Optimizing the embryo transfer technique
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Citation for published version (APA):
Abou-Setta, A. M. (2008). Optimizing the embryo transfer technique

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Chapter 4

Effect of passive uterine straightening during embryo transfer: a systematic review and meta-analysis.

Ahmed M. Abou-Setta

Abstract

Background: Part of the success of ultrasound-guided embryo transfer has been associated with the beneficial effect of uterine straightening by passive bladder distention. Even so, this has not been properly analysed in the literature.

Methods: This is a systematic review and meta-analysis of prospective, randomised, controlled trials, comparing embryo transfer with a full versus empty bladder. Electronic (e.g. PubMed, EMBASE, Cochrane Library) and hand searches were performed to locate trials. Primary outcomes were live-birth, ongoing and clinical pregnancy rates. Secondary outcomes were rates of implantation, miscarriage, multiple and ectopic pregnancies, and retained embryos. Also, the ease of transfer, need for instrumental assistance, and presence of blood on the catheter tip were evaluated. Four studies were identified, of which 1 study was excluded. Meta-analysis was conducted with the Mantel-Haenszel method, utilising the fixed-effect model.

Results: For the primary outcome measures, no data was available for the LBR rate. There was a significantly higher chance of an ongoing pregnancy [OR = 1.44 (95% CI = 1.04 - 2.04)] and clinical pregnancy [OR = 1.55 (95% CI = 1.16 - 2.08)] with a full bladder. For the secondary outcomes, there was a significantly greater incidence of difficulty, or need for instrumental assistance, with an empty bladder. Other outcome measures were not significantly different.

Conclusion: There is evidence in the literature advising to fill the bladder prior to embryo transfer.

Key words: Embryo transfer, bladder distention, meta-analysis, in vitro fertilisation
Background
The embryo transfer (ET) procedure is considered to be the final and most crucial step in an in vitro fertilisation (IVF) cycle. When compared with other aspects of the IVF procedure, the ET is poorly efficient, with up to 85% of transferred embryos not implanting (1). In addition, it is estimated that about 80% of women undergoing IVF will reach the ET stage, but only a small portion will achieve pregnancy. The pregnancy rate after ET is dependent upon multiple factors, including the quality of the embryos, proper endometrial receptivity and development, and the technique by which embryos are transferred (2).
Traditionally, little attention has been focused on the technique of ET. Moreover, no standard clinical protocol is accepted worldwide as an evidence-based protocol for ET. Most clinicians have been left to exercise personal preferences when performing the ET, unlike other aspect of IVF which have been more thoroughly addressed in the literature. This publication bias in the IVF literature has been mainly attributed to the lack of importance of the ET technique as a defining step in the success of the IVF procedure.
Only recently have the techniques and variables affecting the success of ET attracted more interest. Today, in light of global trends, such as single ET, more emphasis has been placed on optimising and standardising the ET protocol. Numerous studies have shown that the success rates in different IVF clinics may be directly associated with the clinical techniques used during ET. Factors, such as ease of procedure (3), catheter choice (4, 5), and dummy ET (6) have proven to improve the clinical outcomes.
During the ET, the aim is to manipulate the catheter atraumatically through the cervix into the uterine cavity, without touching the fundus and minimising trauma to the endometrium. Factors related to tissue trauma, such as the presence of blood and/or mucus on the transfer catheter, debatably, has been shown to decrease implantation and pregnancy rate (7, 8). Therefore, any clinical manoeuver that increases the ease of transfer is highly welcomed.
To date, the possible beneficial role of passive uterine straightening by bladder distension is still a subject of debate. This has been fueled by conflicting results from published clinical trials, with some concluding that bladder distension improves the pregnancy rates following ET, while others reporting no such improvement in their results. Some authors
have even concluded that the success of ultrasound-guided ET is partly due to the use of bladder distention. Even so, many clinicians prefer to perform ultrasound-guided ET with a partially filled bladder, or even an empty bladder, in order to avoid immediate post-transfer micturation. In addition, vaginal ultrasound-guided ET is performed with an empty bladder.

In light of this controversy, and the need to clearly identify the relative efficacy of this simple procedure, we decided to systematically locate, analyse, and review the current best available evidence for the use of bladder distension to passively straighten the utero-cervical angle during ET.
Materials and methods

Criteria for considering studies for this review
All published, unpublished, and ongoing randomised trials reporting data which compared outcomes for women undergoing ET through the cervical route following IVF, or ICSI, and randomised to either having a ‘full bladder’ or an ‘empty bladder’ during the time of transfer were sought in all languages.

Types of outcome measures
The primary outcome measures were the live-birth (LBR), ongoing pregnancy (OPR) and clinical pregnancy (CPR) rates. The secondary outcomes were the implantation, multiple pregnancies, ectopic pregnancy, and miscarriage rates. In addition, the incidences of difficult transfers or need for instrumental assistance during the transfer (e.g. stylette, tenaculum, dilatation, sounding) were evaluated. Lastly, the tips of the post-transfer catheters were evaluated for signs of cervical or endometrial trauma (e.g. presence of blood, mucus, or both), in addition to retained embryos.

Search strategy for identification of studies
Meticulous computerised searches (last performed July 2006) were conducted using MEDLINE (1966 to present), EMBASE (1980 to present), the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 3, 2006, the National Research Register (NRR), and the trial register of controlled trials (www.controlled-trials.com). 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, ongoing and unpublished trials were sought by contacting experts in the field and commercial entities.

Methods of the review
A standardised data extraction form was developed and piloted for consistency and completeness. Trials were considered for inclusion, and trial data extracted. Data management and statistical analyses were conducted using the ‘Review Manager (Rev-Man) 4.2’ and ‘Power and Sample Size Calculations (PS) 2.1.30’ statistical software packages.
Individual outcome data were included in the analysis if they met the pre-stated criteria. Where possible, data were extracted to allow for an intention-to-treat analysis - defined as including in the denominator all randomised cycles. If data from the trial reports were insufficient or missing, the investigators of individual trials were contacted via E-mail 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 of the included studies was determined using the $\chi^2$-test for heterogeneity. In addition, the quantity $I^2$ test was used to attempt quantifying any apparent inconsistency. The $I^2$ test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (9). An $I^2$ value >50% may be considered to represent substantial heterogeneity.

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Meta-analysis was undertaken using the Mantel-Haenszel method, utilising the fixed effect model, and the odds ratio (and 95% confidence intervals (CI)) evaluated.

**Search results**
A total of 4 prospective, randomised, controlled trials were identified (3 full-text manuscripts and 1 conference abstract). Subsequently, the conference abstract (10) was excluded for duplicate publication (e.g. publication as a conference abstract and full-text manuscript). The remaining 3 trials were included, the methodological quality of each trial assessed, and data extracted to allow for an intention-to-treat analysis.

**Description of included studies**
Mitchell et al. (11) conducted a prospective, randomised, controlled trial including 142 women undergoing 142 ET cycles. Patients were allocated into 1 of 2 groups by a random number table to have a ‘partially full’ or ‘empty bladder’ at the time of ET (Table I). Patients in the ‘partially full bladder’ group were asked to empty their bladders, then drink 250 ml of water 1 h prior to the actual ET. Patients in the ‘empty bladder’ group were asked to empty their bladders immediately before the transfer. The number of cycles in each arm was as follows: ‘full bladder’ group
(66 ET cycles), and ‘empty bladder’ group (76 cycles). None of the reported cycles were frozen embryo replacement (FER) or used oocyte donation (OD).

Lewin et al. (12) conducted a prospective, randomised, controlled trial, including 796 women undergoing 796 ET cycles. Using alternate randomisation of days, the cycles were randomised into 2 groups: ‘full bladder’ and ‘empty bladder.’ Patients in the ‘full bladder’ group were asked to urinate, and then drink 1,000 ml of water 1 h prior to the actual ET. At the time of ET, ultrasound was used to demonstrate bladder fullness.

The number of cycles in each arm was as follows: ‘full bladder’ group (411 ET cycles), and ‘empty bladder’ group (385 cycles). None of the reported cycles were FER or used OD.

Lorusso et al. (13) conducted a prospective, randomised, controlled trial including 171 women undergoing 171 ET cycles. Patients were allocated into 1 of 2 groups by a computer-generated randomisation table to have a ‘full bladder’ or an ‘empty bladder’ at the time of ET. The directions given to patients on the day of the ET were not available for review, but since it was mentioned that the transfer was carried out under ultrasound guidance, bladder distention must have been appraised at the time of the ET.

The number of cycles in each arm was as follows: ‘full bladder’ group (67 ET cycles), and ‘empty bladder’ group (64 cycles). None of the reported cycles were FER or used OD.

In addition, the authors mentioned that 40 patients undergoing ET using the clinical touch method was used a control group. This group was not included in the analysis due to the confounding factor of using clinical touch versus ultrasound-guided during the ET.
Results

Primary outcome measures
For the primary outcome measures, no data was available for the LBR rate. Even so, there was a significantly higher chance of an OPR and CPR with a ‘full bladder’ than an ‘empty bladder’ [103/478 versus 72/449 (OR = 1.44; 95% CI = 1.04 - 2.04)] and [148/544 versus 102/525 (OR = 1.55; 95% CI = 1.16 - 2.08)], respectively. Furthermore, when only the properly randomised trials were compared, there was no apparent difference in the chance of an OPR [22/67 versus 21/64 (OR = 1.00; 95% CI = 0.48 - 2.08)], but a significantly increased chance of a CPR [136/478 versus 89/449 (OR = 1.61; 95% CI = 1.19 - 2.22)] with a ‘full bladder’ than an ‘empty bladder’. However, it is important to mention that with regard to the OPR rate, there was only 1 study (13) included in the analysis.

Secondary outcome measures
For the secondary outcome measures, no data were retrievable for the multiple pregnancy and miscarriage rates. In addition, there was no significant difference between the implantation rates between the 2 groups [12/137 versus 18/158 (OR = 0.75; 95% CI = 0.35 - 1.61)]. Even so, there was a significantly greater incidence of difficulty [72/140 versus 36/133 (OR = 2.85; 95% CI = 1.72 - 4.73)], and need for instrumental assistance [47/64 versus 16/67 (OR = 8.81; 95% CI = 4.00 - 19.41)] during ET with an ‘empty bladder’ than with a ‘full bladder’, respectively. Moreover, with regard to the ease of transfer, there was marked heterogeneity between the included studies (p = 0.0001, χ² = 14.40, I² = 93.1%). The other outcome measures (e.g. implantation rate, presence of blood or embryos on the post-transfer catheter) were not significantly different (p > 0.05).
Discussion
Although most patients who undergo assisted procreation, via IVF or ICSI, will reach the ET stage with good quality embryos available for replacement, embryo implantation remains the rate-limiting step in the success of this form of therapy. The aim of the ET procedure is to atraumatically and accurately place embryos within the uterus; in order to allow for proper implantation and fetal development. Studies have shown that different factors may be involved in a successful transfer. These include the experience of the physician (14), ET catheter choice (4, 5), the use of ultrasound guidance (15), the ease of the procedure (3), the presence or absence of blood on the catheter (7), and bacterial contamination of the catheter (16).

In addition, other factors concerning ET that might affect the chance for an OPR have been identified, such as the use of cervical introducers or obturators (17), the value of resting after transfer (18), the position of embryo insertion in the uterus (19, 20), flushing of the cervical canal to remove mucus (21), microbiological factors in terms of the local flora (22), and retention of embryos in the catheter (23).

In order to ascertain the importance of each step involved in the ET procedure, individual factors must be evaluated independently. Therefore, the ET procedure may be arbitrarily divided into four distinct sections: (1) preparation prior to ET (e.g. patient position, cervical preparation, uterine position and the dummy ET); (2) technical aspects related to the ET catheter (e.g. catheter type and catheter loading); (3) the ET procedure (e.g. the site of embryo deposition within the uterus and techniques to assist with the accurate placement of the embryo within the uterus); and (4) post-transfer aspects (e.g. expulsion of fluid/embryos from the cervix after ET and bed rest following ET) (24). Since it would be difficult to accurately compare several factors at the same time, it was decided to concentrate on 1 factor, the beneficial value of bladder distention during the ET procedure.

Sundstrom et al. (25) were the first to identify the beneficial effects of uterine straightening by bladder distension. However, their study had a relatively small sample size (n = 14), and used a historical control. Since then, only a handful of clinical trials have tackled the same issue, therefore emphasising the need for a systematic review of the best available evidence in the literature.

Systematic reviews and meta-analysis of randomised, controlled, trials
have proven to be the highest level of evidence in the hierarchy of medical knowledge. Even so, publication and search biases may confound the results of any systemic review, as studies showing positive results are more likely to be published (26, 27). Therefore, every effort has been made to avoid bias by searching a wide variety of databases, including Medline (PubMed), EMBASE, the Cochrane Library, with no language barriers, in addition to hand-searching the abstract books of major conferences (e.g. ASRM, ESHRE), reference lists of review articles and included trials.

In addition, even though all the included studies in this systematic review were published trials in peer-reviewed journals, every attempt was made to locate abstracts from conference proceedings, unpublished trials, and currently ongoing trials. The objective was to minimise the chance of publication or selection bias in order to strengthen the validity of the results of the systematic review. Failure to identify trials reported in conference proceedings might affect the results or threaten the validity of a systematic review (28).

Another important issue in clinical trials and systematic reviews are sample sizes. It is theorised that smaller studies might not have sufficient sample sizes to detect minor differences between study groups. This current meta-analysis included 1,069 ET cycles, and could detect an absolute difference of 7.5% with 80% power in a two-tailed analysis (assuming a CPR rate of 30% with a ‘full bladder’ and a significance level of 0.05). The absolute difference between full and empty bladder was 7.8%, therefore validating our results.

The results of this systematic review demonstrate that passive uterine straightening with the use of bladder distention during ET catheter placement may be a beneficial tool in optimising the outcome of the ET procedure, regardless of the method used for embryo catheter placement (e.g. ultrasound-guided or clinical touch). However, patient counseling is important, since most patients will need to micturate shortly after the transfer procedure. This action may be presumed to negatively affect the outcome of the IVF procedure. Therefore, proper counseling must be undertaken early in the cycle in order to decrease any anxiety over early mobilisation or micturation following the transfer. Lastly, it is also important to note that until today, no study has reported any direct adverse effects of bladder distention during the ET. Even so, one may argue that the main disadvantages are patient
discomfort, time for bladder distension to take place, and the possible psychological distress caused to patients who are forced to micturate after the transfer procedure.
Conclusion
The results of this systematic review demonstrate that passive uterine straightening by the use of bladder distention during ET may be a beneficial tool in optimising the outcome of the ET procedure. Even so, more randomised, controlled, trials are needed to support the results of this systematic review and to address other issues, such as partial versus complete filling of the bladder, and the amount of fluid intake needed to achieve bladder fullness.
References

15. Abou-Setta AM, Mansour RT, Al-Inany HG, Aboulghar MM, Serour GI, Aboulghar MA. Among women undergoing embryo transfer, is the probability of pregnancy


Table 1. Review table of the included studies, comparing ‘full’ and ‘empty’ bladder during embryo transfer.

<table>
<thead>
<tr>
<th>Included Studies</th>
<th>Patients</th>
<th>ET cycles</th>
<th>A-priori Sample size Calculation</th>
<th>Method of Randomization</th>
<th>Method of Randomization Concealment</th>
<th>Intention-to-treat</th>
<th>Follow-up</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewin et al., 1997</td>
<td>796</td>
<td>796</td>
<td>Not performed</td>
<td>Fixed alternate days</td>
<td>Inadequate</td>
<td>ITT</td>
<td>OPR only</td>
<td>Multiple physicians - Instrumental assistance not recorded</td>
</tr>
<tr>
<td>Mitchell et al., 1989</td>
<td>142</td>
<td>142</td>
<td>Not performed</td>
<td>Random numbers method</td>
<td>Unclear</td>
<td>ITT</td>
<td>CPR only</td>
<td>None evident</td>
</tr>
<tr>
<td>Lorusso et al., 2005</td>
<td>171</td>
<td>171</td>
<td>Not performed</td>
<td>Computer-generated randomization table</td>
<td>Unclear</td>
<td>ITT</td>
<td>OPR only</td>
<td>Multiple studies performed on same patient population</td>
</tr>
</tbody>
</table>

ITT = Intention to treat analysis performed; CPR = Clinical pregnancy rate; OPR = Ongoing pregnancy rate.
Figure 1: Quorum flow diagram.

- Potentially relevant RCTs identified and screened for retrieval (n=4)
  - RCTs excluded, Duplicate publication (n=1)

- RCTs retrieved for more detailed evaluation (n=3)
  - RCTs excluded, (n=0)

- Potentially appropriate RCTs to be included in the meta-analysis (n=3)
  - RCTs excluded (n=0)

- RCTs included in meta-analysis (n=3)
  - RCTs withdrawn (n=0)

- RCTs with usable information, by outcome (n=3)
Figure 2. Meta-analysis forest plot showing ongoing pregnancy rate.

<table>
<thead>
<tr>
<th>Study</th>
<th>'Full Bladder'</th>
<th>'Empty Bladder'</th>
<th>OR (fixed) 95% CI</th>
<th>Weight</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>or sub-category</td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Lewin 1997</td>
<td>81/411</td>
<td>51/385</td>
<td></td>
<td>74.56</td>
<td>1.61 [1.10, 2.36]</td>
</tr>
<tr>
<td>Lorusso 2005</td>
<td>22/67</td>
<td>21/64</td>
<td></td>
<td>25.44</td>
<td>1.00 [0.49, 2.08]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>478</td>
<td>449</td>
<td>100.00</td>
<td>1.44 [1.04, 2.04]</td>
</tr>
<tr>
<td>Total events:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Full Bladder'</td>
<td>103</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Empty Bladder'</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 1.27$, df = 1 ($P = 0.26$), $I^2 = 21.3%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.17$ ($P = 0.03$)</td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 3. Meta-analysis forest plot showing clinical pregnancy rate.

<table>
<thead>
<tr>
<th>Study</th>
<th>'Full Bladder'</th>
<th>'Empty Bladder'</th>
<th>OR (fixed) 95% CI</th>
<th>Weight</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>or sub-category</td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mitchell 1989</td>
<td>12/66</td>
<td>13/76</td>
<td></td>
<td>13.37</td>
<td>1.08 [0.45, 2.56]</td>
</tr>
<tr>
<td>Lewin 1997</td>
<td>110/411</td>
<td>64/385</td>
<td></td>
<td>65.46</td>
<td>1.83 [1.30, 2.59]</td>
</tr>
<tr>
<td>Lorusso 2005</td>
<td>26/67</td>
<td>25/64</td>
<td></td>
<td>21.16</td>
<td>0.99 [0.49, 2.00]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>544</td>
<td>525</td>
<td>100.00</td>
<td>1.55 [1.16, 2.08]</td>
</tr>
<tr>
<td>Total events:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>148 ('Full Bladder'), 102 ('Empty Bladder')</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 3.15$, df = 2 ($P = 0.21$), $I^2 = 36.6%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 2.97$ ($P = 0.003$)</td>
<td></td>
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</table>