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Optimizing Embryo Transfer Outcomes: Determinants for Improved Outcomes Using the Oocyte Donation Model

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1. Introduction

The past decade has seen increased success rates with assisted reproductive technologies (ART), however, the overall pregnancy and implantation rates have remained relatively low. These low rates continue even though we now have improved stimulation protocols and laboratory techniques. Three areas that have gained specific attention include 1) identification of the optimal uterine environment; 2) extended embryo culture to the blastocyst stage; and 3) the embryo transfer (ET) technique, which has historically been viewed as an unimportant variable in the success of an ART treatment cycle.

Discerning the impact on folliculogenesis and the endometrial level is difficult in conventional IVF cycles. Moreover, due to ethical quandaries, any study as complex as embryo and endometrial synchrony and receptivity is difficult to perform and thus reported studies in humans are more suggestive than conclusive. In contrast, the ovum donation model, which has been successfully used in treating infertility for over 25 years (Trounson et al., 1983), allows for the study of isolated parameters that may affect outcome by standardizing for embryo quality and endometrial receptivity and by optimizing the recruitment of high quality oocytes from the egg donor and eliminates the possible adverse effects of ovarian hyperstimulation (Acosta, 2000; Garcia, 1984; Oehninger, 2008).

In this chapter we will review the clinical variables that have gained increasing importance as prognostic determinants of implantation and variables to maximize ET outcomes of oocyte donation in an attempt to control for confounding variables seen in other clinical studies.

2. Endometrial thickness and pregnancy outcome in oocyte donation cycles

To date, significant research has been done to directly assess uterine receptivity including histologic dating, measurement of endometrial sex steroid receptor concentrations using immuno-histochemical methods, assessing pinopod expression through scanning electron microscopy, and more recently the role of cytokines, growth factors, and integrin molecules have been studied (Castelbaum, 1997; Noci, 1995; Noyes, 1950; Paulson, 1997). Although these methods are important in furthering our understanding of uterine receptivity, they are not practical in actual ET cycles.

The measurement of endometrial thickness and its echogenic pattern, however, is an easy, non-invasive technique that has been used to assess endometrial receptivity prior to the embryo transfer. It is generally accepted that a thin endometrial stripe on transvaginal ultrasound is associated with a reduced embryo implantation potential (McWilliams, 2007; Rashidi, 2005; Schild, 2001; Zang, 2005; Zenke, 2004), while others have even reported an adverse effect of an increased endometrial thickness (Amir et al., 2007; Kovacs, 2003; Richter, 2007). The echogenic pattern of the endometrium has also been suggested to be a predictor of pregnancy outcome (Noyes, 2001; Sharara, 1999; Sher, 1991). Conversely, other studies have not shown sonographic assessment of the endometrium to be of any benefit in the characterization of uterine receptivity in IVF patients (Barufi, 2002; Dietterich, 2002; Garcia-Velasco, 2003; Sundstrom, 1998; Yuval, 1999). Nonetheless, despite these reports, the value of endometrial thickness and echogenic pattern are still undetermined as prognostic factors of implantation.

Oocyte donation cycles provide a unique model to eliminate confounding variables that typically occur when comparing groups of patients undergoing autologous IVF, where embryo quality and possible adverse effects of ovarian hyperstimulation on endometrial receptivity cannot be controlled. Endometrial proliferation strongly correlates with ovarian estradiol production, and therefore depends on ovarian function. Since age has an impact on ovarian function, embryo quality, estradiol production, endometrial thickness and pregnancy outcome often change in the same direction. In autologous cycles, poor endometrial development could be the sign of poor ovarian function (reduced estradiol production) and therefore is not independently responsible for lower implantation and pregnancy rates. Using an oocyte donation model, the endometrium can be developed by administration of exogenous sex steroids, with dose adjustment based on response (measured by serum estradiol level or endometrial thickness). Therefore endometrial proliferation becomes independent of ovarian function. In addition, oocyte donors are typically young women with normal ovarian reserve, thus embryos should characteristically be healthy with good implantation potential.

Few studies have evaluated the association between endometrial thickness pattern and pregnancy outcome using an oocyte donation model. Noyes et al., retrospectively analyzed 343 oocyte recipient cycles, in which endometrial thickness and pattern was evaluated on cycle day 12. They found that clinical pregnancy rate and live birth rate were significantly lower when endometrial thickness was less then 8mm than when endometrial thickness was greater than 9mm (Noyes et al., 2001). Zenke and Chetkowski reported in 41 recipient pairs with discordant outcomes that endometrial thickness less than 8 mm one week prior to oocyte retrieval was found in failed cycles (Zenke & Chetkowski, 2004).

In contrast, Remohi et al., performed a retrospective review of 465 oocyte donor cycles and found that there was no correlation between ultrasound appearance of the endometrium the day before embryo transfer and pregnancy rates (Remohi et al., 1997). Garcia-Velasco performed a matched pair analysis of 365 recipients with discordant outcome and found that endometrial thickness measured on cycle day 15 or 16 was not a significant finding (Garcia-Velasco et al., 2003). Barker et al. retrospectively examined endometrial thickness (in both the late follicular and mid-luteal phase) and treatment outcome in 132 oocyte donor IVF-ET cycles, using only blastocyst stage embryos which was thought to provide the best opportunity to assess the effect of these parameters on treatment outcome independent of

other confounding variables (Barker et al., 2009). Other studies using cleavage stage embryo transfer or a mixture of cleavage and blastocyst stage transfer therefore did not maximally control for the embryo factor (Abdalla, 1994; Check, 1993; Garcia-Velasco, 2003; Noyes, 2001; Remohi, 1997; Zenke, 2004). While this study was limited due to its retrospective design and limited power, it suggests that endometrial thickness in both the late-follicular and mid-luteal phase is not predictive of pregnancy outcomes. Moreover, thin endometrium and thickened endometrium (<7 mm, and >13 mm respectively), as well as pattern did not appear to be useful indicators of adverse endometrial receptivity (i.e. clinical outcomes).

In summary, research suggests that endometrial thickness may not be as helpful in predicting success as previously thought. Nonetheless, despite the many reports (some conflicting), the endometrial thickness and endometrial pattern are reassuring as a marker of endometrial receptivity and pregnancy outcomes. Further larger studies should confirm the present observations and what appears to be critical is the need for a uniform agreement by investigators to assess endometrial thickness and pattern in a more rigorous and standardized fashion to gain further insight into their relative importance.

3. Blastocyst embryo transfer is the primary determinant for improved outcomes in oocyte donation cycles

Another area that has drawn considerable attention is the blastocyst ET. Embryo culture has been extended from cleavage to the blastocyst stage transfer secondary to the introduction of sequential media allowing embryos to undergo cell compaction and genomic activation (Braude, 1988; Gardner, 1998). Two large randomized clinical trials and a recent Cochrane meta-analysis (Blake, 2007; Papnikolaou, 2005, 2006) suggest that blastocyst embryo transfers (ET) in good prognosis patients result in overall higher pregnancy and live-birth rates per ET, and has allowed for a reduction in the mean number of embryos transferred. Implantation rates have been reported to be as high as 60 to 65% per embryo transfer (Schoolcraft, 2001; Schillaci, 2002) with some in-vitro fertilization (IVF) programs advocating elective single ET in good prognosis patients (women <36 years of age) (Papnikolaou et al., 2006).

While our understanding of the developmental biology of pre-implantation stage embryos has substantially increased, overall implantation rates have remained relatively low with day-3 cleavage embryo transfers. Many IVF failures of seemingly normal embryos may occur as evidence suggests that extended blastocyst stage transfers result in significantly improved live-birth rates, including a Cochrane review by Blake et al (Blake et al., 2007).

The higher implantation and pregnancy rates appear to have a twofold explanation. First, it is principally thought to be the result of self selection and that only the most viable embryos develop into blastocysts, allowing these embryos to be transferred or cryopreserved (Schoolcraft, 2001; Schillaci, 2002). Studies suggest that a significant proportion of morphologically normal cleavage stage embryos are chromosomally abnormal and not destined to reach the blastocyst stage (Magli, 1998; Staessen, 2004), which appears to account for the high implantation failures seen in most cleavage stage ET cycles. This is despite the use of embryo classification systems including cell number and morphologic features of the fertilized oocyte, and cleavage stage embryos including pronuclei morphology, fragmentation, and blastomere uniformity (De Placido, 2002;

Gamiz, 2003; Gianarolo, 2003; Hnida, 2004; Nagy, 2003; Nikas, 1999; Montag, 2001; Rienzi, 2005; Van Royen, 1999; Ziebe, 1997).

The second factor appears to be related to the contribution of the uterine environment, where endometrial receptivity occurs within a short window of <48 hours and is precisely timed with exposure to progesterone secretion (Nikas, 1999; Valbuena, 2001). However, unlike in-vivo embryos that normally travel through the fallopian tube and do not reach the uterus before the morula stage (four days post-ovulation), in-vitro cultured embryos that are transferred to the uterine cavity at the cleavage stage may be subjected to stress that normally would not occur. Some have argued that this environmental milieu and possible higher uterine contractility during cleavage stage ET results in expulsion of earlier transferred embryos and may account for the exceedingly high implantation failures seen in most IVF programs (Croxatto, 1972; Fanchin, 2001; Valbuena, 2001).

It is apparent that the uterine environment remains a critical component of embryo implantation. A variety of factors from both the blastocyst and endometrium appear to be critical to implantation including apposition, attachment, and invasion during a defined window, however, the blastocyst-endometrial interaction remains the least explored embryonic event (Garcia et al.,) and its role in implantation is not completely understood.

Clearly due to ethical quandaries, any study as complex as embryo and endometrial synchrony and receptivity is difficult to perform, and thus more suggestive than conclusive. Shapiro et al. demonstrated higher implantation and pregnancy rates occurring in day-5 compared to day-6 fresh autologous cycles, yet cryopreserved day-6 embryos in frozen transfer cycles outperformed day-6 fresh autologous cycles, while day-5 and day-6 cryopreserved embryos in frozen transfer cycles resulted in similar outcomes (Shapiro et al., 2008). These findings suggest the presence of different endometrial receptivities, and it is hypothesized that this may be due to better uterine synchrony. The egg donation model also shows that endometrial receptivity clearly plays a significant role, as evidenced by studies looking at discordant outcomes between autologous IVF patients who share half their oocytes to recipients. The recipient group was found to have both higher implantation and pregnancy rates, suggesting the importance of endometrial receptivity and the tenuous nature of the uterine environment (Check, 1999).

Using oocyte donation cycles (n=93), Porat et al. retrospectively evaluated the pregnancy and implantation rates in cleavage stage (day-3) versus blastocyst stage (day-6) embryo transfers (ET); and assessed 1) the predictive value of blastocyst formation rates based on objective cleavage cell stage and morphology grade and 2) evaluate the subjective ability (4 blinded reviewers) to predict formation of high quality blastocysts (fully expanded or hatching, with at least a fair inner cell mass and trophoectoderm, scored ≥4BB using Gardner's scoring system)in 546 normally fertilized embryos (n=546) that were cultured in sequential media (Porat et al., 2010). Cleavage stage cycles resulted in significantly lower pregnancy per ET, clinical pregnancy per ET, and implantation rates (47%; 40%; and 27% compared to blastocyst cleavage stage ET 82%; 73%; and 64%), despite significantly reduced numbers of embryos transferred compared to day-3 cleavage stage ET. In total, HQ blastocysts more likely resulted from HQ day-3 embryos (>6 cells, grades 1 and 1.5 [uniform cells, slight or no fragmentation]) (59%) compared to either good quality (43%) or fair-to poor quality day-3 embryos (55%), respectively. In a Cochrane review published in 2010, a

comparison of cleavage versus blastocyst stage embryo transfer in ART (including 9 randomized controlled studies with 1144 patients) provided evidence of a significant difference in live-birth rate per couple favoring blastocyst culture, with an odds ratio of 1.35 (Blake et al., 2010). Also, clinical pregnancy rate per couple in this review included 17 studies, 2557 patients, with the odds ratio of 1.17 again favoring blastocyst culture.

With respect to the ability to select HQ blastocysts, in cases where ≥6 good and high quality day-3 embryos were available, retrospective-blinded selection of one, two, and three embryo(s) was accurately selected more than 95% of the time and two embryos were correctly selected close to 70% of the time. Given the high likelihood of correctly identifying embryo(s) that would have been picked on day-6 and the increase in implantation rates from day-3 cleavage stage to day-6 blastocyst ET, the data suggest that the improved clinical pregnancy and implantation rates are not only the result of the extended embryo culture (thus allowing for the selection and transfer of the highest quality embryos), but also the more physiologic timing of the ET. Appropriate timing appears to play a significant and underestimated role in optimizing outcomes.

4. The ultrasound guided embryo transfer

Historically, ET has been viewed as an unimportant variable in the success of an ART treatment cycle (Stafford-Bell, 1999) and the technique has typically been performed in a blinded fashion without the use of ultrasound guidance. Recent studies have specifically addressed the technique of ET as being critical for optimizing outcome success, including factors such as the technique itself, the type of catheter, and the use of ultrasound (US) guidance (Abou-Setta, 2005, 2006; Bucket, 2003; Sallam & Sadek, 2003). The application of ultrasound guidance (two-dimensional transabdominal, as well as three-dimensional and four dimensional ultrasound-guided) to ET (Baba et al., 2000) has been described in more than 150 clinical trials including 20 randomized clinical trials and four meta-analyses including a Cochrane review (Abou-Setta, 2007; Brown, 2007; Buckett, 2003; Sallam & Sadek, 2003). These studies suggest that ultrasound-guided ET provides a benefit with respect to increases in clinical pregnancy and implantation rates, compared to the blind, "clinical touch" method and is a critical factor in optimizing pregnancy outcomes. However, other studies including a randomized controlled trial of 2295 embryo transfers by Drakeley et al failed to demonstrate any differences in ultrasound-guided ET compared to the blind, clinical touch which has not been included in any of the meta-analysis (Drakeley et al., 2008).

To date, only two studies have assessed US guided ET using the ovum donation model to eliminate confounding variables. In a retrospective study, Lindheim et al. assessed the impact of US guided easy or difficult ET on pregnancy rates, implantation rates, and multiple gestation rates in 137 cycles with and without US guidance using transvaginal or transabdominal US. US guidance significantly improved implantation and pregnancy rates in cycles with easy ET (29% vs. 18% and 63% vs. 36%, respectively $p<0.05$), without impacting multiple pregnancy rates. Similar trends for pregnancy, implantation, and multiple rates were seen for difficult ET, although statistical significance was not seen.

The only randomized clinical trail in patients undergoing oocyte donation was performed by Garcia-Velasco et al. They attempted to determine whether transabdominal ultrasound

guidance during embryo transfer (ET) was a useful tool for increasing pregnancy rates. In this prospective, randomized, controlled trial that was powered to see a 15% increase chance of pregnancy, 374 patients undergoing oocyte donation were assigned to a transabdominal ultrasound-guided ET or the blind clinical touch.

Comparable pregnancy rates (60% ultrasound vs. 55% control); implantation rates (31% ultrasound vs. 26% control); miscarriage rates (11% ultrasound vs. 9% control); and multiple pregnancy rates (21% ultrasound vs. 23% control) were seen between groups. The authors concluded that that US guided ET did not provide any benefit in terms of pregnancy rate in oocyte recipients for whom ET was performed under direct transabdominal ultrasound visualization of the endometrial cavity.

Though these two studies are limited by their study design and adequate power, the overwhelming data suggest that US guided ET are associated with improved outcomes after IVF compared to the blind, clinical touch method and is a critical factor in optimizing pregnancy outcomes dispelling the historical notion that ET is an unimportant variable in the success of an ART treatment cycle (Brown, Mains & Van Voorhis, 2010). Moreover, it has been suggested that the ultrasound confirms the position of the tip of ET catheter and site of embryo deposition within the uterine cavity, increases the frequency of easy ET's, and avoids endometrial indentation. Most importantly, others argue that it allows for standardization of the transfer technique between physicians thus minimizing variation.

It is known that ease of the ET is strongly correlated to pregnancy outcome, and a difficult transfer, specifically with use of a more rigid catheter or the use of additional instrumentation may lower success rates. Soft catheters (Cook, Wallace) are preferred to the firm catheters (TDT, Frydman, Tomcat, Tefcat, Rocket) because of less cervical and endometrial trauma during the ET procedure, and easier transfer along the uterine axis (Mains, 2010; McDonald, 2002; Sallam, 2003). In comparisons between various soft catheters, pregnancy rates have not been shown to be significantly different (Saldeen et al., 2008).

5. Conclusion

While improved stimulation protocols and laboratory techniques are given the most attention to optimizing outcomes in ART cycles, an increasing awareness to the importance ET has come into focus. Continued research in the area of the ET including endometrial receptivity (endometrial thickness as a surrogate marker), optimal embryo selection and replacement (using the blastocyst transfer), and ET technique (with ultrasound guidance) play significant factors in improving ART outcomes. The oocyte donation model provides a unique environment while eliminating many confounding variables seen in autologous cycles allowing the study of these important variables involved in IVF/ET success.

Current literature supports the notion that an endometrial thickness >7mm increases overall pregnancy outcomes Therefore, consideration of this variable should be noted in the treatment and counseling of patients undergoing IVF/ET. With respect to the timing of embryo transfer, there is clear evidence that blastocyst ET in good prognosis patients results in overall higher pregnancy and live-birth rates per ET. In addition, these enhanced rates have allowed for a reduction in the mean number of embryos transferred. Extending culture to the blastocyst stage, particularly in high quality cleavage-stage embryos, allows for selection of viable chromosomally normal embryos that may have an implantation

advantage due to the timing of transfer on day 5 or 6. Therefore, selection of high quality embryos remain paramount, and if possible delay of transfer to the blastocyst stage can allow for enhanced outcomes and an overall movement towards single embryo transfers. Lastly, US guided ET provides evidence for a standardized approach, minimizing operator variability in technique, and is likely an important asset in the embryo transfer process. There is overwhelming data suggesting that US guided ET are associated with improved outcomes compared to the blind, clinical touch method, and is another critical factor in optimizing pregnancy outcomes.

As reviewed in this chapter, the oocyte donation model has allowed for more precise control of many confounding variables seen in autologous IVF cycles, and should continue to play a vital role in our pursuit for optimizing outcomes. The variables discussed in this chapter, specifically the role of endometrial thickness and pattern, advent of blastocyst embryo transfer, and the assistance of embryo transfer with ultrasound guidance will no doubt continue to be evaluated as important determinants of IVF outcomes.

6. References

Abdalla, HI., Brooks, AA., Johnson, MR., Kirkland, A., Thomas, A., & Studd, JW. (1994). Endometrial thickness: a predictor of implantation in ovum recipients? *Human Reproduction*, Vol.9, No.2, (Feburary 1994), pp.363-5, ISSN 0268-1161

Abou-Setta, AM., Al-Inany, HG., Mansour, RT., Serour, GI., & ABoulghar, MA. (2005). Soft versus firm embryo transfer catheters for assisted reproduction: a systematic review and meta-analysis. *Human Reproduction*, Vol.20, No.11, (November 2005), pp.114-21, ISSN 0268-1161

Abou-Setta, AM. (2006). Firm embryo transfer catheters for assisted reproduction: a systematic review and meta analysis using direct and adjusted indirect comparisons. *Reproductive Biomedicine Online*, Vol.12, No.2, (February 2006), pp.191-8, ISSN 1472-6483

Abou-Setta, AM., Mansour, RT., Al-Inany, HG., Aboulghar, MM., Aboulghar, MA., & Serour, GI. (2007). Among women undergoing embryo transfer, is the probability of pregnancy and live birth improved with ultrasound guidance over clinical touch alone? A systemic review and meta-analysis of prospective randomized trials. *Fertility and Sterility*, Vol.88, No.2, (August 2007), pp.333-41, ISSN 0015-0282

Acosta, AA., Elberger, L., Borghi, M., Calamera, JC., Chemes, H., Doncel, GF, Kliman, H., Lema, B., Lustig, L., & Papier, S. (2000). Endometrial dating and determination of the window of implantation in healthy fertile women. *Fertility and Sterility*, Vol.73, No.4, (April 2000), pp.788–9, ISSN 0015-0282

Amir, W., Micha, B., Ariel, H., Liat, LG., Jehoshua, D., & Adrian, S. (2007). Predicting factors for endometrial thickness during treatment with assisted reproductive technology. *Fertility and Sterility*, Vol.87, No.4, (April 2007), pp.799-804, ISSN 0015-0282

Baba, K., Ishihara, N., Saitoh, M., Taya, J., & Kinoshita, K. (2007). Three-dimensional ultrasound in embryo transfer. *Ultrasound In Obstetrics & Gynecology*, Vol.16, No.4, (September 2000), pp.372-3, ISSN 1469-0705

Barker, MA., Boehnlein, LM., Christianson, MS., Kovacs, P., & Lindheim, SR. (2009). Relationship of Follicular and Luteal Phase Endometrial Thickness plus Echogenic

Pattern and Pregnancy Outcome in Oocyte Donation Cycles. *Journal of Assisted Reproduction and Genetics*, Vol.26, No.5, (May 2009), pp.243-9, ISSN 1573-7330

Baruffi, RLR., Contart, P., Mauri, AL., Peterson, C., Felipe, V., Garbellini, E., & Franco, JG. Jr. (2002). A uterine ultrasonographic scoring system as a method for the prognosis of embryo implantation. *Journal of Assisted Reproduction and Genetics*, Vol.19, No.3, (March 2002), pp.99-102, ISSN 1573-7330

Blake, DA., Farquhar, CM., Johnson, N., & Proctor, M. (2007). Cleavage stage versus blastocyst stage embryo transfer in assisted conception (Review). *Cochrane Database of Systematic Reviews*, Vol. 17, No.4, (October 2007), pp.1-79, ISSN 1469-493X

Braude, P., Bolton, V., & Moore, S. (1988). Human gene expression first occurs between the four and eight-cell stages of pre-implantation development. *Nature*, Vol.332, No.6163, (March 1988), pp.459-61, ISSN 0028-0836

Brown, JA., Buckingham, K., Abou-Setta, A., & Buckett, W. (2007). Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women. *Cochrane Database of Systematic Reviews* , Vol.24, No.1, (January 2007), ISSN 1469-493X

Buckett, WM. (2003). A meta-analysis of ultrasound-guided versus clinical touch embryo transfer. *Fertility and Sterility*, Vol.80, No.4, (October 2003), pp.1037-41, ISSN 0015-0282

Castelbaum, AJ., Ying, L., Somkuti, SG., Sun, J., Ilesanni, AO., & Lessey, BA. (1997). Characterization of integrin expression in well differentiated endometrial a endometrial adenocarcinoma cell line (Ishikawa). *The Journal of Clinical Endocrinology and Metabolism*, Vol.82, No.1, (January 1997), pp.136-142. ISSN 1945-7197

Check, JH., Nowroozi, K., Choe, J., Lurie, D., & Dietterich, C. (1993). The effect of endometrial thickness and echo pattern on in vitro fertilization outcome in donor oocyte-embryo transfer cycle. *Fertility and Sterility,* Vol.59, No.1, (January1993), pp.72-5, ISSN 0015-0282

Check, JH., Choe, JK., Kotsoff, D., Summers-Chase, D., & Wilson, C. (1999). Controlled ovarian hyperstimulation adversely affects implantation following in vitro fertilization-embryo transfer. *Journal of Assisted Reproduction and Genetics,* Vol.16, No.8, (September 1999), pp. 416-20, ISSN 1573-7330

Croxatto, HB., Fuentealba, B., Diaz, S., Patene, L., &Tatum, HJ. (1972). A simple nonsurgical technique to obtain unimplanted eggs from human uteri. *American Journal of Obstetrics and Gynecology*, Vol.112, No.5, (March 1972), pp.662-8, ISSN 0002-9378

De Placido, G., Wilding, M., Strina, I., Alviggi, E., Alviggi, C., Mollo, A., Varicchio, MT., Tolino, A., Schiattarella, C., & Dale, B. (2002). High outcome predictability after IVF using a combined score for zygote and embryo morphology and growth rate. *Human Reproduction*, Vol.17, No.9, (September 2002), pp.2402-09, ISSN 0268-1161

Dietterich, C., Check, JH., Choe, JK., Nazari, A., & Lurie, D. (2002). Increased endometrial thickness on the day of human chorionic gonadotropin injection does not adversely affect pregnancy or implantation rates following in vitro fertilization-embryo transfer. *Fertility and Sterility*, Vol.77, No.4, (April 2002), pp.781-86, ISSN 0015-0282

Drakeley, AJ., Jorgensen, A., Sklavounos, J., Aust, T., Gazvani, R., Williamson, P., & Kingsland, CR. (2005). A randomized controlled clinical trial of 2295 ultrasound. *Human Reproduction*, Vol.23, No.5, (2008), pp.1101-06, ISSN 0268-1161

Fanchin, R., Ayoubi, JM., Righini, C., Olivennes, F., Schonauer, LM., & Frydman, R. (2001). Uterine contractility decreases at the time of blastocyst transfers. *Human Reproduction*, Vol.16, No.6, (June 2001), pp.1115-9, ISSN 0268-1161

Gamiz, P., Rubio, C., de los Santos, MJ., Mercader, A., Simon, C., Remohl, J., & Pellicer, A. (2003). The effect of pronuclear morphology on early development and chromosomal abnormalities in cleavage-stage embryos. *Human Reproduction*, Vol.18, No.11, (November 2003), pp.2413-19, ISSN 0268-1161

Garcia, JE., Acosta, AA., Hsiu, JG., & Jones, HW Jr. (1984). Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin human chorionic gonadotropin for in vitro fertilization. *Fertility and Sterility*, Vol.41, No.1, (January 1984), pp.31–5, ISSN 0015-0282

García-Velasco, JA., Isaza, V., Martinez-Salazar, J., Landazábal, A., Requena, A., Remohí, J., & Simón, C. (2002).Transabdominal ultrasound-guided embryo transfer does not increase pregnancy rates in oocyte recipients. *Fertility and Sterility*, Vol. 78, No.3, (September 2002) , pp.534-9, ISSN 0015-0282

Garcia-Velasco, JA., Isaza, V., Caligara, C., Pellicer, A., Remohí, J., & Simón, C. (2003). Factors that determine discordant outcome from shared oocytes. *Fertility and Sterility*, Vol.80, No.1, (July 2003), pp.54-60, ISSN 0015-0282

Gardner, DK., Schoolcraft, WB., Wagley, L., Schlenker, T., Stevens, J., & Hesla, J. (1998). A randomized trial of blastocyst culture and transfer in in-vitro fertilization. *Human Reproduction*, Vol.13, No.12, (December 1998), pp.3434-40, ISSN 0268-1161

Gianaroli, L., Magli, MC., Ferraretti, AP., Fortini, D., & Griecc, N. (2003). Pronuclear morphology and chromosomal abnormalities as scoring criteria for embryo slection. *Fertility and Sterility*, Vol.80, No.2, (August 2003), pp.341-9, ISSN 0015-0282

Hnida, C., Engenheiro, E., & Ziebe, S. (2004). Computer-controlled, multilevel, morphometric analysis of blastomere size as biomarker of fragmentation and multinuclearity in human embryos. *Human Reproduction*, Vol.19, No.2, (February 2004), pp.288-93, ISSN 0268-1161

Kovacs, P., Matyas, S., Boda, K., & Kaali, SG. (2003). The effect of endometrial thickness on IVF/ICSI outcome. *Human Reproduction*, Vol.18, No.11, (November 2003), pp.2337-41, ISSN 0268-1161

Lindheim, SR., Cohen, MA., & Sauer, MV. (1999). Ultrasound guided embryo transfer significantly improves pregnancy rates in women undergoing oocyte donation. *International Journal of Gynaecology and Obstetrics,* Vol. 66, No.3, (September 1999), pp.281-4, ISSN 0020-7292

Magli, MC., Gianaroli, L., Munne, S., & Ferratetti, AP. (1998). Incidence of chromosomal abnormalities from a morphologically normal cohort of embryos in poor-prognosis patients. *Journal of Assisted Reproduction and Genetics*, Vol.15, No.5, (May 1998), pp.297-301, ISSN 1573-7330

Mains, L., & Van Voorhis, BJ. (2010). Optimizing the technique of embryo transfer. *Fertility and Sterility*, Vol.93, No.3, (August 2010), pp.785-790, ISSN 0015-0282

McDonald JA, Norman RJ. A randomized controlled trial of a soft double lumen embryo transfer catheter versus a firm single lumen catheter: significant improvements in pregnancy rates. Hum Reprod 2002;17:1502–6

McWilliams, GD., & Frattarelli, JL. (2007). Changes in measured endometrial thickness predict in vitro fertilization success. *Fertility and Sterility*, Vol.88, No.1, (July 2007), pp.74-81, ISSN 0015-0282

Montag, M., & van der Ven, H. (2001). Evaluation of pronuclear morphology as the only selection criterion for further embryo culture and transfer: results of a prospective randomized multicentre study. Human *Reproduction*, Vol.16, No.11, (November 2001), pp.2384-89, ISSN 0268-1161

Nagy, ZP., Dozortsev, D., Diamond, M., Rienzi, L., Ubaldi, F., Adelmassih, R., & Greco, E. (2003). Pronuclear morphology evaluation with subsequent evaluation of embryo morphology significantly increases implantation rates. *Fertility and Sterility*, Vol.80, No.1, (July 2003), pp.67-74, ISSN 0015-0282

Nikas, G., Develioglu, OH., Toner, JP., & Jones, HW. Jr. (1999). Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles. *Human Reproduction*, Vol.14, No.3, (March 1999), pp.787-92, ISSN 0268-1161

Noci, I., Borri, P., Chieffi, O, Scarsselli, G., Biaglotti, R., Moncini, D., Paglierani, M., & Taddei, G. (1995). Aging of the human endometrium: a basic morphological and immunohistochemical study. *European Journal of Obstetrics & Gynecology, and Reproductive Biology*, Vol.63, No.2, (December 1995), pp.181-85, ISSN 0301-2115

Noyes, N., Hampton, BS., Berkeley, A., Licciardi, F., Grifo, J., & Krey, L. (2001). Factors useful in predicting the success of oocyte donation: a 3-year retrospective analysis. *Fertility and Sterility*, Vol.76, No.1, (July 2001), pp.92-97, ISSN 0015-0282

Noyes, RW., Hertig, AT., & Rock, J. (1950). Dating the endometrial biopsy. *Fertility and Sterility*, Vol.1, No.3, (March 1950), pp.1-3, ISSN 0015-0282

Oehninger, S. (1950). Revealing the enigmas of implantation: what is the true impact of ovarian hyperstimulation? *Fertility and Sterility*, Vol.89, No.1, (January 1950), pp27–30, 0015-0282

Papnikolaou, EG., D'haeseleer, E., Verheyen, G., Van de Velde, H., Camus, M., Van Steirteghem, A., Devroey, P., & Tournaye, H. (2005). Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage transfer when at least four embryos are available on day 3 of culture. A randomized prospective study. *Human Reproduction*, Vol.20, No.11, (November 2005), pp.3198-203, ISSN 0268-1161

Papnikolaou, EG., Camus, M., Kolibianakis, EM., Landuyt, LV., Van Steirteghem, A., & Devroey, P. (2006). In vitro fertilization with single blastocyst-stage versus cleavage-stage embryos. *New England Journal of Medicine*, Vol.354, No.11, (March 2006), pp.1139-46., ISSN 00284793

Paulson, RJ., Sauer, MV., & Lobo, RA. (1997). Potential enhancement of endometrial receptivity in cycles using controlled ovarian hyperstimulation with antiprogestins: a hypothesis. *Fertility and Sterility*, Vol.67, No.2, (February 1997), pp.321-25, ISSN 0015-0282

Porat, N., Boehnlein, LM., Barker, MA., Kovacs, P., & Lindheim, SR. (2010). Blastocyst Embryo Transfer is the Primary Determinant for Improved Outcomes in Oocyte Donation Cycles. *Journal of Obstetrics and Gynaecology Research*, Vol.36, No.2, (April 2010), pp.357-63, ISSN 1447-0756

Rashidi, BH., Sadeghi, M., Jafarabadi, M., & Tehrani Nejad, ES. (2005). Relationships between pregnancy rates following in vitro fertilization or intracytoplasmic sperm injection and endometrial thickness and pattern. *European Journal of Obstetrics,*

Gynecology, and Reproductive Biology, Vol.120, No.2, (June 2005), pp.179-184, ISSN 0301-2115

Remohí, J., Ardiles, G., García-Velasco, JA., Gaitán, P., Simón, C., & Pellicer, A. (1997). Endometrial thickness and serum oestradiol concentrations as predictors of outcome in oocyte donation. *Human Reproduction,* Vol.12, No.10, (October 1997), pp.2271-2276, ISSN 0268-1161

Rienzi, L., Ubaldi, F., Iacobelli, M., Romano, S., Minasi, MG., Ferrero, S., Sapienza, F., Baroni ,E., & Greco, E. (2005). Significance of morphological attributes of the early embryo. *Reproductive Biomedicine Online*, Vol.10, No.5, (May 2005), pp.669-681, ISSN 1472-6483

Richter, KS., Bugge, KR., Bromer, JG., & Levy, MJ. (2007). Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. *Fertility and Sterility*, Vol.87, No.1, (January 2007), pp.53-59, ISSN 0015-0282

Sallam HN, Agameya AF, Rahman AF, Ezzeldin F, Sallam AN. Impact of technical difficulties, choice of catheter, and the presence of blood on the success of embryo transfer: experience from a single provider. J Assist Reprod Genet 2003;20:135–42

Sallam, HN., & Sadek, SS. (2003). Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials. *Fertility and Sterility*, Vol.80, No.4, (October 2003), pp.1042-6, ISSN 0015-0282

Schild, RL., Knobloch, C., Dorn, C., Fimmers, R., van der Ven, H., & Hansmann, M. (2001). Endometrial receptivity in an in vitro fertilization program as assessed by spiral artery blood flow, endometrial thickness, endometrial volume, and uterine artery blood flow. *Fertility and Sterility*, Vol. 75, No.2, (February 2001), pp.361-66, ISSN 0015-0282

Schillaci, R., Castelli, A., Vassiliadis, A., Venzia, R., Sciacca, GM., Perino, A., & Cittadini, E. (2002). Blastocyst stage versus day 2 embryo transfer in IVF cycles. *Abstracts of the 18th Annual Meeting of ESHRE, Vienna*, 2002, P-418.

Schoolcraft, WB., & Gardner, DK. (2001). Blastocyst versus day 2 or 3 transfer. *Seminars in Reproductive Medicine,* Vol.19, No.3, (September 2001), pp.259-268, ISSN 1526-8004

Shapiro, BS., Daneshmand, ST., Garner, FC., Aguirre, M., & Ross, R. (2008). Contrasting patterns in in vitro fertilization pregnancy rates among fresh autologous, fresh oocyte donor, and cryopreserved cycles with the use of day 5 or day 6 blastocysts may reflect differences in embryo-endometrium synchrony. *Fertility and Sterility*, Vol.89, No.1, (January 2008), pp.20-26, ISSN 0015-0282

Sharara, FI., Lim, J., & McClamrock, HD. (1999). Endometrial pattern on the day of oocyte retrieval is more predictive of implantation success than the pattern or thickness on the day of hCG administration. *Journal of Assisted Reproduction and Genetics*, Vol.16, No.10, (November 1999), pp.523-28, ISSN 1573-7330

Sher, G., Herbert, C., Maassarani, G., & Jacobs, MH. (1991). Assessment of the late proliferative phase endometrium by ultrasonography in patients undergoing in-vitro fertilization and embryo transfer (IVF-ET). *Human Reproduction*, Vol.6, No.2, (February 1991), pp.232-37, ISSN 0268-1161

Staessen, C., Platteau, P., Van Assche, E., Michiels, A., Tournaye, H., Camus, M., Devroey, P., Liebaers, I., & Van Steirteghem, A. (2004). Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in

couples with advanced maternal age: a prospective randomized controlled trial. *Human Reproduction*, Vol.19, No.12, (December 2004), pp.2849-58, ISSN 0268-1161

Sundström, P. (1998). Es Stafford-Bell, MA. (1999). Which factors are important for successful embryo transfer after in vitro fertilization? *Human Reproduction*, Vol.14, No.10, (October 1999), pp.2678-9, ISSN 0268-1161tablishment of a successful pregnancy following in-vitro fertilization with an endometrial thickness of no more than 4 mm. *Human Reproduction*, Vol.13, No.6, (June 1998), pp.1550-52, ISSN 0268-1161

Trounson, A., Leeton, J., Besanko, M., Wood, C., & Conti, A. Pregnancy established in an infertile patient after transfer of a donated embryo fertilized in vivo. *British Medical Journal*, Vol.286, No.6368 (March 1983), pp.835-838, ISSN 0959-8138

Valbuena, D., Martin, J., dePablo, J., Remohi, J., Pellicer, A., & Simon, C. (2001). Increasing levels of estradiol are deleterious to embryonic implantation because they directly affect the embryo. *Fertility & Sterility*, Vol.76, No.5, (November 2001), pp.962-8, ISSN 0015-0282

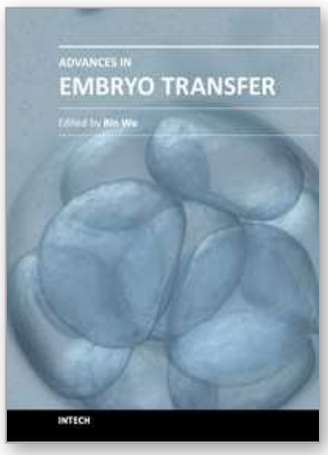
Van Royen, E., Mangelschotrs, K., De Neubourg, D., Valkenburg, M., Van de Meerssche, M., Ryckaert, G., Estermans, W., & Gerris, J. (1999). Characterization of a top quality embryo, a step towards single-embryo transfer. *Human Reproduction*, Vol.14, No.9, (September 1999), pp2345-49, ISSN 0268-1161

Yuval, Y., Lipitz, S., Dor, J., & Achiron, R. (1999). The relationships between endometrial thickness, and blood flow and pregnancy rates in in-vitro fertilization. *Human Reproduction*, Vol.14, No.4, (April 1999), pp.1067-71, ISSN 0268-1161

Zenke, U., & Chetkowski, RJ. (2004). Transfer and uterine factors are the major recipient-related determinants of success with donor eggs. *Fertility and Sterility*, Vol.82, No.4, (October 2004), pp.850-56, ISSN 0015-0282

Zhang, X., Chen, CH., Confino, E., Barnes, R., Milad, M., & Kazer, RR. (2005). Increased endometrial thickness is associated with improved treatment outcome for selected patients undergoing in vitro fertilization-embryo transfer. *Fertility and Sterility,*Vol.83, No.2, *(*February 2005), pp.336-40, ISSN 0015-0282

Ziebe, S., Peterson, K., Lindenberg, S., Andersen, AG., Gabrielsen, A., & Andersen, NA. (1997). Embryo morphology or cleavage stage: How to select the best embryos fro transfer after in-vitro fertilization. *Human Reproduction*, Vol.12, No.7, (July 1997), pp.545-49, ISSN 0268-1161



Advances in Embryo Transfer

Edited by Dr. Bin Wu

ISBN 978-953-51-0318-9
Hard cover, 248 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

Embryo transfer has become one of the prominent high businesses worldwide. This book updates and reviews some new developed theories and technologies in the human embryo transfer and mainly focus on discussing some encountered problems during embryo transfer, which gives some examples how to improve pregnancy rate by innovated techniques so that readers, especially embryologists and physicians for human IVF programs, may acquire some new and usable information as well as some key practice techniques. Major contents include the optimal stimulation scheme for ovaries, advance in insemination technology, improved embryo transfer technology and endometrial receptivity and embryo implantation mechanism. Thus, this book will greatly add new information for readers to improve human embryo transfer pregnancy rate.

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