Optimizing the embryo transfer technique
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Chapter 14

General Discussion
Since the early days of in vitro fertilization, emphasis has mainly been on methods of ovarian stimulation and laboratory methods for embryo manipulation. The results of countless hours of laboratory and clinical research are evident in the marked advancement of these refined techniques, and the excellent results available today. As a consequence, most patients who enter an assisted reproduction program today will reach the stage of embryo transfer with adequate numbers of well-developed embryos. Even so, the majority will fail to become clinically pregnant. This phenomenon makes the understanding of the elements related to embryo implantation, and the techniques by which human embryos are transferred into the recipient uterus, vital for the advancement of assisted reproduction.

Traditionally, the steps involved in the transfer of embryos into the receptive uterus have mainly been left up to personal preferences. This is reflected by both the scarce volume of scientific publications regarding the embryo transfer technique as a whole, or its subunits in particular, compared with other aspects of IVF.

The only way a program can expect stability in clinical outcomes and a decrease in the often marked fluctuations between different clinicians and time periods is to implement a standardized protocol based upon evidence for all phases of the IVF cycle, including the embryo transfer technique. However, many of the steps involved in the transfer technique are enforced empirically and are still highly debated in the literature.

Many centres have opted to using a retrospective or observational approach to improving their pregnancy rates. This mainly utilizes a method of identifying the aspects leading to success by different operators and forcing all clinicians to mimic the procedures of the most successful operators. Even though this may beneficial is some circumstances, it is both low on the ‘evidence pyramid’, may be highly biased, and is often incorrect.

In the early days of IVF, the embryo transfer technique was mainly built on the descriptions provided by Edwards et al. (1). Over the years, many aspects of the embryo transfer technique have been put to the test, modified and perfected in order to provide the best pregnancy rates, and lowest chances of complications (e.g. ectopic pregnancies) possible. Unfortunately, this is not true for all aspects of the procedure, some of which have been neglected, while others have been accepted as
they are, without much questioning of the clinical effectiveness or efficiency.

The individual technical performance of the clinician performing the embryo transfer has been demonstrated to be one of the most critical factors affecting success (2 – 3). Inter-operator variation in subtle issues as catheter type or gentleness in inserting the catheter has been shown to dramatically affect the results in the same assisted fertilization programme (4 – 5). One study comparing the pregnancy rates following embryo transfer by different physicians in the same assisted reproduction programme revealed several key factors affecting the outcomes (6). The authors examined 393 clinical pregnancies resulting from 854 embryo transfers, in which the number and quality of embryos transferred did not differ significantly between the different operators. Even so, pregnancy rate fluctuations more than three-fold (range: 17.0% to 54.3%) were observed in different operators.

Some authors have noted that success rates are correlated to operator experience (7), denoting that acquired experience helps to fine-tune a physician’s clinical judgement when performing an embryo transfer. These data have been interpreted as meaning that training and experience are the two most important issues in embryo transfer. Accordingly, it has been argued that well trained nurses may perform the embryo transfer as well as physicians (8), which now has become standard practice in many centres. Regardless of the academic qualifications of the individual (qualified clinician, in-training physician or trained nurse) performing this highly sensitive and meticulous step in IVF, it is clear that technical skills and experience are important factors. But this should not lead to a programme founded on personal experience complemented with a method of trial and error. In the same way that there is no reason to re-invent the wheel, there is also no reason to re-investigate each and every step in the ET technique by every operator.

An excellent example of how clinical intuition alone has failed in the past is the discovery of the negative effects of uterine contractions at the time of embryo transfer. These contractions have been adequately demonstrated to lead to embryo expulsion following embryo transfer (9). Before this important discovery was made, it was customary to determine the site of embryo transfer by introducing the embryo
transfer catheter, containing the embryos, until the tip touches the uterine fundus, then pulling back ~ 1 cm and depositing the embryos. What is needed is an adequate assessment of what is known and how the evidence supports these aspects of the transfer technique. Fortunately, during the last years more and more publications discussing ways of improving embryo transfer and hopefully pregnancy rates have been published. In short, among the multiple factors shown to affect the success of embryo transfer are the experience of the physician (7, 10), the use of ultrasound guidance (11 – 13), the ease of the procedure (14 – 15), the presence or absence of blood on the catheter (16) and bacterial contamination of the catheter (18). In addition, other factors that might affect the chance for an ongoing pregnancy have been identified, such as the use of cervical introducers or obturators (19), resting after transfer (20), the position of embryo insertion in the uterus (21 – 22), flushing of the cervical canal to remove mucus (23), microbiological factors in terms of the local flora (24) and retention of embryos in the catheter (25 - 26). Since it would be difficult to determine the effect that each aspect of the transfer technique may have on limiting the success of the embryo transfer, we have divided the embryo transfer technique into four distinct sections: (i) preparation prior to embryo transfer; (ii) technical aspects related to the embryo transfer catheter; (iii) the embryo transfer procedure; and (iv) post-transfer aspects. The aim of this thesis was to address several of the individual points that make up each step of the procedure in order to determine what is beneficial and what is not when performing embryo transfer. Regarding the first phase of embryo transfer, the preparation prior to embryo transfer, we compared the outcome of cervical mucus removal prior to embryo transfer to no aspiration, and whether passive uterine straightening during embryo transfer affects pregnancy rates. We determined that both cervical mucus aspiration and passive uterine straightening are beneficial prior to embryo transfer. Therefore it was our recommendation that both should be performed in women prior to the actual embryo transfer procedure. Even so, there are other aspects in this phase that were not covered in our research, and which might affect the clinical outcomes. These include the patient position (e.g. lithotomy, knee-chest, or supine position), mock (or dummy) embryo transfers prior to the actual
procedure, cervical dilation (in cases of expected difficulty in transfer) and medications to decrease uterine irritability (e.g. oxytocin antagonists). Future research into these clinical queries is sure to add more efficiency and effectiveness to the transfer procedure by decreasing the rates of difficult transfers and improving the outcomes.

Regarding the second phase of embryo transfer, the technical aspects related to the embryo transfer catheter, we tested the theories that both catheter type and catheter loading techniques could affect the clinical outcomes. Our research demonstrated that in general soft catheters performed better than firmer catheters, except under ultrasound-guidance. In addition, we determined that two of the commonly used catheters have similar outcomes. Finally, we determined that the use of air bubbles to bracket the embryo containing media inside the embryo transfer catheter does not affect the clinical outcomes.

Other areas for future consideration include the use of different commercially available catheters, the use of echogenic catheters compared to non-echogenic catheters during ultrasound-guided embryo transfer and the use of different transfer medias (e.g. enriched with hyaluronic acid).

Regarding the third phase of embryo transfer, the embryo transfer procedure, we investigated the use of ultrasound-guidance to assist in the accurate placement of the embryo within the uterus, and attempted to determine the best site of embryo deposition within the human uterus. Our results showed that ultrasound-guidance during embryo transfer was highly beneficial, and that a lower (e.g. ~20 mm) site of transfer seems to be preferable over the commonly used 10 mm distance from the uterine fundus. With regards the latter, more trials are needed to clarify the exact site for transfer.

Last but not least, regarding the fourth phase of embryo transfer, the post-transfer aspects, we did not investigate these factors in this thesis. Issues still under debate include bed rest (and what period of length) following embryo transfer, and methods of decreasing embryo expulsion following transfer.

In addition to the former points that were discussed, we also investigated whether the day of transfer, the presence of blood on the post-transfer catheter and the use Propofol anaesthesia during difficult transfers could affect the clinical outcomes. The results of these investigations revealed that the day of transfer (day 2 vs. day 3) and
the use of Propofol anaesthesia did not negatively affect the outcomes negating these decisions to a case by case scenario and the preference of the clinical staff. Even so, we did notice that the presence of blood on the post-transfer catheter was related negatively to the pregnancy rates; this denoting that an easy transfer results in more preferable outcomes.

Finally, it is important to reflect back on the cumulative achievements of the research presented in this thesis and how it should be implemented into everyday clinical work. It is important to note that the most important measure of success in IVF is neither the results of ovarian stimulation nor the quantity/quality of embryos produced in the laboratory. The most important criterion of success is patient satisfaction, and this will not be accomplished without a pregnancy. This is what patients undergoing IVF desire, and it is our duty as clinicians to perform everything in our power to attain this goal.

What is evident from this research presented here, is that as part of the standard protocol of embryo transfer in every assisted reproduction program, passive uterine straightening and cervical mucus aspiration should be performed prior to embryo transfer. In addition, soft catheters under abdominal 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. The site of deposition may also be more toward the center of the uterine cavity. Finally, it is of paramount importance to decrease the rates of difficult transfers by any method possible. Our experience with light anaesthesia (e.g. Propofol) has been shown to be effective and should be implemented in patients with anticipated difficulty in traversing the unrelenting cervix. Finally, embryo transfers may be scheduled on day 2 – 3 following oocyte pick-up according to clinical judgement, patient scheduling, and center flow on a case-by-case scenario without fearing any change in clinical outcomes.

In conclusion, it is important to note that the embryo transfer technique, as other areas of assisted reproduction, is becoming more evidence-based, relying on good, solid evidence to help modify the available protocols of practice. Even so it is important to note, that just as any other clinical procedure, in the end a human factor is involved. This factor needs to be trained and fine-tuned according to the best available evidence today so that the efficiency and effectiveness of this procedure can reach the great success as other aspects of assisted
reproduction. This will not take place until clinicians realize that personal preferences and experience do not out way the evidence, but on the contrary, complement and modify the evidence. Once we reach this point, we will truly have reached the optimum level of performance of this highly sensitive procedure.
References:
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