and cycles in each arm was as follows: 184 patients underwent 375 insemination cycles (Tomcat catheter group) and 180 patients underwent 372 cycles (Wallace catheter group). It is important to note that patients underwent insemination with the assigned catheter regardless of the number of cycles.

Miller et al. (2005) conducted a trial including 100 patients undergoing 100 IUI cycles. With the use of sealed envelopes, the cycles were randomized into two groups: Tomcat catheter group and Cook catheter group. The number of patients and cycles in each arm was as follows: Tomcat catheter group (51 patients undergoing 51 insemination cycles) and Cook catheter group (49 patients undergoing 49 insemination cycles) (i.e. one cycle per patient).

Fancsovits et al. (2005) conducted a trial including 251 patients undergoing 779 IUI cycles. With the use of a computer-generated number table, the cycles were randomized into two groups: Gynetics catheter group and Makler catheter group. The number of cycles in each arm was as follows: Gynetics catheter group (124 patients underwent 402 cycles) and Makler catheter group (127 patients underwent 377 cycles). Only one catheter type was assigned to each patient at the time of inclusion, no matter the number of subsequent cycles performed.

**Sample size calculation**

A priori sample size calculations are important in randomized controlled trials in order to determine the needed number to treat (NNT) and to help prevent the occurrence of type II errors. Two of the included studies (Smith et al., 2002; Miller et al., 2005) performed power calculations. Smith et al. (2002) concluded that 136 cycles would be needed in each study arm to identify a statistically significant difference of 10% in the CPR; although this was determined for clinical pregnancy per cycle, but not for the pregnancy rate per woman. Miller et al. (2005) determined that 670 patients would be required in each study arm to conclude a true difference to identify a 6% difference in the clinical pregnancy per woman.

For the purpose of this systematic review, a sample size calculation was done to show the number needed to be treated. With a power of 80% and an α of 0.05, we determined that 1134 subjects would be needed in each study arm to conclude a true difference of 5% (e.g. 20 versus 25%). As our current review has 766 included patients, we can conclude that we do not have enough patients to conclude that a true difference exists.

**Publication bias**

A funnel plot was used to assess publication bias, quality and heterogeneity of the included studies (Figure 2A). The funnel plot was noted to have an asymmetrical appearance with a gap in the bottom corner of the graph. This asymmetry may be due to a small, unpublished trial not being included in the analysis, shown as an unfilled circle in the trim and fill funnel plot (Figure 2B).

**Table 1.** Review table of the prospective, randomized controlled studies analysed, comparing intrauterine insemination (IUI) catheters

<table>
<thead>
<tr>
<th>Included studies</th>
<th>IUI catheter choice</th>
<th>Sample size (patients)</th>
<th>Sample size (cycles)</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segal et al. (1998)</td>
<td>Tomcat</td>
<td>17</td>
<td>17</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Wallace IUI</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wallace IVF</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Smith et al. (2002)</td>
<td>Tomcat</td>
<td>184</td>
<td>375</td>
<td>Quasi-randomization</td>
</tr>
<tr>
<td></td>
<td>Wallace IUI</td>
<td>180</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cook</td>
<td>51</td>
<td>49</td>
<td>Dark-sealed envelopes</td>
</tr>
<tr>
<td>Miller et al. (2005)</td>
<td>Tomcat</td>
<td>127</td>
<td>377</td>
<td>Computer-generated random number table</td>
</tr>
<tr>
<td>Fancsovits et al. (2005)</td>
<td>Makler</td>
<td>124</td>
<td>402</td>
<td></td>
</tr>
</tbody>
</table>
Results

Primary outcome measures

For the CPR per randomized woman, data were available from all the included studies (n = 4), but data on the LBR per randomized woman were available from only one study (Fancsovits et al., 2005). Analysis of the firm catheters compared to the soft catheters with regard to the CPR and LBR revealed no statistically significant difference (P = 0.28; OR = 0.96, 95% CI = 0.70–1.32 and P = 0.56; OR = 0.82, 95% CI = 0.43–1.58, respectively) (Figure 3A and B).

Secondary outcome measures

Data on the MPRs per clinical pregnancy following the usage of soft versus firm catheters were not significantly different (P = 0.81; OR = 1.19, 95% CI = 0.28–5.13). For the chance of having a difficult IUI procedure using the assigned catheter, data were available from one study (Fancsovits et al., 2005). There was a statistically significant higher probability of having patient discomfort with the soft catheter, when compared to the firm one (P = 0.0005; OR = 12.95, 95% CI = 3.03–55.31).

Discussion

Each year countless numbers of couples undergo treatment for male and/or female subfertility. Many of these cases are mild in nature and can be overcome with proper diagnosis and treatment. A common first line of treatment prescribed by many andrologists, gynaecologists and reproductive endocrinologists alike is a series of three to six cycles of IUI (Mansour et al., 1989; Aboulghar et al., 2001; Khalil et al., 2001). This is because even if more advanced IVF techniques are available, IUI costs only a fraction of the cost, is less invasive, and in many cases, the pregnancy rates are similar (Cohlen, 2005). A recent Cochrane review has recommended the use of IUI in patients with unexplained infertility as the success rates are similar to those achieved with IVF/ICSI in this patient population (Pandian et al., 2005).

IUI is a procedure by which washed spermatozoa are introduced into the uterine cavity, thereby bypassing several of the natural barriers in the female genital tract. In combination with, or without, controlled ovarian hyperstimulation, it has proven to be a cost-effective line of treatment for infertility (Cohlen, 2005). Its main indications are mild male factor, cervical factor or cases of unexplained infertility (Mansour et al., 1989; Dickey et al., 2002).

In the literature, the pregnancy rate per cycle of IUI has shown marked variability (e.g. <5 to >30%) (Campana et al., 1996; Hughes, 1997; Dmowski et al., 2002). This great variation in pregnancy rates might be due to the differences in the characteristics of the study populations, ovarian stimulation protocols and/or insemination techniques used (Campana et al., 1996).

Various types of catheters used in AI are commercially available. Catheters vary in length, calibre and location of the distal port (end- or side-dispersion systems). They also differ in the degree of firmness and rigidity.

Today, new trends in assisted reproduction have made marked changes in the practice of IVF as a whole but are only starting to affect AI practices. These include the use of soft catheters (Abou-Setta et al., 2005a) and ultrasound guidance.
IUI catheters for assisted reproduction

Abou-Setta et al., 2005b). Both these new revelations are built on the theory of decreasing the trauma caused to the endocervix and endometrium during embryo transfer.

Lavie et al. (1997) sonographically assessed the triple-layer endometrial image, so commonly identified at the time of ovulation, following the use of soft and firm catheters. They demonstrated that the stiffer Tomcat catheters disrupted the normal trilaminar pattern in 50% of procedures, compared with 12.5% with the softer Wallace catheters. This image disruption was presumed to represent endometrial trauma. Ironically, even though the pregnancy rates were not statistically different between the two groups, this correlation of possible endometrial damage by firmer catheters drove investigators to test the theory that decreased endometrial trauma and, therefore, preservation of the normal, receptive architecture for an implanting blastocyst may be of vital importance during embryo transfer.

What is certain is that only limited data are available regarding the effect of the catheter during insemination on pregnancy and LBRs. A search of the literature revealed over two dozen prospective randomized controlled trials evaluating different embryo transfer catheters, but only a limited number evaluating different IUI catheters. This discrepancy is interesting as IUI is not only a much older, more widely available procedure than IVF, but that it is also more widely used in assisted reproduction than IVF.

One possible explanation for this phenomenon is publication bias in the literature. This is evidenced by the funnel plot for the included studies in this review. The funnel plot is a graphical display of study precision plotted against the effect size. It is used to investigate whether there is a link between study size and treatment effect. The funnel plot of the included studies shows asymmetry that may be due to publication bias. Even so, it is important to note that there may be other aetiologies for the asymmetry found in the funnel plot, including selection biases (e.g. location bias, language bias, citation bias and multiple publication bias), poor methodological quality of smaller studies (e.g. poor methodological design, inadequate analysis and fraud), true heterogeneity (i.e. size of effect differs according to study size), artefactual and just by chance (Deeks et al., 2005).

Duval and Tweedie (2000) have proposed the ‘trim and fill’ method for defining the extent of publication bias. It is based on adding studies to a funnel plot so that it becomes symmetrical. Then the smaller studies are omitted until the funnel plot is symmetrical (trimming). The trimmed funnel plot is used to estimate the true ‘centre’ of the funnel, and then the omitted studies and their missing ‘counterparts’ around the centre are replaced (filling). This provides an estimate of the number of missing studies and an adjusted treatment effect, including the ‘filled’ studies.

In a recent study, Sutton et al. (2000) evaluated 48 meta-analyses using the trim and fill method and estimated that 56% of them had at least one study missing, whereas the number of missing studies in 10 was statistically significant. Still, other studies have shown that the trim and fill method may detect ‘missing’ studies in a meta-analysis, even in the absence of
bias (Sterne and Egger, 2000). This was argued to be due to random variation in study outcomes and not particularly missing studies. Therefore, publication bias cannot completely be ruled out but at the same time cannot be absolutely confirmed.

What still remains as a mystery is why the results of this systematic review on IUI catheters have a different outcome than that for embryo transfer catheters. There are several confounders to consider. First of all, our previous meta-analysis contained a much larger number of included studies (n = 10) and number of cycles (>4000). This systematic review contained a smaller number of included studies (n = 4) and randomized patients (n = 766). We determined that for this systematic review, 1134 subjects would be needed in each study arm to conclude a true difference of 5% (e.g. 20 versus 25%); therefore, at this time, we do not have sufficient power to test the null hypothesis.

Secondly, in contrast to embryo transfer, the importance of preventing junctional uterine contractions by using soft catheters may be of less value during IUI. This is evidenced by the observation that even though there may be noticeable regurgitation of fluid from the cervix during the insemination procedure, many patients will still become pregnant. This is because the embryo transfer procedure is a very critical one compared to IUI. During embryo transfer, only a limited number of embryos (as few as two or even one) are transferred into the uterine cavity, and any initiation of uterine contractions may result in the expulsion of the embryos and failure of the whole procedure. On the other hand, IUI involves the injection of a much larger volume of washed sperm into the uterine cavity.

Furthermore, there is a disparity between the location and chronology of events surrounding normal fertilization and implantation in IVF and IUI. In the case of IVF, embryo apposition and attachment to apical membrane proteins in the endometrium, the earliest stages of implantation, are expected to occur within days after transfer. If one presumes that endometrial trauma occurs with IUI, the most immediate event, fertilization, takes place within the fallopian tube in an environment protected from the trauma. The ensuing days before embryo attachment may be enough time for natural healing of the disrupted areas.

Ironically, a recent theory suggests increased, not decreased, endometrial receptivity following endometrial healing. Recent evidence has shown that IVF pregnancy rates after endometrial biopsy in the month preceding the embryo transfer might create a more favourable environment for implantation, by creating a cycle of trauma and healing (Barash et al., 2003). Further confirmation of this theory is needed.

Lastly, the possible factor of publication bias cannot be ruled out. In this situation, the effect calculated in the meta-analysis could be an overestimate of the treatment effect (in this case being the firm catheters) (Egger et al., 1997; Villar et al., 1997). Even if this is the case, as only one small study is needed to correct the asymmetry, this is unlikely to be significantly affecting the results, as noted by the trim and fill funnel plot (Figure 2B).

Finally, with the current limited volume of data available on this topic, the results of this systematic review should prove valuable to providers offering IUI to their patients. As no statistically significant difference was shown for our primary outcomes, we concluded that our review failed to identify one catheter group superior to the other. In addition, further well-powered and properly randomized studies are needed to support our conclusions.

Conclusions

There is lack of evidence to suggest that softer catheters are superior to firmer ones during IUI procedures. Furthermore, larger investigations are warranted to draw definitive conclusions and support the results of this systematic review.

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Dmowski WP, Pry M, Ding J and Rana N (2002) Cycle-specific and fecundity to IUI. During embryo transfer, only a limited number of embryos (as few as two or even one) are transferred into the uterine cavity, and any initiation of uterine contractions may result in the expulsion of the embryos and failure of the whole procedure. On the other hand, IUI involves the injection of a much larger volume of washed sperm into the uterine cavity.

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