DEBATE

Embryo transfer: does ultrasound guidance make a difference?

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Ever since the birth of the first in-vitro fertilization (IVF) baby in 1978 (1), the advancement in ovulation stimulation regimes, oocyte collection and culture mediums has been phenomenal. However, the technique of uterine embryo transfer remains largely unchanged, since it was first described. The vast majority of transferred embryos fail to implant in spite of improvements in ovulation induction, fertilization and embryo cleavage. On average, up to 90% of apparently healthy zygotes transferred in utero are destined to vanish, giving no signs of trophoblastic attachment and production of human chorionic gonadotrophin (HCG) (2).

Though factors relating to the embryo itself (quality, aneuploidy etc), hostile uterine environment (e.g. reflux of hydrosalpinx), inadequate endometrial development or uterine cavity anomalies and uterine contractions contribute to this failure, definitely the technique itself contributes to loss of some potentially favorable embryos for implantation.

The wide variability between clinicians working in the same center (which to an extent nullifies the potential difference in the laboratory circumstances) clearly demonstrates the role of the clinician in embryo transfer and the magnitude of problem.

The technique of embryo transfer that was used for long time was the clinical touch. It simply means that you feel the internal os and then either you advance the catheter till the fundus is felt and withdraw the catheter for 1 or 2 cm and position the embryos. Alternatively the clinician advances the inner catheter after feeling the resistance of the internal os by 3-4 cm based on previous measurement of the uterine cavity. Woolcott and Stanger studied 121 consecutive transvaginal ultrasound-guided embryo transfers (3). Observation was made of the guiding cannula and transfer catheter placement in relation to the endometrial surface and uterine fundus during embryo transfer. They concluded that tactile assessment of embryo transfer catheter placement was unreliable since, in 17.4% of transfers, the outer guiding catheter inadvertently abutted the fundal endometrium, the outer guiding cannula indented the endometrium in 24.8% and the transfer catheter embedded in the endometrium in 33.1%. Unavoidable sub-endometrial transfers occurred in 22.3% and avoided accidental tubal transfer in 7.4%.

The possible use of US guidance to facilitate embryo transfer was first reported by Strickler et al (4), and shortly afterwards by Leong et al., (5). However the technique did not gain popularity till the last few years where several reports have claimed improved pregnancy rate after adoption of ultrasound guided transfer (6, 7).

This article will try to debate the following points:
1. Does ultrasound guided transfer improve pregnancy rate?
2. Does it make the procedure easier?
3. Which route abdominal, rectal or vaginal ultrasound is better?
4. Where to place the embryos?
5. 2D versus 3-D in ultrasound embryo transfer
6. Which catheter?
1. Does ultrasound guided embryo transfer increase pregnancy rate?

The reports regarding the effect of guiding the transferred embryo deposition by ultrasound are conflicting. In a prospective study using abdominal ultrasound (8), it was found that there was no significant effect of ultrasound on pregnancy outcome. In a large prospective study comparing clinical and ultrasound-guided embryo transfer (9), there was still no significant improvement seen in either pregnancy or implantation rates. Two studies demonstrated significant differences between the clinical touch method and transabdominal ultrasound-guided embryo transfer, retrospectively (7) and prospectively (10) followed. To confuse the situation more, a study by Prapas et al. (11) found that ultrasound guided embryo transfer increases pregnancy rate at day 3 or 4 but not if the transfer occurs at day 5. In a recent study Bedawy et al. (12) could not demonstrate significant increase in pregnancy rate if an experienced operator performed the procedure with or without ultrasound. A meta-analysis by Buckett et al. (13) concluded that Ultrasound-guided embryo transfer significantly increases the chance of clinical pregnancy and significantly increases the embryo implantation rate.

2. Does it make the procedure easier?

It is generally accepted that an atraumatic embryo transfer is essential for successful implantation (14-16). Mansour et al. (17) found that Dummy embryo transfer: a technique that minimizes the problems of embryo transfer and improves the pregnancy rate in human in vitro fertilization. Frequency of embryo transfers reported as difficult differs widely. In a series of 876 embryo transfer procedures, 1.3% were impossible, 3.2% very difficult and 5.6% difficult (15). In more recent surveys, while some authors refer to 2-3% of difficult transfers (10), others have reported rates of 14% (18) and 19% (6). Coroleu et al. did not observe significant differences in the difficulty of the procedure between US-guided and clinical touch transfer, (10). Kan et al. reported no differences in the difficulty of transfers, but they excluded from their study patients in whom a difficult transfer was anticipated. On the other hand, they had a relatively high frequency of difficult transfers in both populations (10-11%) (9). In a retrospective report, whereas no significant differences were found in the difficulty of embryo transfer, it was reported that when the uterus was acutely anteflexed, the subjective feeling was that US-guided embryo transfer was easier and followed a straighter course by filling the bladder (7). Matorras et al. (19) in a prospective study found that ultrasound abdominal embryo transfer had significantly decreased the number of difficult transfer. Sallam et al. (20) in a trial to increase the percentage of easy transfer tried to measure the uterovesical angle and mould the catheter before insertion into the cavity and found that this procedure increase the proportion of easy embryo transfer.

3. Which ultrasound route is better?

The majority of the published studies were done with abdominal ultrasound. Sallam et al. (7-10, 19, 20). The value of abdominal ultrasound in addition of visualizing the catheter is to straighten the uterovesical angle which my make the insertion of the catheter easier. Kojima et al. (21) tried to use vaginal ultrasound as it allows visualization of the tip of the catheter precisely and concluded that it increases the pregnancy and implantation rate; in the same time they admitted that it technically more difficult. The procedure did not gain popularity because of it's discomfort to the patient. Isobe et al. (22) compared the transrectal approach in retroflexed uterus and found that it increases the incidence of easier transfer and pregnancy rate; however, there was no comment on the acceptance of the procedure.

4. Where to place the embryos?

While it has been traditionally accepted that the embryos should be placed ~10 mm below the fundal endometrial surface (23, 24), some authors have suggested that placing embryos rather lower in the uterine cavity may improve pregnancy rates (24-26). Finally, other reports have indicated that the depth of the replacement has no influence on
the implantation rate provided that the transfer is in the ‘upper half’ of the uterine cavity (8, 27, 28). Coroleu et al. (29) found that embryos should be replaced 15-20 mm from the fundus endometrial surface rather than performing high fundal placement in order to improve implantation rates. Pop et al. (30) found that for every additional millimeter embryos are deposited away from the fundus, the odds of clinical pregnancy increased by 11%.

5. 2D versus 3D in ultrasound embryo transfer

Baba et al. (31) examined the feasibility of using three-dimensional (3D) ultrasound (US) guidance in routine embryo transfer (ET) procedures. Seventy-five ETs were performed using a 3D US scanner to locate the catheter tip in the uterine cavity. Three-dimensional ultrasound could show the exact position of the tip of the catheter in the uterine cavity quickly enough in most cases. They concluded that it should be used in ET for seeking an optimal transfer area in the uterine cavity to assist in achieving high success rates and less complications.

6. Which catheter?

Coroleu et al. (32) In a pilot study suggested that the use of the echogenic Wallace catheter simplifies ultrasound-guided embryo transfer as it facilitates catheter identification under ultrasound, and thus the duration of the embryo transfer procedure was significantly shorter in the echogenic catheter group as compared with the standard catheter group. However, they could not find a definite benefit in terms of pregnancy rates. In contrast, the use of the new catheter was associated with a significant increase in the number of twin pregnancies.

CONCLUSION

Traditionally, embryo transfer has been performed blindly. Any additional means to ensure the proper deposition of the transferred embryos should be welcomed. The use of abdominal ultrasound seems to offer better pregnancy rate in most of the published reports particularly for junior, inexperienced clinicians. It also appears that ultrasound guided transfer can ensure the exact position of embryo deposition. If larger studies confirm that deposition in the mid or lower cavity increases pregnancy rate, then ultrasound would be invaluable in embryo transfer. The newly marketed echo dense catheters needs to be evaluated more to prove it facilitates recognition of the tip position.

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Despite the major advancements made in ovarian controlled hyperstimulation protocols and in vitro embryo development, over the years the pregnancy and embryo implantation rates following embryo transfer have remained relatively low, and to some extend plateau (1). Attempts at improvement have come about by scrutinizing every aspect of the in vitro fertilization (IVF) procedure, especially analysis of different patient populations, choice of stimulation protocols, culture techniques, and embryo selection guidelines. Even so, the standard embryo transfer technique has relatively been unmodified.

Due to its seemingly simple nature by comparison with the complicated processes of ovarian stimulation, gonadotrophin releasing hormone (GnRH) analogue administration, oocyte retrieval or methods for embryo culture, this innate process of returning the newly created embryos back into the recipient uterus has received little recognition as a decisive step in the success of the IVF procedure.

In general, the pregnancy rate following embryo transfer has been shown to be dependent upon multiple factors including embryo quality, endometrial receptivity and the technique of the embryo transfer itself (2). The aim of the embryo transfer procedure is to atraumatically and accurately place embryos within the uterus; in order
to allow for proper implantation and fetal development.

In a recent awakening, clinicians are beginning to realize the full extent of this highly delicate procedure on the success rates. In a wave of publications, different factors that constitute the embryo transfer technique as a whole have begun to be tested and analyzed. Factors as ease of the procedure, catheter choice, and dummy embryo transfer, among others, have proven to improve the clinical outcomes.

Today, more than twenty-years since the first reports of the beneficial effect of ultrasound guidance during the ‘blind’ embryo transfer procedure were published (3, 4), the routine use of ultrasonography to guide the intrauterine embryo transfer catheter placement are still highly debated. This has been fueled by the conflicting results of published clinical trials, with some concluding that ultrasound guidance improves the clinical pregnancy, and implantation rates, while others reporting no such improvement in their results.

In light of this controversy several systematic reviews of the evidence have been performed to determine the possible beneficial effect of this adjunctive technique. This is of importance since systematic reviews and meta-analyses of randomized controlled trials have proven to be the highest level of evidence in the hierarchy of medical knowledge.

The first reports were performed by Sallam et al. (5) and Buckett (6). Both demonstrated that the use of ultrasonography was a beneficial tool during the embryo transfer procedure by increasing the clinical pregnancy rates.

In addition, a recent systematic review and meta-analysis of randomized trials demonstrated that the patients undergoing embryo transfer under ultrasound-guidance has a significantly higher likelihood of achieving a live birth, ongoing pregnancy and clinical pregnancy than patients undergoing the standard ‘clinical touch’ embryo transfer (7). Moreover, subgroup analyses of only the properly randomized trials, fresh non-donor cycles, and the frozen embryo replacement cycles revealed similar results (Figure 1, 2, 3).

It is also important to note that to date all the published randomized trials regarding ultrasound guidance during embryo transfer have examined the role of 2-Dimensional (2D) trans-abdominal ultrasound guidance. Even so, vaginal ultrasound-guided embryo transfer (8), as well as the use of three-dimensional (3D) (9) and fourth-dimensional (4D) ultrasound-guided embryo transfer have been reported in observational and non-randomized trials.
The exact mechanism whereby ultrasound-guided embryo transfer improves pregnancy rates and embryo implantation remains unclear. Several theories have been proposed to identify the mechanisms whereby the transfer technique is optimized. These include confirming the position of the tip of the embryo transfer catheter within the uterine cavity, the site of embryo deposition, increasing the frequency of “easy” embryo transfers, and avoiding endometrial indentation.

Nevertheless, some clinicians argue that the real benefit of ultrasound guidance lies in the ability of increasing the clinical appreciation of the pelvic anatomy during transfer. They infer that ultrasound guidance, compared with the standard clinical touch alone, will not significantly increase the pregnancy rates when embryo transfer is performed by experienced professionals. Even so, this simple modification will allow for standardization of the transfer technique and therefore decrease any unexpected variation in pregnancy rates among different clinicians in the same center.

Whatever the underlying mechanism, the overall conclusion is that ultrasound-guided embryo transfer is significantly more effective than embryo transfer by clinical touch alone. It is hoped that this evidence will be quickly translated from the medical literature to everyday clinical practice.

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Study or sub-category | US-guided | Clinical Touch | OR (fixed) | OR (fixed) |
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Figure 3. Meta-analysis forest plots showing clinical pregnancy rate following US-guided versus clinical touch embryo transfer. "Reprinted from Fertility and Sterility, with permission from the American Society for Reproductive Medicine.


Comment by: Mohamed A. Bedaiwy, M.D. Ohio, USA

Despite its obvious simplicity compared to other steps in any given IVF-ET cycle, embryo transfer is probably the most critical one influencing the cycle outcome. Little and probably late attention has been paid to the role of ET methodology and its overall impact on success rates. Of all factors influencing the ET process, ultrasound guidance of the ET has been studied the most over the past decade. Issues related to the ET technique, ET provider/physician, transferred embryos and unloading site in the uterus and their relationship to ultrasound guidance were the most debatable aspects of the process. Of all confounding variables, the following controversial issues will be discussed.
1. Ultrasound guidance: is evidence a must?

Three approaches have been adopted for embryo transfer. The first approach used was a fundus-contact approach also called “blind-ET” whereby the transfer catheter was advanced to the uterine fundus, then withdrawing the catheter 5–10 mm and unloading the embryos into the uterine cavity. Simply it is a contact the fundus-withdraw-unload method. This approach was quickly abandoned because it provokes bleeding and initiates uterine contractions which in-turn will jeopardize the cycle outcome. The second approach was an atraumatic one commonly known as “clinical touch” transfer. It simply entails all techniques in which ultrasound is not performed, but contact with the fundus is avoided. Finally, any ET approach in which we use ultrasound guidance is called US-guided ET. Consequently US guidance is a way to monitor the transfer step whether we touch the fundus or not. Indeed it could be beneficial if executed atraumatically, however it might not be as helpful and even implying false-sense of security if the fundus is touched or frequent to-and fro- movements of the catheter at the time of the transfer were experienced. Practically speaking ET techniques come down to 2 methods; fundus contact method and non-contact method whether we use ultrasound or not.

Although many studies found no extra advantage for the use of abdominal US ultrasonography in ET (1, 2), its use was associated with easier transfers (3) less use of tenaculum and less incidence of blood contaminated catheters (4). Moreover it gives a sensation of comfort to both the patient and the physician by observing the air bubble and assuring that the embryos remain in the cavity.

The results of two recent meta-analyses of prospective, randomized comparisons (5, 6) strongly promoted the use of US guidance to improve the results. However, differences in study design and execution may limit the statistical value by overstating the effect of ultrasonography and underestimating the important differences in study design. For instance the meta-analysis by Buckett demonstrated that none of the prospective randomized studies included has enough power to detect a 5% difference in clinical pregnancy rates.

The clinical touch method depends very much on the experience of the performer thus it will give inconsistent results in different hands. It was found that when the uterine length was ultrasonographically measured before ET, the results were comparable to those of ultrasonographically performed ET (7). Consequently, ultrasound guidance may improve outcome when endometrial cavity length has not been previously accurately measured, but when it has been reliably performed, ultrasound guidance may have no effect. In many programs with high pregnancy rates including ours, adoption of US-guided ET has not been shown to have a significant effect on outcome measures (8). Obviously, there is lack of evidence to justify the routine use of US guidance during ET. However, in 2003 Smith and Pell published an impressive article titled: "Parachute use to prevent death and major trauma due to gravitational challenge (9). They used the lack of randomized controlled trials in testing parachutes to show that situations still exist where such trials are unnecessary. The use of simple step as US guided-ET could be used to justify their cause!

2. Does the adoption of ultrasound guidance improve the providers’ own performance?

The impact of ultrasound guidance on the pregnancy rate per provider (before and after the adoption of ultrasound guidance) was recently evaluated by our group. We found that US guidance did not reduce the time of the ET procedure. In addition, it did not reduce the percentage of bloody catheters at the end of the procedure. More importantly, no statistical difference was seen in the presence or number of gestational sacs following embryo transfer either before or after the adoption of the transabdominal ultrasound guidance for 3 equally experienced providers (8).

3. Which ultrasound? Transvaginal (TVUS) or transabdominal (TAUS)? 2D, 3D or 4D?

One limitation of TAUS is the need to be performed with a full bladder and a sonographer should be present at the time of the procedure. This
in turn can lead to the discomfort of the patient and her anxiety to empty it shortly after the procedure. Moreover in cases of obesity or retroversion, TAUS is not ideal. However, performing TAUS with a full bladder helps in straightening the uterocervical angle facilitating the procedure. It was claimed that TVUS allows more precise embryo placement than the TAUS since the catheter tip could be better delineated. Also it probably minimize endometrial trauma as it gives clear fine images of the uterine flexion and the endometrial midline curve, compared to TAUS (10). However, TAUS is the approach adopted by the majority of IVF programs.

With the recent advances in acoustic imaging, the application of 3-dimensional, or “4-D” (“real-time” 3-dimensional) ultrasonography to ET might be helpful in many ways. The 3D US allows viewing the catheter tip in a frontal as well as a sagittal and transverse plans, thus it facilitates precise embryo placement inside the uterus. However, it does not seem to be vital in maximizing the success rate at the current time. Given the limitation of the currently available 2D machines in monitoring embryo migration after transfer, 3-D ultrasonography could prove beneficial in this regard as embryos may be propelled by uterine contractions to other locations, including out of the cavity at the end of ET. Despite the growing interest in adopting this new technology, it should improve catheter placement, pregnancy rates, and nullify ectopic pregnancy to be justifiable.

4. What does ultrasound guidance actually guide?

Ideally ultrasound should guide catheter placement, unloading of embryos and catheter withdrawal. The primary focus of the vast majorities of the current studies dealt with the issue of US-ET was on accurate placement of the catheter near the optimal target site. The optimal site of transfer, which most probably represents an area rather than a single point, is yet to be identified. US may confirm the location of the catheter inside the uterus, however, it may not facilitate catheter entry particularly with tortuous cervical canal of acute cervico-uterine angle. Due to the limited acoustic window if any given transducer, it might not be possible to show the entire length of the catheter along its path. Consequently the current value of ultrasonography is the correct identification of the distal position of the catheter. The golden rule that easily visualized catheters may require less manipulation to be identified ultrasonographically, should control which catheter to use for ET. Although bladder distension has been suggested to improve visualization, many trials concluded that no difference was seen after transfer with a full or an empty bladder.

Little attention, if any, has been paid to the unloading step and the catheter withdrawal at the conclusion of the transfer. From my perspective, unloading of the embryos and removal of the catheter could prove to be as critical for cycle outcome as accurate catheter placement. The unloading technique should be adjusted to be as smooth as possible without the use of forceful pressure on the syringe plunger. If the catheter tip is put close to the fundus, vigorous pressure on the plunger may result in the ET droplet hitting the fundus with the subsequent spraying the droplet back on the tip of the catheter or towards the tubal ostia. This may affect the outcome in many ways by reducing the pregnancy rate, increasing the possibility of retained embryos or even ectopic pregnancy. Unloading of the embryos, should be monitored by US to allow each provider to optimize his own technique. The tactile sense of adequate plunger pressure that allow adjusted-unloading of the embryos is a skill that will develop with experience.

Similarly catheter withdrawal may be as critical to the cycle outcome. Ultrason sound should also guide the catheter withdrawal as sudden withdrawal may create a negative pressure that may either displaced the droplet in the lower cavity or even suck it back in the catheter particularly when catheters with outer and inner pieces are implemented. Future research in this area should account for the unloading step and catheter withdrawal as confounding factors.

5. Conclusions

Although there is no adequate evidence to
support the routine use of US during ET, we believe that its use nowadays become a sort of helpful risk-free practice. Moreover, it gives reassurance and comfort to the patient seeing the air bubble. In addition, the provider is now not entering blindly but everything is visible and clear, consequently there is less probability of contacting the fundus or unloading the embryos in undesirable locations. A very important point to consider is that not all physicians have the same clinical skills and experience. Consequently, it will be fairer and comforting to use US guided ET as a routine especially with trainees. Improvements in ultrasound technology and catheter design with the subsequent increase of the visibility may be particularly useful, even if pregnancy rates are not appreciably improved.

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