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ORIGINAL ARTICLE

How to maximize the pregnancy rate with no increase in multiple pregnancy rates following blastocyst embryo transfer? Is blastocyst transfer time the missing ingredient?

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KEYWORDS

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Abstract *Background:* Multiple births after assisted reproduction techniques are associated with adverse outcome. Transferring one blastocyst is the best way to reduce the rate of multiple births but it may also decrease the clinical pregnancy rate if not used wisely. *Methods:* In this study we reviewed the records of 170 women who undergone transfer of 1–3 blastocysts on day 5 or day 6 after in vitro fertilization from 2008 to 2010 to explore the outcome of elective single blastocyst transfer (SBT) compared with multiple blastocyst embryo transfer (MBT) and determine how this affects multiple pregnancy rates. *Results:* The result suggested increasing the number of blastocysts transferred based on advanced age or poor blastocyst quality did not result in any significant increase in CPR while there was significant increase in multiple pregnancy rate (MPR). On the other hand, using the time of transfer as main criteria to decide the number of blastocysts transferred increased the CPR significantly, without significant increase in MPR. *Conclusion:* Our study identified blastocyst transfer time (in hours) could be the best criteria to transfer single blastocyst (SBT) versus double blastocyst (DBT), as that showed to maximize the clinical pregnancy rate with no increase in multiple pregnancy rate. The likelihood of pregnancy is significantly higher in the group of women who had 2 blastocysts transferred after 140 h compared to SBT, with no increase in the multiple pregnancy rate.

1. Introduction

There is a worldwide trend toward reducing the number of embryos transferred in order to reduce the rate of multiple pregnancies. Multiple births following ART are associated with increased risks of adverse perinatal outcomes (1,2) and

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maternal complications (3). The most successful way to decrease multiple pregnancies in IVF is to transfer only one embryo or blastocyst, which might reduce the efficacy of treatment.

In fact, shifting from high order embryo transfer (3 or more embryos) to double-embryo transfer (DET) apparently does not interfere in the results of IVF/ICSI cycles, while the option for SET instead of DET can lower pregnancy and live birth-rates (4). Roberts et al. reported for any one transfer, single embryo transfer (SET) has about a one-third loss of success rate relative to double embryo transfer (DET), which can be mitigated to some extent by selection of patients for SET (5). Furthermore van Montfoort et al. undertook a randomized controlled trial of single-embryo transfer versus double-embryo transfer and concluded that undertaking single-embryo transfer in unselected patients will halve the pregnancy rate compared with double-embryo transfer. Only in selected patient groups, which have a good prognosis of pregnancy establishment following IVF, would a less drastic effect of single-embryo transfer on pregnancy rate be observed compared with double-embryo transfer (6).

Recent advances in cell culture media have led to a shift in IVF practice from early cleavage embryo transfer to blastocyst stage transfer. Cochran systematic review on cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology provides evidence that there is a significant difference in pregnancy and live birthrates in favor of blastocyst transfer with good prognosis patients and there is emerging evidence to suggest that in selected patients, blastocyst culture may be applicable for single embryo transfer (7). Blastocyst transfer became of great interest to most assisted reproductive technology clinics to select the best embryos to transfer in order to increase pregnancy rates and to replace lower numbers of embryos to reduce the likelihood of an unwanted multiple pregnancy. Because blastocyst stage embryo transfer generally increases the chance of implantation and live birth compared with cleavage stage embryo transfer, SBT should be performed in good-prognosis patients who have good quality blastocysts available (8). Some consider patients under the age of 38 with available good quality blastocyst the criteria for good prognosis group (8), while others found that presence of good quality blastocyst alone is the suitable criteria for (SBT) (9).

At Bristol Centre of Reproductive Medicine (BCRM) we had a policy to transfer single blastocyst for patients below age 35 when there is at least one fair or good quality blastocyst available. However in those with poor quality, DBT will be performed. Other group of patients would be candidate for DBT if the patient is between 35 and 39, or 2–3 blastocysts if patient is 40 or above. Otherwise if patient has medical condition contraindicated for multiple pregnancies or based on patient choice a single blastocyst may be transferred. Blastocyst transfer can be done on day 5 or day 6, depending on when the blastocyst fully developed and time suitable for the patient and the laboratory. The blastocyst transfer time is calculated in hours rather than days which can be easily converted to days by dividing the hours by 24.

2. Materials and method

This study was conducted within the local research ethics committee's guidelines, and all couples gave written consent for clinical procedures

2.1. Study type and analysis

This was a retrospective cohort study of all women in whom blastocyst culture was undertaken between January 2008 and October 2010. The center policy was for all patients intended for blastocyst transfer to proceed with blastocyst culture if 4 excellent quality embryos (criteria) were observed on day 3. All IVF and ICSI patients who succeeded in having a transfer on day 5 or 6 depending on time of blastocyst expansion and development were included in this analysis. The time from IVF or ICSI procedure to the blastocyst transfer was calculated in hours for each case and saved as the time to embryo transfer (BTT). Data collected after the proposal retrospective study idea discussed, reviewed and approved by the unit in their assigned meetings. The data included age at egg collection, retrieved blastocyst quality, time to embryo transfer and number of blastocyst transferred were also evaluated.

Outcome data included clinical pregnancy (CPR), and multiple birthrates (MPRs). Clinical pregnancy defined as presence of intrauterine gestational sac with fetal heart at 4–5 weeks from embryo transfer. Statistics were done using chi-square test, Fisher test and SPSS 17 Software.

2.2. Fresh cycle stimulation protocol

Fresh-cycle controlled ovarian hyperstimulation was accomplished using long luteal gonadotropin-releasing hormone (GnRH) agonist or occasionally (GnRH) antagonist. Patients received recombinant FSH (Gonal-F or puregon) or highly purified human Menopausal Gonadotropins (Menopur) daily dosages were adjusted based on the anticipated follicular response. Follicular development was monitored by transvaginal ultrasonography. Once at least 3 follicles reached $\geqslant$17 mm, and 6500 IU hCG was administered. Oocyte retrieval was performed 34–36 h later.

2.3. Embryo culture protocol

Fertilization was performed 3–6 h post-retrieval by either conventional insemination or intracytoplasmic sperm injection (ICSI) as indicated (day 0). Oocytes inseminated by ICSI were cultured overnight. Evidence of fertilization was determined at approximately 18 h post-insemination by the presence of two pronuclei.

Patients having >3 high-grade embryos on day 3 of embryo development were candidates for blastocyst transfer. On day 5 or day 6, those embryos achieving the blastocyst stage were evaluated morphologically and the best appearing were selected for transfer. For those patients not meeting these criteria, day 3 embryo transfers were performed. A modified grading system was used to determine the developmental level. Initial scoring scores 1–6, based on the degree of expansion, hatching status, inner cell mass (ICM) and trophectoderm (TE). 6 refers to hatched blastocyst, while 1 refers to blastocoel less than half the volume of the embryo. Second stage scoring is for blastocysts graded 3–6 (i.e. full blastocyst onwards) the development of the inner cell mass (ICM) and (TE) is assessed from A to C, where A is the top score while C is the least.

Embryo quality for the sake of the study was categorized according to the criteria set forth by the Society for Assisted Reproductive Technology (SART) guidelines ('SART