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

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Chapter 15

Summary
The aim of this thesis was to determine the best available evidence on procedures used to optimize the embryo transfer technique. Intrauterine transfer of human embryos into the recipient uterus may, at present, well be the rate limiting procedure and many factors have been shown to affect clinical outcome. In order to determine which embryo transfer techniques are truly associated with better outcomes, we performed some clinical trials and systematic reviews of the medical literature. Accordingly, the thesis aimed – as outlined in chapter I – to answer the following twelve specific clinical queries.

In addition, two appendices have been provided. The first details the author’s contributions to each publication in accordance with the Guidelines on Good Publication Practice published by the Committee on Publication Ethics (COPE). The second provides a broad search strategy that can be modified to allow readers to perform a comprehensive search on the topic of embryo transfer.

Chapter 2 addresses the first question

*Is the pregnancy rate improved by delaying embryo transfer from 'day two' to 'day three'?*

To answer this question, we conducted a prospective quasi-randomized controlled trial comparing the outcome of embryo transfer on day two versus day three post-oocyte pick-up. We included a total of 927 consecutive embryo transfers (626 transfers on day 2 and 301 on day 3) following IVF/ICSI. The results demonstrated that there was no significant difference in the pregnancy rate between ET on day 2 (319/626) and ET on day 3 (152/301) (O.R = 1.02, 95% CI = 0.77 to 1.34. Although our study was not randomized, selection bias is probably minimal, as patients who had egg retrieval on Wednesdays and Thursdays had their ET on day 3, and those who had egg retrieval on other days of the week had their ET done on day 2. Criteria for giving hCG was fixed all through the study when the lead follicle was 19mm in diameter in the presence of three or more follicles. We therefore concluded that embryo transfer could be done on days 2 or 3 according to the convenience of the patient and the medical team, without fear of comprising the clinical pregnancy rate.
The results of this study are reassuring to both medical staff and patients since it allows for more flexibility in scheduling the day of transfer. Even so, it should be noted that the optimum number of embryos transferred per patient during the study period was somewhat different than what is current practice today. The effects of day 2 versus 3 might be substantial if only 1 – 2 embryos were replaced, as opposed to the higher numbers transferred during this trial. Even so, it should be noted that even though single embryo transfer has become a common practice in Europe, this policy is only beginning to become accepted in countries where IVF expenses are not covered by government or medical insurance. In these regions, the primary target is a clinical pregnancy and subsequent live birth, regardless the number of embryos transferred to accomplish this goal.

Chapter 3 addresses the second question:
Does removal of cervical mucus prior to embryo transfer improve the results?

To answer this question, we conducted a prospective controlled trial comparing the outcome of cervical mucus removal prior to embryo transfer to no aspiration. We included a total of 286 women undergoing embryo transfers that were divided into two groups according to whether the cervical mucus was scheduled to be aspirated (group A) or not (group B). In addition, all transfers were performed in a similar manner by one operator (Dr. Mamdouh Eskandar). The clinical pregnancy rate was found to be significantly higher in group (A) (63/143) than group (B) (38/143) (P =0.003; OR = 2.18, 95% CI = 1.32–3.58), although there was a higher frequency of easy transfers in group (B) than group (A) (OR = 3.00, 95% CI = 1.05–8.55). This demonstrated that even though embryo transfers were easier to perform when the cervical mucus was left in place, aspiration resulted in an increased chance of clinical pregnancy, which is of more clinical importance. Even so, randomized controlled studies with adequate sample sizes should be performed to confirm these findings, and to determine if there is a true relationship between the presence of a difficult embryo transfer and the presence of retained embryos.
Chapter 4 addresses the third question: 
What is the effect of passive uterine straightening during embryo transfer on pregnancy rate?

The first group to advocate the 'full bladder' in order to assist straightening the cervico-uterine angle were Sundstrom and colleagues (1984). They described the use of a 'full bladder' using both ultrasound-guided and standard clinical touch methods for embryo catheter placement.

To answer the clinical question of whether passive uterine straightening during embryo transfer affects pregnancy rates, a systematic review and meta-analysis of prospective, randomised, controlled trials, comparing embryo transfer with a full versus empty bladder was conducted. 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. Three studies (1109 ET cycles in women) were included. Meta-analysis was conducted with the Mantel-Haenszel method, utilizing the fixed-effect model. For live birth rate no data were available. Pooling of the results revealed a significantly higher chance of an ongoing pregnancy (OR = 1.44, 95% CI = 1.04 to 2.04) and clinical pregnancy (OR = 1.55, 95% CI = 1.16 to 2.08) with a full bladder. In addition, there was a significantly greater incidence of difficulty, or need for instrumental assistance, with an empty bladder. For the other secondary outcomes no differences were found. This current meta-analysis 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. 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. It was concluded that the evidence in the literature supports the use of bladder filling prior to
embryo transfer. Whether this is also applicable to patients with a retroverted uterus, or for patients undergoing vaginal ultrasound-guided embryo transfer, we do not know since there are no prospective clinical trials comparing ‘empty’ to ‘full bladders’ in patients undergoing embryo transfer with these two pre-requisites.

Chapter 5 addresses the fourth question:
Is there a difference in clinical outcomes when two soft embryo transfer catheters are compared for embryo transfer?

To answer this question, we performed a two-center prospective randomized controlled clinical trial, in order to compare the performance of two soft embryo transfer catheters. Four hundred consecutive women aged less than 40 years of age, and undergoing ET with two fresh embryos were included. The women were randomly allocated to undergo ET with one of the two catheters, with possible catheter change in case of insertion difficulties. Main outcome measures were clinical pregnancy rate and live birth rate. No significant difference in the clinical pregnancy rate (O.R = 0.99; 95%CI = 0.66-1.47) and live-birth rates (O.R = 1.09; 95%CI = 0.72-1.65) was found between the two catheters. It was therefore concluded from this trial that the pregnancy and live-birth rates were not significantly different with the two tested soft catheters.

Chapter 6 addresses the fifth question:
Is there a difference in clinical outcomes between firm and soft embryo transfer catheters when embryo transfer is performed under ultrasound guidance?

To answer this question, we performed a detailed chart review of all IVF cycles performed in our center from 2004 to 2006 (n = 666). The primary outcome of this study was the clinical pregnancy rate per woman. Secondary outcomes were the incidence of detecting indirect signs of cervical and/or uterine injury (e.g., blood, mucus) on the catheter tip and the incidence of difficult transfers with the respective catheters.
Details on patient demographics, cycle characteristics, and outcomes were extracted and compared for a semifirm catheter compared with soft catheters. The results of the study showed no significant difference between the clinical pregnancy rates between the individual catheters compared. Also, no significant differences were found with regard to the secondary outcomes. We concluded that under ultrasound guidance, the degree of firmness of the embryo transfer catheter may not be a critical variable.

Chapter 7 addresses the sixth question

*Are soft embryo transfer catheters more favourable than firm catheters during embryo transfer?*

Following up on the previous question, we decided to systematically review the evidence provided in the literature so that we may evaluate a single variable in relation to a successful transfer, the firmness of the embryo transfer catheter. Electronic (e.g. PubMed, EMBASE, Cochrane Library) and hand searches of the literature revealed a total of ten trials, (4141 ET in women) comparing soft versus firm embryo catheters and were included. The primary outcome measures used for this systematic review were implantation rate (IR), clinical pregnancy rate (CPR) and ongoing/take-home baby rate. Of these outcomes, the most important primary outcome was considered to be the ongoing/take-home baby rate. The secondary outcomes were ease of transfer (catheter failure rate) and simultaneous occurrence of traumatic events (e.g. use of a tenaculum, stylette, sounding, and/or dilatation). In addition, the presence of blood, mucus and/or retained embryos on the tip of the catheter was evaluated.

Meta-analysis was conducted using the Mantel–Haenszel method (fixed-effect model). Pooling of the results demonstrated a statistically significantly increased chance of clinical pregnancy following embryo transfer using the soft (643/2109) versus firm (488/2032) catheters [P=0.01; odds ratio (OR) = 1.39, 95% confidence interval (CI) = 1.08 – 1.79]. When only the truly RCT were analysed, the results were again still in favour of using the soft embryo transfer catheters [soft (432/1403) versus firm (330/1402)], but with a greater significance (P < 0.00001; OR = 1.49, 95% CI = 1.26 – 1.77).
Softer catheters may produce better results by decreasing the trauma to the endometrium. The softer the materials used, the lesser the chance for damage to the endometrium and the lesser the chance for uterine contractions. The soft transfer catheters follow the natural curvature of the uterine cavity better than the firmer catheters, possibly reducing the risk of burrowing into the posterior endometrium in the anteflexed uterus, or stimulating uterine junctional zone contractions. We concluded from this study that using soft embryo transfer catheters for embryo transfer results in a significantly higher clinical pregnancy rate as compared to firm catheters.

Chapter 8 addresses the seventh question: What is the effect of using air to bracket embryos in the transfer catheter?

To answer this question, a systematic review and meta-analysis of randomized trials was performed to determine the beneficial or detrimental effect of using air bubbles to bracket the embryo-containing medium during embryo transfer. Electronic (e.g. PubMed, EMBASE, Cochrane Library) and hand searches of the literature revealed three studies of which two were included (298 women). The primary outcome measures were live birth, ongoing and clinical pregnancy rates. Of these outcomes, the most important primary outcome was considered to be the live-birth rate. The secondary outcome measures were the rates of implantation, miscarriage, multiple and ectopic pregnancies and retained embryos. Meta-analysis was conducted using the Mantel–Haenszel method (fixed-effect model). The results demonstrated that there were no significant differences between the two methods with regards to live birth (OR = 1.34; 95% CI = 0.59 – 3.07), ongoing pregnancy (OR = 1.34; 95% CI = 0.59 – 3.07) and clinical pregnancy (OR = 1.13; 95% CI = 0.70 – 1.83) rates. For the secondary outcomes, there were no significant differences between the two groups. It was therefore concluded that there is insufficient evidence to suggest that the fluid-only method is superior to the use of air brackets during embryo loading. More well-designed and powered randomized trials are needed to determine any possible benefit to either method.
Chapter 9 addresses the eighth question:
*What is the best site in the uterine cavity for embryo replacement?*

To answer this question, and in order to determine the best site for embryo deposition during embryo transfer, a meta-analysis of randomized trials comparing different uterine deposition sites was undertaken. Electronic (e.g. PubMed, EMBASE, Cochrane Library, LILACS) and hand searches were performed to locate trials. Outcomes measures were the live-birth, ongoing pregnancy and clinical pregnancy rates. Assessments of the endometrial cavity length (ECL) and the distance from the fundus to the tip of the catheter (DTC) were utilized. Out of the identified six studies, three trials (2170 ET in women) were included. Meta-analysis was conducted with the Mantel-Haenszel method, utilizing the fixed-effects model. The live-birth rate and ongoing pregnancy rates showed an increasing trend when transfers were performed to the lower half of the uterine cavity. For the DTC, all rates were significantly higher for the ~20 mm versus ~10 mm distance from the uterine fundus, supporting the results of the ECL analysis. The results of this systematic review showed that there is limited evidence of the superiority of lower cavity transfers (e.g. ~20 mm) compared with the traditional high cavity (e.g. ~10 mm) transfers. More well-designed and powered randomized trials are needed to confirm this conclusion.

Chapter 10 addresses the ninth question:
*Does ultrasound-guidance during embryo transfer improve the outcomes when performed by a single operator?*

To answer this question, we performed a prospective, single-operator, randomized, controlled trial comparing ultrasound to clinical touch methods of embryo catheter guidance. The study randomized 378 women to transcervical, intrauterine embryo transfer with (183 women) or without ultrasound guidance (190 women). In addition, all the transfers were performed in a similar manner by one operator (Dr. Mamdouh Eskandar). Primary outcomes were the live-birth/ongoing pregnancy and clinical pregnancy rates per randomized woman. Of these outcomes, the most important primary outcome was considered to be the live-birth/ongoing pregnancy rate. Secondary outcomes were the
incidences of difficult transfers, blood and/or mucus on the catheter tip, spontaneous miscarriages and ectopic pregnancies. The results of this trial demonstrated that the live-birth/ongoing pregnancy rate was significantly higher in the US-ET group [68/183 (40.98%)] than the CT-ET group [50/190 (28.42%)] (O.R= 1.66, 95%CI= 1.07-2.57). In addition, there was a significantly higher number of clinical pregnancies in the US-ET group [75/183 (40.98%)] than the CT-ET group [54/190 (28.42%)] (O.R= 1.75, 95%CI= 1.14-2.69). Secondary outcomes were not significantly different between the two groups.

The exact mechanism whereby ultrasound-guidance improves the outcomes following embryo transfer remains unclear. Confirming the position of the catheter tip within the uterine cavity, properly determining the site of embryo deposition, and decreasing the frequency of “difficult” embryo transfers or increasing the clinical appreciation of the pelvic anatomy have all been proposed as possible factors. Whatever the mechanism, from this trial it seems that ultrasound-guided embryo transfer significantly increases the chance of ongoing/live-birth and clinical pregnancy rates compared to the clinical touch method when performed by a single operator.

Chapter 11 addresses the tenth question:
*Is the probability of pregnancy and live birth improved with ultrasound-guidance than with clinical touch alone?*

To answer this question, we performed a systematic review of prospective, randomized, controlled trials comparing ultrasound with clinical touch methods of embryo catheter guidance. Meticulous electronic (e.g., PubMed, EMBASE, CENTRAL) and hand searches were performed to locate trials. Primary outcome measures were the live-birth, ongoing pregnancy, and clinical pregnancy rates. Of these outcomes, the most important primary outcome was considered to be the live-birth rate. Secondary outcome measures were the implantation, multiple pregnancies, and miscarriage rates. In addition, the incidences of ectopic pregnancies and difficult transfers were evaluated. Twenty-five studies were retrieved, of which five were excluded, leaving twenty studies (5,968 ET cycles in women) for analysis. Pooling of the data was
conducted by using the Mantel-Haenszel method (fixed-effect model). The results revealed that there was a significantly increased chance of a live birth (odds ratio [OR] = 1.78, 95% confidence interval [CI] = 1.19 to 2.67), ongoing pregnancy (OR = 1.51, 95% CI = 1.31 to 1.74), clinical pregnancy (OR = 1.50, 95% CI = 1.34 to 1.67), embryo implantation (OR = 1.35, 95% CI = 1.22 to 1.50), and easy transfer rates after ultrasound guidance (OR = 0.68, 95% CI = 0.58 to 0.81). There was no difference in multiple pregnancy, ectopic pregnancy, or miscarriage rates.

We therefore concluded that ultrasound-guided ET significantly increases the chance of live birth and ongoing and clinical pregnancy rates compared with the clinical touch method and we hope that this evidence will be easily and quickly translated from the medical literature to everyday clinical practice.

However, clinicians should perform in-house cost-effective analyses to determine the best combination of needed equipment, personnel, and catheter choice to provide the most efficient and cost-effective treatment options for their patients.

Chapter 12 addresses the eleventh question:
*What is the effect of blood found on the tips of the post-transfers on clinical outcomes?*

To answer this question, we performed a detailed chart review of 943 women, aged 18–39 years old, who underwent 1,122 ETs between January 1, 2005 and December 31, 2006. A semi quantitative system for grading and recording the difficulty of transfer, presence of retained embryos, mucus and blood found inside and outside the transfer catheter after ET was used to determine the correlation of each factor with the clinical pregnancy rate. The results demonstrated that an easy transfer (O.R = 4.52, 95% CI = 2.00 to 10.20) and absence of blood on the outside (O.R = 2.20, 95% CI = 1.38 to 3.52; P = 0.001) or inside O.R = 1.63, 95% CI = 0.94 to 2.82) of the transfer catheter after ET was associated with increased clinical pregnancy rates. In addition, there was a correlation between difficult transfers and the presence of blood. In contrast, presence of retained embryos or mucus did not significantly affect the outcomes. It was therefore concluded that the
relationship between difficult embryo transfer and the presence of blood on the outside or inside of the transfer catheter decreases the chance for a clinical pregnancy rate. Therefore every effort should be made to minimalize difficulty, and hence bleeding, during embryo transfer.

Chapter 13 addresses the twelfth question:

*Does the use of Propofol anaesthesia improve the clinical outcomes of difficult embryo transfers?*

To answer this question, we performed a detailed patient chart review of 198 women undergoing embryo transfer with difficulty during the procedure from January 2000 - December 2002. We included 99 women requiring general anesthesia (Group I), and a matching group of women with difficult ET, without anesthesia (Group II) as a control group. Primary outcome measures were embryo implantation rate and clinical pregnancy rate. The results showed that there were no significant differences in implantation (Group I = 19.15%, Group II = 20.86%) or clinical pregnancy rates (Group I = 36.36%, Group II = 33.33%) (O.R = 1.14, 95% CI = 0.64 to 2.05; P = 0.77). Therefore it was concluded that the use of Propofol general anesthesia during difficult embryo transfer does not seem to affect the implantation and pregnancy rates. Therefore, Propofol anesthesia may offer clinicians a complementary measure while dealing with a difficult embryo transfer. Even so, prospective randomized trials are needed to confirm these findings.

Conclusions

1. Passive uterine straightening and cervical mucus aspiration should be performed prior to embryo transfer as part of the standard protocol of embryo transfer.
2. Soft catheters under ultrasound-guidance should be used to assist in the accurate placement of the embryos within the uterus at an average of ~20 mm from the uterine fundus.
3. It is of paramount importance to decrease the rates of difficult transfers by any method possible.