

Performing the embryo transfer: a guideline

Practice Committee of the American Society for Reproductive Medicine

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A systematic review of the literature was conducted which examined each of the major steps of embryo transfer. Recommendations made for improving pregnancy rates are based on interventions demonstrated to be either beneficial or not beneficial. (*Fertil Steril*® 2017;107:882–96. ©2017 by American Society for Reproductive Medicine.)

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One of the most critical steps in the process of in vitro fertilization (IVF) is the embryo transfer. Studies have consistently demonstrated that embryo transfer pregnancy rates differ depending upon the clinician performing the procedure (1–3). In addition, data are accumulating that demonstrate a paucity of training in current fellowship programs or for practitioners who may have embryo transfer success rates consistently below the mean. A recent survey of Society for Assisted Reproductive Technology (SART) medical directors demonstrates that essentially all practitioners are allowed to perform embryo transfer if they desire, no matter what their skill (4). Half of the programs allow clinicians to perform embryo transfer using their personal “procedure” rather than having a standard protocol for all clinicians to follow. The results of that comprehensive survey demonstrate the breakdown of responses for 84 questions. From that survey, steps were identified for which the majority of practitioners demonstrated concordance, others were found to have nearly equal discordance, and, for most, a few outliers were identified. From those data a Common Practice Protocol was

developed (4). The purpose of this guideline for performing embryo transfer is to examine the various steps of the Common Practice Protocol by a systematic review of the literature to determine which of the steps, if any, are supported by sufficient data.

METHODS

This clinical practice guideline was based on a systematic review of the literature. A systematic literature search of relevant articles was performed in the electronic database MEDLINE through PubMed in December 2016, with a filter for human subject research. No limit or filter was used for time period or English language, but articles were subsequently culled for English language. A combination of the following medical subject headings or text words/keywords were used: acupuncture; acupuncture therapy; afterloading; ambulation; analgesia; analgesic; analgesics; anesthesia; anti anxiety; antibacterial hand soaps; antibiotic; antibiotics; antibiotic prophylaxis; bed rest; bed rest; birth; bleeding; blastocyst transfer; blood; catheter; catheter remains; catheter remnants; catheterization;

catheterization/adverse effects; catheterization/methods; cervix; Chinese medicine; cleanse; cleanser; cleansing; deposition; disinfection; duration; ejection; embryo retention; embryo transfer; embryo transfer catheter; embryo transfer/instrumentation; embryo transfer/methods; embryo transfer protocol; embryo transfer techniques; endometrial; endometrial cavity; endometrium; expel; expulsion; flushing; gloves; hand disinfection; hand hygiene; hand washing; hand washing/behavior; hand washing/behaviors; hand disinfectant; hand disinfectants; hand washing/glove; implantation; injection; in vitro fertilization; IVF; load; loading; massage; medicine, Chinese traditional relaxant; mucus; mucous; physician; physician’s role; placement; plunge; plunger; pregnancy; pressure; recumbency; recumbent; recumbent position; recumbent posture; release; replacement; rest; retained embryos; sedation; simulation; skin scrub; speed; stiletto; stylet; stylette; success; success rate; supine; surgical gloves; surgical scrub; time; time factors; time interval; transcutaneous electrical acupoint stimulation; transcutaneous electrical nerve stimulation; transfer techniques; ultrasound; ultrasound guidance; ultrasound guided embryo transfer; uteri; uterus; vaginal flush; vaginal preparation.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed for inclusion/

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exclusion criteria. Protocols and results of the studies were examined according to specific inclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: level I or II studies that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, implantation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles. This guideline focuses principally on pregnancy rate since most of the studies report pregnancy rates rather than live-birth rates.

Three members of an independent task force reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

The quality of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendation, either for or against.

Grade B: There is fair evidence to support the recommendation, either for or against.

Grade C: There is insufficient evidence to support the recommendation, either for or against.

Number of studies identified in electronic search and from examination of reference lists from primary and review articles: 2,086. Number of studies included: 143.

Summary of Inclusion/Exclusion Criteria

When current meta-analyses were not available to combine existing data, selected meta-analyses of studies were performed by the American Society for Reproductive Medicine

(ASRM) Practice Committee to estimate the pooled relative risk (RR) ratios of outcomes of interest. Statistical analyses and construction of forest and funnel plots were performed with Stata version 12.1. RR ratios, and 95% confidence intervals (CIs) were calculated for each outcome. Random effects models were used for the meta-analyses. Heterogeneity was assessed with the use of the I^2 test. Publication bias was assessed by constructing funnel plots. Tables listing inclusion/exclusion criteria are available online as [Supplemental Material](#).

CLINICAL PRACTICE

Is Patient Preparation, including Acupuncture, Relaxant, Sedation, or Antibiotics, before Embryo Transfer Necessary and Does It Affect Pregnancy and Live-birth Rates?

Over the past two decades there has been significant interest in maximizing assisted reproductive technology (ART) pregnancy rates through enhancing patient preparation prior to embryo transfer. These attempts have included acupuncture, analgesics, anesthesia, massage, transcutaneous electrical acupoint stimulation (TEAS), whole-systems traditional Chinese medicine (WS-TCM), and prophylactic antibiotics. These interventions provide theoretical benefits, which include modulating hormones, altering energy flow throughout the body, enhancing blood flow to the uterus, reducing stress, and reducing microbial colonization of the genital tract.

Acupuncture. Acupuncture has been the focus of significant interest and research, as it is an important tradition in Chinese medicine that dates back over 3,000 years. Acupuncture involves the insertion of fine needles through the skin intended to alter the flow of energy throughout the body. There are a variety of different acupuncture protocols based upon the underlying diagnosis. Protocols can include varying acupuncture points and treatment intervals during ovarian stimulation, retrieval, and before and after transfer.

A review of the medical literature is challenging as there is no consensus regarding a particular acupuncture protocol, and studies vary in regard to their inclusion and exclusion criteria, investigator blinding, and treatment of the control groups, including sham acupuncture.

A number of randomized controlled trials (RCTs) on acupuncture have been published with contradictory results. There are five RCTs showing some benefit of acupuncture (5–9). Anxiety levels were lower ($P < .05$) and clinical pregnancy, implantation, and live-birth rates were higher ($P < .017$) in the auricular acupuncture groups vs the sham auricular acupuncture and control groups in the largest of the trials, which included 305 IVF patients (7). In another trial of 273 women treated with IVF-intracytoplasmic sperm injection (ICSI), the treatment group received acupuncture on the day of embryo transfer and had a clinical pregnancy rate of 39% compared with a control group that had no acupuncture 24% ($P = .038$) (9). A meta-analysis of seven trials and 1,366 patients also showed an improved clinical pregnancy rate (odds ratio [OR] 1.65, 95% CI 1.27–2.14; seven trials) and live-birth rate (OR 1.91, CI 1.39–2.64; four trials) when acupuncture was given with embryo transfer (10).

A systematic review did not show significant improvement in clinical pregnancy rate with acupuncture on the day of embryo transfer, 25 minutes before and after the transfer. It found a pooled benefit when performed 30 minutes after transfer and at implantation (RR 1.76, 95% CI 1.22–2.55; four trials) and also in the follicular phase and 25 minutes before and after transfer (RR 1.56, 95% CI 1.04–2.33; four trials) (11). In addition, there was a 3-fold increased rate of pregnancy (95% CI 0.8, 8.0) and lower stress (not significant [NS]) associated with acupuncture in an observational cohort study of 57 women (12).

While there were five RCTs that showed some benefit, seven RCTs showed no benefit to acupuncture (13–19). In a trial of 416 women less than 36 years of age undergoing IVF with ICSI, the treatment group received acupuncture 25 minutes before and after embryo transfer with a pregnancy rate of 40.4% compared with the control group without acupuncture of 32.3% ($P=.652$) (15). Four meta-analyses similarly found no difference between acupuncture and control patients (11, 20–22). In addition, a systematic review of eight studies (N=2,505) in which acupuncture was performed on or around the day of embryo transfer showed no evidence that acupuncture improved live-birth rate in ART (OR=1.22, 95% CI 0.87–1.70) (Fig. 1) (23).

Failure to demonstrate a difference in pregnancy rates with acupuncture could be a failure of the actual protocol tested rather than acupuncture itself. There may be some circumstances where pregnancy rates are improved with acupuncture, but there is no consistent evidence that live-birth rates are improved with acupuncture. Overall, the trials

vary in design and have different findings, which make firm conclusions challenging.

Summary statement:

- There is fair evidence that acupuncture performed around the time of embryo transfer does not improve live-birth rates in IVF. (Grade B)

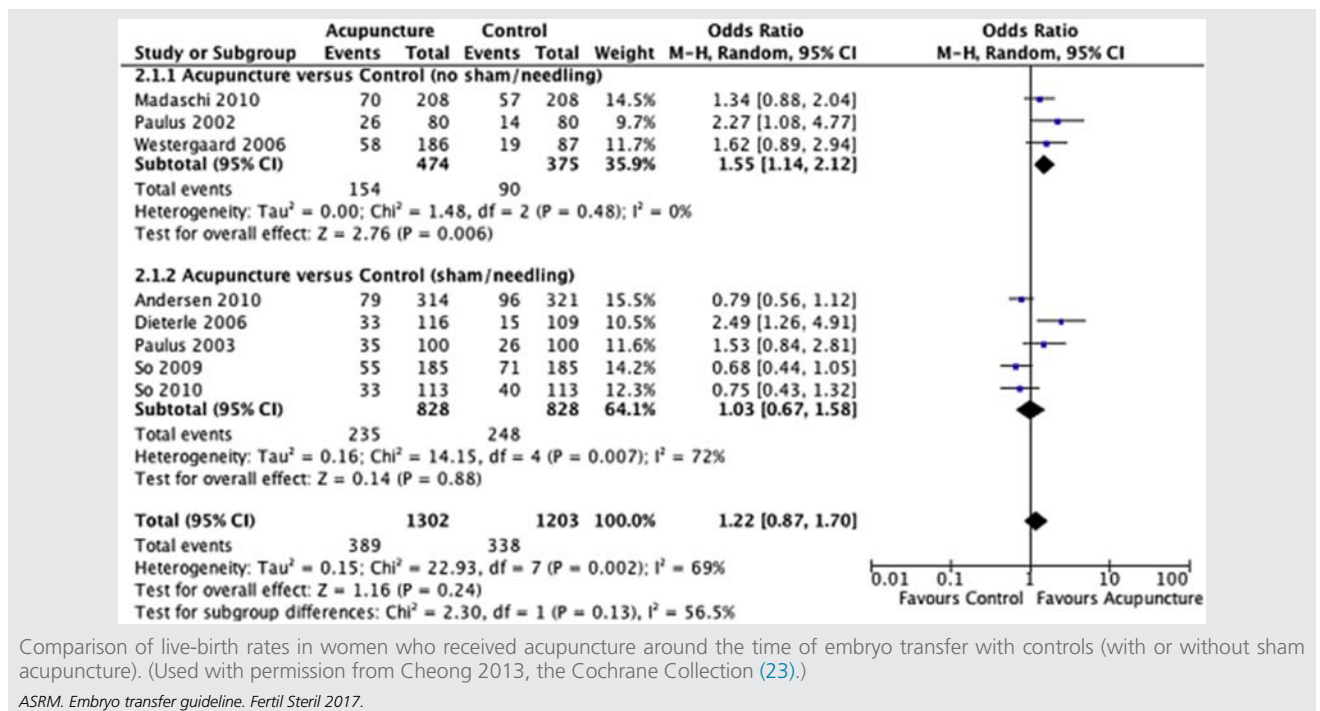
Analgesics. Analgesics are occasionally recommended to help improve ART outcomes; however, there were no relevant studies identified through the literature search showing that the use of analgesics are associated with embryo transfer outcomes.

Summary statement:

- There is insufficient evidence to recommend for or against analgesics to improve IVF-embryo transfer outcomes. (Grade C)

Anesthesia. In an uncontrolled preliminary study, IVF outcomes were compared for patients who did or did not receive general anesthesia for embryo transfer. In this preliminary analysis, anesthesia showed benefit on the pregnancy rate in patients who received sodium thiopentone and alfentanil (36%; n=86) vs matched controls who did not receive anesthesia (21%; n=131). However, when these investigators subsequently analyzed their data for two larger cohorts: one (n=603 embryo transfers) without anesthesia before the analysis, and a second group (n=795 embryo transfers) that received general anesthesia after the study, the pregnancy rate was 18% in the embryo transfers without anesthesia,

FIGURE 1



Comparison of live-birth rates in women who received acupuncture around the time of embryo transfer with controls (with or without sham acupuncture). (Used with permission from Cheong 2013, the Cochrane Collection (23).)

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and 19% in the embryo transfers with anesthesia. In this larger comparison, general anesthesia did not have a beneficial impact on pregnancy rate (24).

Summary statement:

- There is insufficient evidence that anesthesia during embryo transfer improves pregnancy rates. Given that there is no clear benefit and that there are inherent risks associated with anesthesia, routine anesthesia is not recommended to improve IVF-embryo transfer outcomes. (Grade C)

Massage. Massage therapy is proposed as a way to relieve physical and psychological discomfort and has been suggested as a therapeutic modality without significant risk or side effects in an IVF cycle prior to embryo transfer. Only one study—a retrospective, observational analysis—assessed massage therapy before blastocyst transfer in cryopreservation cycles and demonstrated evidence of improved pregnancy and live-birth rates (25).

Summary statement:

- There is insufficient evidence to recommend for or against massage therapy to improve IVF-embryo transfer outcomes. (Grade C)

Transcutaneous electrical acupoint stimulation. One prospective, randomized trial on the effect of transcutaneous electrical acupoint stimulation (TEAS) on embryo transfer in 309 patients showed that electrodes placed on acupoints instead of needles improved the clinical pregnancy and live-birth rates relative to controls (26). No statistically significant demographic differences were noted among the three groups (group I, mock TEAS; group II, single TEAS; group III, double TEAS; all treatments 30 minutes after embryo transfer). Also, the authors state that the number of transfers were not different among the three groups, but did not include these data in the manuscript. Clinical pregnancy and live-birth rates increased significantly in patients who received TEAS on the day of embryo transfer; the clinical pregnancy rate was 29.3% with mock TEAS vs 42.7% with single TEAS treatment ($P=.044$), and the live-birth rate was 21.2% with mock TEAS vs 37.3% with single TEAS treatment ($P=.011$). In patients who received TEAS also on the day before embryo transfer, the clinical pregnancy rate further increased to 50% ($P=.003$) and live-birth rate increased to 42% ($P=.002$) (26). No additional studies of TEAS are available.

Summary statement:

- There is fair evidence based on only one RCT that TEAS improves IVF-embryo transfer outcomes. (Grade B). However, given the lack of any other studies, a recommendation for or against TEAS to improve IVF-ET outcomes cannot be made.

Whole-systems traditional Chinese medicine. Whole-systems traditional Chinese medicine (WS-TCM) as an approach to improve pregnancy rates in IVF can include acupuncture, Chinese herbal medications, diet, and lifestyle recommendations. Only one observational study of 119 non-donor and

21 donor patients was identified assessing WS-TCM and IVF-embryo transfer outcomes. This retrospective cohort study showed an improved live-birth rate of 61.3% with WS-TCM relative to 50.8% in the acupuncture group and 48.2% among controls in non-donor cycles ($P=.03$) (27). However, a number of limitations existed, including the retrospective nature of the study with lack of randomization, the fact that patients chose their treatment, and the lack of control of differing embryo quality between the groups.

Summary statement:

- There is insufficient evidence to recommend for or against WS-TCM to improve IVF-embryo transfer outcomes. (Grade C)

Prophylactic antibiotics. Another intervention that has been considered to improve embryo transfer success rates is the use of prophylactic antibiotics. Only one RCT has addressed this issue (28). In that trial, 350 patients were randomized to receive either prophylactic antibiotics or no antibiotics. Those randomized to the treatment group received amoxicillin and clavulanic acid on the day before and the day of transfer. The catheter tips were cultured after the transfer. While the antibiotics significantly reduced catheter contamination rates, the clinical pregnancy rates between the two groups were not different. Live-birth rates were not an outcome of that trial. A systematic review of the literature in 2012 did not find any additional studies to help determine whether prophylactic antibiotics for embryo transfer were helpful, particularly for improving live-birth rates (29). Their conclusion was that the finding of this single study did not support the use of amoxicillin and clavulanic acid to improve IVF success rates and that the effect of other regimens on IVF outcomes is unknown.

Summary statement:

- There is fair evidence based on a single RCT that an antibiotic regimen that includes amoxicillin and clavulanic acid given on the day before and the day of embryo transfer does not improve pregnancy rates. (Grade B). Given these results and the lack of other evidence in the literature to support prophylactic antibiotics at embryo transfer, a recommendation for routine prophylactic antibiotics cannot be made.

Does Physician Preparation, including the Use of Sterile Latex-free Gloves, before an Embryo Transfer Procedure Affect Pregnancy and Live-birth Rates?

Given that optimal handling of the embryo is imperative during embryo transfer, it is natural to consider the effect of the type of glove worn by the clinician performing the embryo transfer on outcome. There is no question that both powdered and unpowdered gloves are toxic when in direct contact with embryos. However, with the potential transmission of the powder from the gloves to the embryo transfer catheter through the air, particular concern has been raised regarding the use of powdered gloves during embryo transfer. Only one randomized controlled study addresses the impact of the type of glove utilized for embryo transfer on pregnancy rate. This

study of 712 women evaluated the effect of powdered gloves on clinical pregnancy rate in IVF (37.6%) in comparison with unpowdered gloves (37.4%) and did not find a difference in pregnancy rate with the use of powdered gloves ($P=1.0$) (30). These investigators concluded that as long as direct contact is avoided, powdered gloves can safely be used in embryo transfer. There are no studies assessing glove use and live-birth rates. Therefore, although some physicians may opt to avoid non-sterile, latex, or powdered gloves in hopes of minimizing embryo toxicity, no data support the usage of a particular type of glove to optimize pregnancy rate.

Summary statement:

- There is fair evidence based on one, single-center RCT that powdered gloves worn during embryo transfer do not have an adverse effect on pregnancy rates. (Grade B). No specific type of glove is recommended for embryo transfer.

Does Routine Use of Abdominal Ultrasound for Guidance during Embryo Transfer Improve Pregnancy and Live-birth Rates?

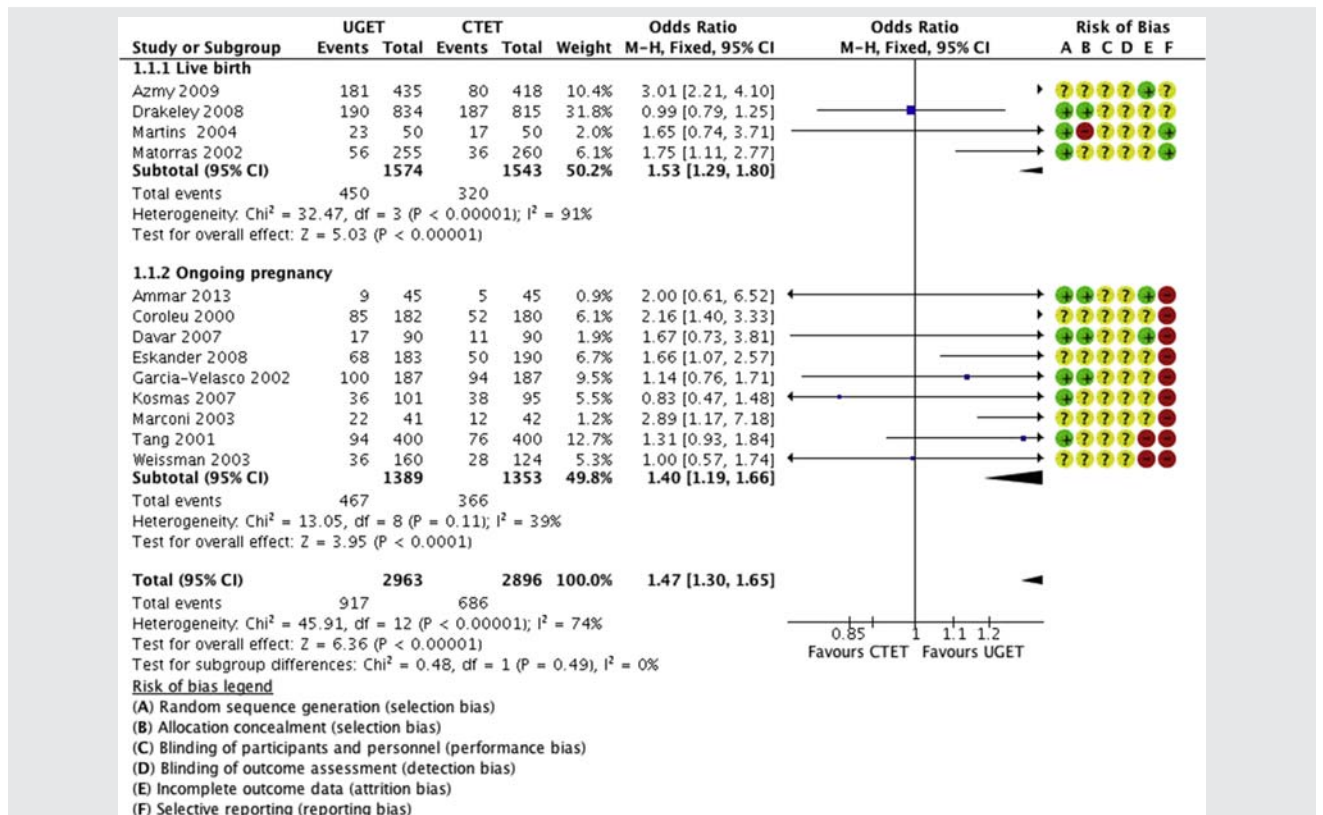
There are 35 RCTs and cohort studies among other published data that examine the use of abdominal ultrasound guidance

during embryo transfer. Ultrasound was introduced with the hope that it would diminish the likelihood that the embryo transfer catheter would traumatize the endometrium as compared with a blind approach or touch technique.

With regard to the transfer of fresh embryos in eight RCTs and four cohort studies, transabdominal (TA) ultrasound-guided embryo transfer was found to improve the implantation rate and/or pregnancy rate (31–40), clinical or ongoing clinical pregnancy rates, and/or live-birth rate (33, 36, 41–43). These findings were supported by five meta-analyses or systematic reviews (44–48). A recent review found that ultrasound-guided embryo transfer was associated with improved clinical pregnancy rate (OR 1.31, 1.17–1.45; 20 trials; N=6,711 women) and live-birth rate/ongoing pregnancy rate (OR 1.47, 1.30–1.65; 13 trials; N=5,859 women), compared with clinical touch (Fig. 2) (48). Studies have also shown improved outcomes using ultrasound guidance with frozen embryo transfer and programmed recipient cycles using donor eggs (32, 49).

In contrast to the preponderance of studies that have shown improved IVF outcome with the use of TA ultrasound guidance, a few studies have not been able to replicate these findings. One RCT of 374 patients found a similar pregnancy rate between ultrasound-guided and blind transfers (50). Likewise, an RCT of day-3 embryo transfers that included

FIGURE 2



Comparison of live-birth and ongoing pregnancy rates between ultrasound-guided embryo transfer and clinical touch embryo transfer. Used with permission from Brown 2016, the Cochrane Collection (48).

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50 fresh cycles found no statistically significant difference between ultrasound-guided and clinical touch transfers (51). In addition, a cohort study showed that the pregnancy rate was equivalent in 241 embryo transfers performed with and without ultrasound (52). Two underpowered RCTs showed a trend toward a benefit of TA ultrasound guidance that did not reach statistical significance (53, 54). Two RCTs showed no benefit of TA ultrasound guidance (55, 56).

The level of difficulty of embryo transfer has also been the subject of investigation. One RCT showed that ultrasound guidance offered no improvement if a mock transfer was performed and found to be easy (57), while another showed no improvement if the uterine cavity length had previously been recorded prior to embryo transfer (58). One cohort study suggested that ultrasound prior to embryo transfer helped identify potentially difficult transfers (59), while another suggested that tactile technique was not as reliable as ultrasound for confirmation of catheter placement (60). In cases of difficult embryo transfer, two studies found benefit with ultrasound guidance (43, 61).

Limited centers have utilized transvaginal (TV) ultrasound for embryo transfer (62–65). A few studies have compared TA and TV ultrasound guidance for embryo transfer. One study found that TV guidance improved patient comfort relative to TA ultrasound due to the lack of bladder filling but increased the duration of the procedure (64). Similarly, an RCT comparing TA-guided transfer to TV uterine length measurement, immediately followed by an unguided, cleaved embryo placement based on the calculated distance, showed no difference in pregnancy rates. However, in this study the TV approach had less moderate to severe discomfort largely attributable to lack of bladder filling (65).

Summary statements:

- There is good evidence based on 10 RCTs to recommend TA ultrasound guidance during embryo transfer to improve clinical pregnancy rate and live-birth rate. (Grade A)
- While selected ultrasound guidance for an anticipated difficult embryo transfer may be an alternative to routine ultrasound guidance, there is insufficient evidence to recommend for or against this practice. (Grade C)

Does Removing Mucus from the Endocervical Canal Improve Pregnancy and Live-birth Rates?

Some studies have indicated that cervical mucus interferes with embryo transfer by blocking the passage of embryos through the tip of the catheter, pulling embryos back from the site of expulsion, or contaminating the intrauterine environment with cervical flora. However, it has been suggested that removing cervical mucus might stimulate uterine contractility or cervical bleeding, with a possible negative impact on pregnancy outcomes.

One RCT (66) and a prospective cohort study (67) demonstrated that removing mucus from the endocervical canal with sterile cotton swabs or aspiration with a catheter, respectively, improves clinical outcomes. An additional published RCT was not comparable since the mucus was removed with

a cervical brush (68). A systematic review was unable to make a definitive conclusion on this topic, which was limited by the inclusion of an abstract that was never subsequently published and a study using the cytobrush (69). Therefore, data from the only well-designed RCT (N=530) and a prospective, controlled cohort study (N=286) were used for the recommendation (66, 67). The RCT showed improved clinical pregnancy rate (39.2% study vs 22.6% controls, $P < .001$) and live-birth rate (33.6% study vs 17.4% controls, $P < .001$) with the removal of cervical mucus (66). The clinical pregnancy rate was significantly higher in the group that had mucus aspiration compared with the group with no aspiration ($P = .003$; OR = 2.18, 95% CI = 1.32–3.58) in the cohort study (67).

Summary statement:

- There is fair evidence based on one RCT and one prospective cohort study that there is a benefit to removing cervical mucus at the time of embryo transfer to improve clinical pregnancy and live-birth rates. (Grade B)

Does the Type of Catheter Used for Embryo Transfer Affect Pregnancy and Live-birth Rates?

While the literature is fraught with ambiguity, there exist a number of controlled trials that provide insight into the role that the transfer catheter plays in IVF outcomes. The data assessing the influence of embryo transfer catheter type and IVF outcomes span almost three decades. Varying definitions of soft and firm (also called hard) catheters complicate the analysis. For this analysis, any embryo transfer catheter with a soft inner catheter was classified as soft; the remainder were classified as hard catheters. In some cases, the catheters were reclassified.

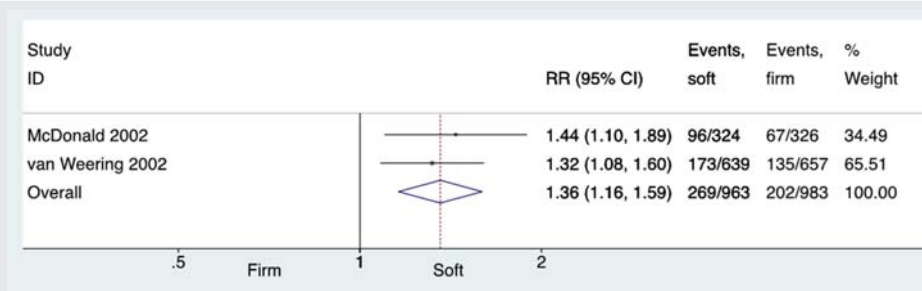
Two RCTs were designed to determine if different firm catheters affected IVF outcomes (70, 71). In both trials, the Tight Difficult Transfer (TDT) catheter (Prodimed) appeared inferior. Of firm catheters studied, Tomcat (Meditech; Sherwood Medical) and Frydman® (Eurosurgical; Prodimed) catheters seemed to confer a higher pregnancy rate than the Tefcat (Cook) or TDT (Meditech; Prodimed) (52, 70–73). However, data on firm catheters are mostly from the year 2000 or earlier and therefore are mainly of historical significance. Firm catheters are no longer used as a first choice for today's embryo transfer. The use of firm catheters has been supplanted by soft transfer catheters.

Two RCTs and two cohort studies favor soft over firm catheters as a means of improving IVF pregnancy rates (40, 74–76). In order to obtain pooled estimates from the two well-designed RCTs comparing soft vs firm catheters as currently defined, a meta-analysis was performed by the ASRM Practice Committee using a random-effects model. This analysis showed that pregnancy rates were higher using soft catheters for embryo transfer compared with firm catheters (RR 1.36, 95% CI 1.16–1.59) (74, 75) (Fig. 3). No controlled trial favors firm over soft catheters (77).

A cohort study assessing the influence of catheter type on difficult embryo transfers failed to find benefit in using a soft catheter (78). In total, the data do not support benefit of using a firm catheter for routine use. In a trial in which patients were

FIGURE 3

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Comparison of pregnancy rates with the use of soft and firm embryo transfer catheters.

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alternately assigned to either the Edwards-Wallace catheter (H.G. Wallace Ltd.) or the rigid metal Erlangen catheter (not a true randomization), the rigid system showed higher pregnancy rates (19% Wallace vs 30% Erlangen, [recalculated] $P = .0381$) (77). In this study, the transfer technique was also different depending on the catheter system used. The combination of a non-randomization system, the variable use of a cervical tenaculum, and the lack of ultrasound guidance may account for the lack of benefit seen with the Edwards-Wallace catheter. Three meta-analyses (44, 79, 80) comparing soft vs “hard” or “firm” catheters were excluded from this analysis, because the authors of these studies categorized the Rocket Embryon[®], TDT, and Labotect catheters, with soft inner and firm outer components, as firm catheters.

The majority of the literature, including 10 RCTs and 1 cohort study, shows no difference in IVF outcomes (clinical pregnancy rate, pregnancy rate, implantation rate) when comparing different types of soft catheters (81–91). A single RCT and one cohort study favored the Edwards-Wallace catheter compared with rigid catheters when looking at pregnancy rate (92, 93). None of the trials included demonstrated a difference in birth rates when comparing soft catheters to one another. The totality of the data strongly supports similar pregnancy rates and, in some studies, implantation rates when comparing transfers using a variety of soft catheters.

It appears that no soft embryo transfer catheter is clearly superior and that commercially available soft catheters perform similarly. Personal choice and cost can guide differential use of one soft catheter over the other.

Summary statement:

- There is good evidence to recommend the use of a soft embryo transfer catheter to improve IVF-embryo transfer pregnancy rates. (Grade A). Data on live-birth rates and specific types of soft catheters are limited.

Does Positioning the Catheter at the Time of Embryo Transfer Affect IVF-Embryo Transfer Implantation, Pregnancy, and Live-birth Rates?

In terms of embryo transfer technique, it is widely accepted that avoiding touching the uterine fundus is one of the

most important factors leading to a successful transfer. However, what is unclear is the ideal location for embryo placement within the uterine cavity. Four RCTs were designed to answer this question (94–97). One RCT examined three different placement locations (1.0, 1.5, and 2.0 cm) from the uterine fundus (94). It found statistically significantly ($P < .05$) higher implantation rates for placement between 1.5 cm and 2.0 cm compared with 1.0 cm, and statistically significantly higher ($P < .05$) pregnancy rates when the selected location was approximately 2 cm from the uterine fundus compared with 1 cm from the fundus (94). When placement was compared between <1 cm and 1–1.5 cm, one randomized controlled study demonstrated improved pregnancy rates and implantation rates at the location farther from the fundus (97). Two additional randomized controlled studies found no difference in implantation rate and pregnancy rate, with one study dividing placement into the upper vs lower half of the endometrial cavity (95) and the other comparing 2 cm from the fundus vs the uterine cavity midpoint (96). Five cohort studies (98–102) assessing the influence of embryo placement produced mixed results. Only one of those studies found no impact on pregnancy outcome based on embryo placement position (98). However, it was the oldest of the studies, reported in 1996.

The majority of the studies found that embryo placement impacted pregnancy rates, with pregnancy rates highest when the embryo was placed in the upper or middle area of the uterine cavity, at least 1 cm away from the fundus (94, 96, 97, 99–102). A 2015 RCT that demonstrated no difference when the catheter tip was 2 cm from the fundus or in the middle third of the uterine cavity further supports placement in the upper or middle uterine cavity for embryo expulsion (96). One difficulty when comparing studies examining optimal embryo placement is the lack of consistency in comparative placements, with some studies assessing exact distances from the fundus, and others dividing the uterine cavity into areas.

Finally, the placement of the outer catheter may also affect pregnancy rates. In a cohort study of 408 patients who underwent embryo transfer, overall pregnancy rates were significantly better in those patients ($n = 218$) for whom the outer sheath did not go beyond the internal os compared with patients ($n = 190$) for whom the catheter was

placed through the internal os, 57.3% vs 43.1%, $P=.0054$ (103).

Summary statements:

- There is fair evidence based on six studies (two RCTs and four cohort studies) that embryo transfer catheter placement affects implantation and pregnancy rates. (Grade B)
- There is fair evidence based on seven studies (three RCTs and four cohort studies) that placement of the catheter tip in the upper or middle (central) area of the uterine cavity, greater than 1 cm from the fundus for embryo expulsion, optimizes pregnancy rates. (Grade B)
- There is insufficient evidence for more specific recommendations regarding the positioning of the catheter at the time of embryo transfer. (Grade C)

Does the Time Interval before Withdrawing the Catheter Affect IVF-Embryo Transfer Pregnancy and Live-Birth Rates?

Once the embryo(s) is discharged from the embryo catheter the physician has the option of immediately withdrawing the transfer catheter or pausing before withdrawal of the catheter. A randomized, controlled study of 100 patients (104) compared immediate withdrawal to a 30-second delay and found no difference in pregnancy rates. A follow-up cohort study of 218 patients (105) examined immediate withdrawal compared with a 60-second delay before withdrawal, and similarly found no difference in pregnancy rates based on timing of catheter withdrawal. It can therefore be concluded that a delay in catheter withdrawal after embryo placement does not lead to improved pregnancy rates.

Summary statement:

- There is fair evidence based on one RCT and one cohort study to recommend immediate withdrawal of the embryo transfer catheter after embryo expulsion. (Grade B)

Is the Presence of Mucus on the Catheter (after It Is Removed) Associated with Pregnancy and Live-birth Rates?

The goal of embryo transfer is to attain a smooth, atraumatic passage of the catheter through the endocervical canal and lower uterine segment. Clinicians have debated whether the presence of mucus on the catheter after the embryo transfer adversely affects IVF success rates.

Seven cohort studies (106–112) showed that the presence of mucus in or on the catheter (once it is withdrawn) does not adversely affect clinical pregnancy rate or live-birth rate. In a cohort study that compared direct embryo transfer with the afterload technique, a higher pregnancy rate, not statistically significant, was found with the afterload technique vs the direct technique. For the latter, more catheters were contaminated with mucus, which was statistically significant (113). This was the only study that implicated a negative outcome with the presence of mucus contamination after withdrawing the catheter.

Summary statement:

- There is fair evidence based on seven cohort studies that the presence of mucus on the embryo transfer catheter, once it is withdrawn, is not associated with a lower clinical pregnancy rate or live-birth rate. (Grade B)

Does the Presence of Blood on the Catheter (once It Is Withdrawn) Make a Difference in Pregnancy or Live-birth Rate?

The presence of blood on the catheter once removed at the time of embryo transfer and its possible implications have been studied often, suggesting an increased interest and concern about blood and embryo transfer techniques. A total of 17 studies (1 RCT, 1 systematic review/meta-analysis, and 15 cohort studies) were evaluated. Many of the cohort studies were performed 10 to 15 years ago. A small RCT (70) compared pregnancy outcomes in patients randomized to embryo transfer with the Tomcat catheter ($n=32$) vs the TDT catheter ($n=34$). They reported the presence of blood and/or mucus on the catheter as a secondary outcome measurement and found no impact of blood on clinical pregnancy rate and implantation rate. A large cohort study from an Australian database (109) also demonstrated no significant difference on clinical pregnancy rate based on catheter tip contamination (30.2% no contamination, 24% mucus only, 30% blood only, 39.1% mucus and blood, 26.4% much mucus and blood, $P=NS$). One systematic review/meta-analysis (114) and six other cohort studies (78, 108, 110, 111, 115, 116) were in agreement.

In contrast to the RCT (70), meta-analysis (114), the recent large Australian cohort study (109), and five other cohort studies showing no adverse association between pregnancy rates and blood on the withdrawn embryo transfer catheter, eight other cohort studies (44, 106, 112, 117–121) demonstrated an opposite finding. A 2002 cohort study of 640 IVF-ICSI cycles showed that clinical pregnancy rate was significantly ($P<.01$) higher when there was no blood during transfer vs with blood. The OR was 0.54 (0.35–0.84) for diminished pregnancy rate in cycles with blood during embryo transfer vs bloodless (120). In another cohort study (584 consecutive cycles), blood on the catheter was the most important transfer characteristic in predicting implantation rate ($P=.042$) and clinical pregnancy rate ($P=.018$) (106). The presence of blood on the catheter was associated with decreased clinical pregnancy rate (31.7% blood vs 51.7% no blood, $P=.004$; strength of association: $P=.01$) or implantation rate (19.5% blood vs 31.3% no blood, $P=.015$; strength of association: $P=.04$), when only high-grade embryos or blastocysts were transferred (106). There is a suggestion that embryos are more likely to be retained in a catheter when it is contaminated with mucus or blood, but retention of embryos has not been associated conclusively with poorer outcomes.

Summary statement:

- Given the mixed results of studies, there is insufficient evidence to state conclusively that the presence of blood

on the catheter, once it is withdrawn, is associated with implantation or pregnancy rates. (Grade C)

Does the Rate of Injection of the Catheter Load Affect Pregnancy and Live-birth Rates?

The ideal speed at which the embryo should be injected at the time of embryo transfer is unknown, as this may be one of the most difficult aspects to quantify and thus compare. The earliest attempt at assessing the ideal velocity of injection was in 2003 when a computational model suggested that high injection speeds may lead to ectopic pregnancies (122). This hypothesis was corroborated by several studies using both mathematical and simulated in vitro models. These studies all suggested that the injection velocity of the embryo could impact the trajectory of the placement, and therefore potentially impact implantation rate and the risk of ectopic pregnancy if a fast speed was used too near the fundus (123–126). A 2012 simulation study assessed standardization of injection speed by evaluating a pump-regulated embryo transfer (PRET) device compared with manual injection. The PRET device generated reliable and reproducible injection speeds, whereas manual injection showed large variation in speed even with a standardized protocol (127). A non-blinded randomized trial also utilizing the same PRET device resulted in less variance in embryo positioning as assessed by ultrasound measurement compared with manual injection (128).

Summary statement:

- Given the paucity of data, there is insufficient evidence to recommend any specific injection speed of the catheter at the time of embryo transfer. (Grade C)

Do Retained Embryos in the Transfer Catheter and Immediate Re-transfer of Them Affect Implantation, Clinical Pregnancy, or Spontaneous Abortion Rates?

Retained embryo(s) after the initial transfer attempt is an uncommon, but clinically worrisome event, creating anxiety for patients and practitioners. The majority of studies addressing this question report an incidence of retained embryo(s) of <3%; however, three studies reported rates of 5%, 7.5%, and 10%, respectively (106, 121, 129).

The nature of this problem precludes an RCT. All published studies report an immediate re-transfer and retrospective analyses of this variable. The evaluated data include 12 studies (secondary outcome of 1 RCT, 10 cohort studies, 1 series) (85, 106, 107, 111, 121, 129–135). In all but one report, the clinical outcomes of implantation, clinical pregnancy, and spontaneous abortion rates were statistically unchanged for patients undergoing re-transfer after embryo retention. That study reported a statistically significant decline in implantation rate from 17% to 13% ($P=.03$) after 29/584 re-transfers of embryos at either the cleavage or blastocyst stage. There was no statistical difference in clinical pregnancy rate (106).

Summary statement:

- There is fair evidence based on the secondary outcome of one RCT, nine cohort studies, and one series that retained embryos in the transfer catheter and immediate re-transfer do not affect implantation, clinical pregnancy, or spontaneous abortion rates. (Grade B)

Does Bed Rest or Ambulation Affect IVF-Embryo Transfer Pregnancy and Live-birth Rates?

Among the many empiric practices of embryo transfer that have been scrutinized by studies designed to improve IVF success rates, bed rest has emerged as a prime candidate to study. In particular, a number of studies were designed to focus on the duration of time patients remained at bed rest following the transfer of embryos into the endometrial cavity. During the early years of IVF compared to recent times, the longest variations of time that patients were kept supine existed in hopes of avoiding uterine contractions and “premature expulsion” of embryos from the uterus. Anecdotal reports have included durations of bed rest for many that extended up to 24 hours and for some as long as 2 weeks.

Of 14 studies included from this systematic literature review, none of them demonstrated a benefit of bed rest of any duration. Three RCTs between 1997 and 2004 included 712 patients randomized to different periods of bed rest and showed no benefit of any of the following durations: 1 hour vs 24 hours ($N=378$), 20 minutes vs 24 hours ($N=182$), and immediate ambulation vs 30 minutes ($N=152$) (136–138). One additional RCT randomized 120 patients to either bed rest for 15 minutes or immediate ambulation and followed outcome of the air bubbles in the endometrial cavity by ultrasound, demonstrating no difference between the two groups (139). Three systematic reviews ($N=724$; $N=542$; $N=757$, respectively) (140–142) corroborated the findings of these RCTs. Furthermore, three cohort studies (143–145) ($N=677$) and two patient series (146, 147) ($N=112$) demonstrated that bed rest of different durations did not benefit pregnancy outcomes. One additional series followed the endometrial air bubbles with ultrasound in patients who stood up immediately after transfer and found a similar position of the air bubbles before and after standing, concluding that for these 101 IVF cycles “standing shortly after embryo transfer does not play a significant role in the final position of embryo-associated air...” (148).

In contrast to the studies that have shown no benefit, one well-designed recent RCT demonstrated possible harm (149). Two hundred-forty patients undergoing their first IVF cycle were randomized to either 10 minutes of bed rest or immediate ambulation. This study demonstrated that the live-birth rates were significantly ($P=.02$) higher in the no bed rest group (56.7%) when compared to 10 minutes of rest (41.6%). Given that this study was performed in recent years benefiting from more current success rates, used a more homogeneous patient population of first-time IVF cycles with similar demographic and cycle data between the two groups, and demonstrated a statistically significant lower success rate for the relatively short duration of bed rest of 10 minutes, the suggestion of harm for bed rest is noteworthy.

Summary statement:

- There is good evidence not to recommend bed rest after embryo transfer. (Grade A)

SUMMARY**Good Evidence (Grade A)**

- There is good evidence based on 10 RCTs to recommend TA ultrasound guidance during embryo transfer to improve clinical pregnancy rate and live-birth rate. (Grade A)
- There is good evidence to recommend the use of a soft embryo transfer catheter to improve IVF-embryo transfer pregnancy rates. (Grade A). Data on live-birth rates and specific types of soft catheters are limited.
- There is good evidence not to recommend bed rest after embryo transfer. (Grade A)

Fair Evidence (Grade B)

- There is fair evidence that acupuncture performed around the time of the embryo transfer does not improve live-birth rates in IVF. (Grade B)
- There is fair evidence based on only one RCT that transcutaneous electrical acupoint stimulation (TEAS) improves IVF-embryo transfer outcomes. (Grade B). Given the lack of any other studies, a recommendation for or against TEAS to improve IVF-embryo transfer outcomes cannot be made.
- There is fair evidence based on a single RCT that an antibiotic regimen that includes amoxicillin and clavulanic acid given on the day before and the day of embryo transfer does not improve pregnancy rates. (Grade B) Given these results and the lack of other evidence in the literature to support prophylactic antibiotics at embryo transfer, a recommendation for routine prophylactic antibiotics cannot be made.
- There is fair evidence based on one, single-center RCT that powdered gloves worn during embryo transfer do not have an adverse effect on pregnancy rates. (Grade B) No specific type of glove is recommended for embryo transfer.
- There is fair evidence based on one RCT and one prospective cohort study that there is a benefit to removing cervical mucus at the time of embryo transfer to improve clinical pregnancy and live-birth rates. (Grade B)
- There is fair evidence based on six studies (two RCTs and four cohort studies) that embryo transfer catheter placement affects implantation and pregnancy rates. (Grade B)
- There is fair evidence based on seven studies (three RCTs and four cohort studies) that placement of the catheter tip in the upper or middle (central) area of the uterine cavity, greater than 1 cm from the fundus for embryo expulsion, optimizes pregnancy rates. (Grade B)
- There is fair evidence based on one RCT and one cohort study to recommend immediate withdrawal of the embryo transfer catheter after embryo expulsion. (Grade B)
- There is fair evidence based on seven cohort studies that the presence of mucus on the embryo transfer catheter, once it

is withdrawn, is not associated with a lower clinical pregnancy rate or live-birth rate. (Grade B)

- There is fair evidence based on the secondary outcome of one RCT, nine cohort studies, and one series that retained embryos in the transfer catheter and immediate re-transfer do not affect implantation, clinical pregnancy, or spontaneous abortion rates. (Grade B)

Insufficient Evidence (Grade C)

- There is insufficient evidence to recommend for or against analgesics to improve IVF-embryo transfer outcomes. (Grade C)
- There is insufficient evidence that anesthesia during embryo transfer improves pregnancy rates. Given that there is no clear benefit and that there are inherent risks associated with anesthesia, routine anesthesia is not recommended to improve IVF-embryo transfer outcomes. (Grade C).
- There is insufficient evidence to recommend for or against massage therapy to improve IVF-embryo transfer outcomes. (Grade C)
- There is insufficient evidence to recommend for or against whole systems—traditional Chinese medicine to improve IVF-embryo transfer outcomes. (Grade C)
- While selected ultrasound guidance for an anticipated difficult embryo transfer may be an alternative to routine ultrasound guidance, there is insufficient evidence to recommend for or against this practice. (Grade C)
- There is insufficient evidence for more specific recommendations regarding the positioning of the catheter at the time of embryo transfer. (Grade C)
- Given the mixed results of studies, there is insufficient evidence to conclusively state that the presence of blood on the catheter, once it is withdrawn, is associated with lower implantation or pregnancy rates. (Grade C)
- Given the paucity of data, there is insufficient evidence to recommend any specific injection speed of the catheter at the time of embryo transfer. (Grade C)

RECOMMENDATIONS

Embryo transfer is considered a critical step in the IVF process. Extensive literature exists regarding all aspects of embryo transfer, which supports its importance to overall IVF success. While there are insufficient data to provide guidance on a number of techniques used during embryo transfer, the literature does provide guidance for many aspects of this critical component of IVF.

The following interventions are supported by the literature for improving pregnancy rates:

- Abdominal ultrasound guidance for embryo transfer
- Removal of cervical mucus
- Use of soft embryo transfer catheters
- Placement of embryo transfer tip in the upper or middle (central) area of the uterine cavity, greater than 1 cm from the fundus, for embryo expulsion
- Immediate ambulation once the embryo transfer procedure is completed

The following interventions have been shown not to be beneficial for improving pregnancy rates:

- Acupuncture
- Analgesics, massage, general anesthesia, whole systems–traditional Chinese medicine
- Prophylactic antibiotics to improve embryo transfer outcomes
- Waiting after expulsion of embryos for any specific period of time before withdrawing the embryo transfer catheter

CONCLUSIONS

A systematic review of the literature allowed the development of this guideline for standardization of the embryo transfer process. Many, but not all, of the current techniques employed are supported by the literature as evidenced by the recommendations made above. For other techniques used to enhance pregnancy rates during the embryo transfer, such as TEAS, more studies are needed. In designing the ASRM embryo transfer protocol, data from the survey of medical directors helped determine the most commonly used technique when the literature did not inform an outcome-based recommendation.

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