Embryo transfer (ET) is the final step in the IVF treatment process, and the one followed by success or, more often, failure. Up till then, most patients achieve successful pituitary desensitisation, ovarian stimulation, egg collection, fertilisation and embryo cleavage, with about 80% reaching the ET stage. However, on average only 15% of transferred embryos implant. This relative inefficiency of the ET process has been apparent since the early days of Edwards and Steptoe, who described it as the "...the weakest part of our technique"(1). Why does this happen, or more practically, what could be done to make the ET technique more successful? Despite this question being as old as human IVF, it is only in recent years that a number of good quality studies have shed much needed light on this issue. In this opinion paper I will summarise the salient points in these studies and indicate my views -hopefully baked by evidence - on what it takes to achieve a successful ET.

Difficult ET: Does it exist?

Some practitioners deny the existence of difficult ET, on the basis of their own experience.
Difficult ETs are rare, but they do occur. They occurred at the days of Edwards and Steptoe (1) and their frequency is not dissimilar from what was reported back in 1985 by Wood et al. in their report of 867 ETs, when 5.6% were difficult (requiring manipulation in and out to introduce the catheter), 3.2% were very difficult (requiring manipulation for over 5 minutes or cervical dilatation) and 1.3% were impossible to perform (2).

Difficult ET: Does it affect the results?

Having agreed that difficult ETs occur, some would have you believe that "So what? They don't matter". Indeed, some studies have shown that the pregnancy rate is no different between easy and difficult transfers (3). Most other studies, however, reached the opposite conclusion, that difficult transfers are associated with reduced pregnancy rate. A meta-analysis had shown a significant drop in implantation rate with difficult ET - OR=0.64, 95% CI 0.52-0.77 (4).

Difficult ET: What not to do.

Even before the evidence for the existence of difficult ET and for its negative impact on the pregnancy rate, most clinicians thought so on the basis of common sense. Also, on the basis of common sense, some advice was given, and is being followed in thousands of IVF cycles all over the world on how to perform ET to make it less difficult and more successful. For example, one should pre-flush the cervical canal with culture medium, use a soft catheter, add biological glue (fibrin sealant) to the embryos transferred, withdraw the catheter gently, ask the patient to rest in bed for variable periods ranging from 30 minutes to 24 hours, and advise no sexual intercourse for a few days after ET. All this advice was sensible, all of it is followed to a large extent by many units, and - more recently - all of it has been found not to increase the success rate (5). A randomised controlled trial (RCT) showed no effect of pre-flushing the cervical canal; a meta-analysis of RCTs showed no difference in pregnancy rate between soft and hard catheters; two RCTs showed no benefit from using fibrin sealant; an RCT showed no benefit from slow withdrawal of the catheter; and a large cohort-control study and a smaller RCT showed no benefit from bed-rest (5). Even sexual intercourse was tested with an RCT and in fact was found to be beneficial, i.e. couples randomised to sexual intercourse around the time of ET had significantly higher pregnancy rate (6). Obviously our beliefs and common sense were not true. Bertrand Russell once noted that "the extent to which beliefs are based on evidence is very much less than believers suppose".

Difficult ET: What to do.

Some might think that this paper should have started here. Surely you are reading it to find out what to do (rather than what not to do) in order to get a successful ET. However, it is essential to start with the belief that an easy, atraumatic ET will increase the chances of success. Otherwise, why bother trying to make it easy if it doesn't matter? Also, it is important not to waste your time and efforts in doing the things that might appear to be helpful, but actually are not. ET is a simple technique, and the simpler it is, the easier. Adding layers of unnecessary steps can only make it more complex, and more likely to go wrong.

Like any other step in life, planning is helpful. It has been suggested from the early days of IVF that performing a mock ET (some call it trial/ dummy/ dry run) before the actual transfer can increase the chances of success. The operator gets acquainted with the size and direction of the uterus, and where difficulty is likely to be met. Time can be taken in sorting out these factors (e.g. bending/ changing the catheter) with out worrying about the embryos being outside the incubator. Indeed, an RCT had reported that performing an interval (in the previous cycle) mock-transfer increased the proportion of easy transfers and the implantation rate (7). Better still, this mock transfer could be performed as an immediate step, before the actual transfer, thus obviating the need for a separate interval procedure (8).

Additionally, and along the same lines of planning, doing the transfer under ultrasound guidance has been shown by many RCTs and a
meta-analysis to be associated with increased chance of implantation (9).

Yet surprisingly, despite having robust data to show the value of mock ET and ultrasound guidance, these are probably the interventions least used in practice. In a survey of 50 IVF clinicians to assess the relative importance of 12 variables affecting the success of ET, mock transfer and ultrasound guidance were rated third and second from the bottom of list (10).

Another factor that had been shown to increase the chance of an easy and successful transfer is the full bladder. A quasi-RCT (where patient allocation was done on alternate day basis) showed a significant improvement. (11). The full bladder is thought to straighten the acutely anteverted uterus and make the transfer easier. It is probably not needed in all patients, but the problem is that you do not know whom it is needed in till they are having their (hopefully mock) transfer. Therefore, doing it routinely is advisable (8).

The impossible ET: What to do.

About 1-2% of ETs are impossible to do (2). Possible reasons are cervical stenosis or congenital abnormalities, but in most cases no cause is found. Alternatives are cervical dilatation, but this has not shown consistent results in various studies. So what to do? The answer is ultrasound-guided transmyometrial ET (TMET). It has been used for a number of years in some units (such as ours in Birmingham and Kato’s in Japan) with results similar to those achieved in easy transcervical transfers (12).

An RCT has been reported between transmyometrial and transcervical transfer in patients with previously failed IVF and/or cervical stenosis (13). Twenty such patients were included in each arm, and no significant difference was detected. However, the majority of patients (60%) had repeated previous unexplained IVF failures with no problems with the transcervical transfer. Therefore, only 8 patients with cervical stenosis were included in the trial; a wholly inadequate number to get a meaningful answer. The best available evidence suggests the TMET is the method of choice is cases of impossible transcervical ET.

The operator's factor: Do the golden fingers exist?

A number of studies have shown that some operators achieve higher pregnancy rates after transfers, even when other factors such as patient's age and embryo quality have been controlled for (14). Some of this is due to the learning curve effect, as some operators' results improve overtime. However, this was not true in many, and the available evidence suggests that, for unknown reasons, some of us would get better results after ET compared with others who may apparently use the same technique. This may sound un-scientific because many would like to believe that similar techniques should lead to equal results. However, to paraphrase George Orwell: "all operators are equal, but some operators are more equal than others". After all, the magic is in the magician, not the wand.

REFERENCES

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Until recently, embryo transfer (ET) has received limited clinical attention despite being one of the most critical steps in any IVF cycle (1). Arguably, ET accounts for 20% of the chances of success of IVF treatment (2) and poor ET technique is responsible for up to 30% of all IVF failures (3). Attempts at standardisation of the procedure have encountered great difficulties because of the limited data available in the literature, the large number of variables involved in the procedure (Table 1) and, more importantly, because operator's experience is a major confounding variable (4) that is likely to introduce bias when comparing data from various studies.

This debate will focus on two variables involved in the procedure of ET; the first, because it is pivotal in the success of ET and the second because it has been the subject of numerous recent studies.

a) Cervical canal cleaning and mucous removal

If dragged into the endometrial cavity with the transfer catheter, cervical canal mucous can entangle the embryos, interfere with implantation and increase the risk of cervical expulsion of the embryos (5, 6).

It has also been suggested that the presence of cervical mucous can prevent the embryos from leaving the catheter by acting as a "plug" at the catheter tip (1). Although this latter theory is credible, embryo retention is unlikely to compromise significantly the chances of treatment success since implantation rate is not reduced when the embryos are immediately transferred into the cavity in a second attempt (7, 8).

Another benefit of cervical cleaning and mucous removal is to reduce the risk of bacterial contamination of the catheter and endometrial cavity. Evidence that endocervical pathogens are present in a considerable number of patients at the time of ET exists. Furthermore, contamination of the catheter tip with micro-organisms such as streptococci (groups B and D), E. coli, staphylococci, mycoplasma and ureaplasma has been shown to reduce implantation and pregnancy rates by 40%-60% (9-13) even when prophylactic antibiotics have been used. Cleaning the cervical canal, therefore, can play a beneficial role by modifying the cervical micro-environment and reducing the risk of introducing pathogens into the endometrial cavity.

b) Use of ultrasound guidance

Interest in the use of ultrasound (US) has arisen from knowledge that position of the catheter in the uterine cavity can influence the chances of pregnancy. Mid fundal transfer ensuring a distance of about 20 mm from the uterine fundus has been shown to be associated with significantly improved implantation and pregnancy rates compared to high fundal transfers (14, 15). Consequently, clinicians tended to use abdominal US to guide embryo placement in the cavity. Some authors even went further and even suggested the use of transvaginal