Original Article

Comparison between Single and Double Cleavage-Stage Embryo Transfers, Single and Double Blastocyst Transfers in a South East Asian In Vitro Fertilisation Centre

Lee Koon Kwek, [1]*MBBS, MRCS (Edin)*, Seyed Ehsan Saffari, [2], Heng Hao Tan, [3]*MBBS, MRCOG*, Jerry KY Chan, [3,4]*FRCOG, PhD (London)*, Sadhana Nadarajah, [3]*MBBS, MRCOG*

Abstract

Introduction: This study investigated the differences in clinical pregnancy rate (CPR), live birth rate (LBR) and multiple pregnancy rate (MPR) between double cleavage-stage embryo transfers compared to single and double blastocysts stage embryo transfers in a single academic medical centre. Materials and Methods: This was a retrospective cohort study performed at the KK Women's and Children's Hospital In Vitro Fertilisation (KKIVF) Centre of all women who underwent fresh-cycle in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) cycles over a 5-year period. The outcome measures were CPR, LBR and MPR. The study included 5294 cycles, of which 539 patients underwent single embryo transfer (SET); 4533 patients underwent double embryo transfer (DET); 84 patients underwent double blastocyst transfer (DBT); and 65 patients underwent single blastocyst transfer (SBT). Results: The mean age of patients undergoing single blastocysts stage embryo transfer was lower than the other 2 groups. The DET, single and double blastocysts stage embryo transfer groups achieved similar LBR (33.9%, 38.7%, 35.4%, *P* >0.05) and CPR (42.4%, 46.2%, 46.9%). Conclusion: We found that single blastocysts stage embryo transfer is associated with similar LBR and CPR compared to double blastocysts stage embryo transfer and DET, with lower MPRs, and should be offered as standard practice, where possible.

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Key words: Infertility, Pregnancy outcomes

Introduction

The development of a reliable blastocyst culture system presents the opportunity to perform single blastocyst stage embryo transfer that avoids multi-pregnancies and its attendant morbidities, while maintaining pregnancy rates of cleavage-stage double embryo transfers (DETs). Blastocyst culture has proven to have more favourable outcomes by identifying embryos that are most able to establish a pregnancy.[1,2] A prospective randomised trial reported a higher pregnancy rate among women undergoing a single blastocyst transfer (SBT) versus a cleavage-stable embryo transfer.[3,4] Studies have also shown that SBTs have significantly less multiple pregnancy rates while maintaining clinical pregnancy rates (CPRs).[5,6] The strategy of performing single embryo transfer (SET) has been implemented in our institution over the past few years. Here, we asked if there were differences between double cleavage-stage embryo transfers compared to single and double blastocysts stage embryo transfers in a retrospective cohort study performed in KK Women's and Children's Hospital (KKH).

Materials and Methods

In this retrospective cohort, we included a total of 5414 consecutive fresh-cycle assisted reproductive technique (ART) performed at the KKH In Vitro Fertilisation (KKIVF)

[1]Department of Obstetrics & Gynaecology, KK Women's and Children's Hospital, Singapore
[2]Centre for Quantitative Medicine, Office of Research, Duke-NUS Medical School, Singapore
[3]Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore
[4]Programme in Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore
Address for Correspondence: A/Prof Jerry Chan Kok Yen, Department of Reproductive Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: jerrychan@duke-nus.edu.sg

Centre. We included all cases that underwent fresh-cycle ART for single cleavage-stage embryo transfers on Day 2 to 3, double cleavage-stage embryo transfers on Day 2 to 3, double blastocyst transfers (DBTs) and SBTs over a 5-year period between 2009 to 2014. We then followed them up for a 1-year period thereafter to obtain the total number of live births.

We excluded 132 cycles, where there were more than 2 cleavage embryos (n = 130) or more than 2 blastocysts transferred (n = 2).

The outcome measures we looked at were CPR, live birth rate (LBR) and multiple pregnancy rate (MPR). CPR is defined as the presence of gestational sac on transvaginal scan at 6 weeks gestation. LBR is defined as the number of deliveries that resulted in at least 1 live born neonate (>24 weeks gestation). Patients were encouraged to inform KKH if deliveries were conducted in other hospitals. However, of note, some patients were lost to follow-up after the IVF cycles and may not have reported after delivery. MPR refers to the number of deliveries that resulted in 2 or more live born neonates (>24 weeks gestation). Miscarriage was defined as a clinical pregnancy that ended up in pregnancy loss prior to 24 completed weeks' gestation.

Data were extracted for statistical analysis using SAS software version 9.3 for Windows (SAS, Inc. Cary, NC). Baseline demographics and clinical features were compared among SET, DET, SBT and DBT using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables. To investigate the association between number of oocytes obtained with CPR and LBR, we used multivariable logistic regression analysis and adjusted the odds ratios for age. Statistical significance was set at $P \leq 0.05$.

Results and Discussion

Of the patients who underwent ART (n = 5294), a total of 539 patients underwent SET, 4533 patients underwent DET, 84 patients underwent DBT and 65 patients underwent SBT. Demographic details are illustrated in Table 1. Patients who underwent SET were significantly older compared to patients undergoing DET, single blastocysts stage embryo transfer and double blastocysts stage embryo transfer (mean age 36.5 vs 34.4, 33.5, 35.8, P <0.001). SET patients had a lower number of oocytes retrieved (5.6 vs 14.2, 17.8, 20.1, P <0.001), and lower CPR (16.0% vs 42.5%, 45.2%, 42.9%, P <0.001) and LBR (11.7% vs 34.0%, 38.1%, 36.9%, P <0.001) than the other 3 groups. Patients undergoing SET in our institution had only 1 usable embryo for transfer, and are therefore of poor prognosis. Thus, the SET group was not used for comparison with the other groups.

Table 1. Demographics

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Total no. of transfers	4533	84	65	
Age	34.4 ± 3.7	33.5 ± 3.5	35.8 ± 4.2	<0.001
No. of oocytes obtained	14.2 ± 8.1	17.8 ± 8.5	20.1 ± 11.6	<0.001

Patients who underwent single blastocysts stage embryo transfer were significantly younger than those who had DET and DBT (33.5 vs 34.4, 35.8, P <0.001). Single blastocysts stage embryo transfer patients also had similar CPR and LBR as compared to DET and DBT patients (Table 2). There was no multiple pregnancy live birth deliveries in single blastocysts stage embryo transfer patients in contrast to patients who had DET and DBT.

Next, we analysed the neonatal outcomes of the patients who delivered in our centre (Table 3). Among the singleton pregnancies, there was a similar rate of term deliveries, mean gestational age (GA) and birth weight (BW). However, among the multiple pregnancies, there was a significantly higher rate of full-term deliveries in the double blastocysts stage embryo transfer group compared to the DET group (83.3% vs 38.2%, P <0.05) with a significantly higher mean GA at delivery (37 vs 35.1, P <0.05). The mean BW was not significantly different between these 2 groups.

We conducted further analysis using data from all 4 groups to look at the overall impact of age and number of eggs retrieved on CPR and LBR. We found a progressive decrease in CPR and LBR with rising age (Figs. 1 and 2). There was a significant impact of maternal age on CPR and LBR, with a 9% decrease in both CPR (OR 0.91, 0.90-0.93, P <0.0001) and LBR (OR 0.91, 0.89-0.92, P <0.0001) with

Table 2. Delivery Outcomes of Patients

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Clinical pregnancy rate	1925 (42.5%)	38 (45.2%)	32 (42.9%)	0.487
Miscarriages (before 24 weeks)	355 (7.83%)	6 (7.14%)	7 (10.77%)	0.662
Stillbirths (after 24 weeks)	11 (0.24%)	0	0	NA
Total live birth	1540 (34.0%)	32 (38.1%)	24 (36.9%)	0.651
Singleton	1161 (75.4%)	32 (100%)	17 (70.6%)	
Total multiple pregnancies	379 (24.6%)	0	7 (29.2%)	
Twins	377 (24.5%)	0	7 (29.2%)	
Triplets	2 (0.1%)	0	0	

NA: Not applicable

Table 3. Neonatal Outcomes of Babies Delivered in KKH

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Total no. of transfers	4533	84	65	
Total no. of live births reported	1921	32	31	
Total no. of live births in KKH	1910	32	29	
Full-term delivery (37 weeks and above)	1251 (65.8%)	27 (84.4%)	25 (86.2%)	0.007
Mean GA at delivery	36.7 ± 2.8 (23 – 42)	37.2 ± 3.91 (24 – 40)	37.5 ± 1.02 (36 – 40)	0.225
Mean BW	2718.5 ± 1217.1	2855.8 ± 751.9	2708.1 ± 507.6	0.814
Singleton (n)	1144	32	17	
Full-term delivery (37 weeks and above)	955 (84.1%)	27 (84.4%)	15 (88.2%)	0.896
Mean GA at delivery	37.8 ± 2.16 (23 – 42)	37.2 ± 3.91 (24 – 40)	37.9 ± 1.1 (36 – 40)	0.264
Mean BW	2995.3 ± 1022	2855.8 ± 751.9	3040.6 ± 349.3	0.730
Multiple pregnancies (n)	757	-	12	
Full-term delivery (37 weeks and above)	289 (38.2%)	-	10 (83.3%)	0.001
Mean GA at delivery	35.1 ± 2.91 (23 – 41)	-	37 ± 0.6 (36 – 38)	0.027
Mean BW	2303.4 ± 1364.6	-	2264.8 ± 301.6	0.922

BW: Birth weight; GA: Gestational age; KKH: KK Women's and Children's Hospital

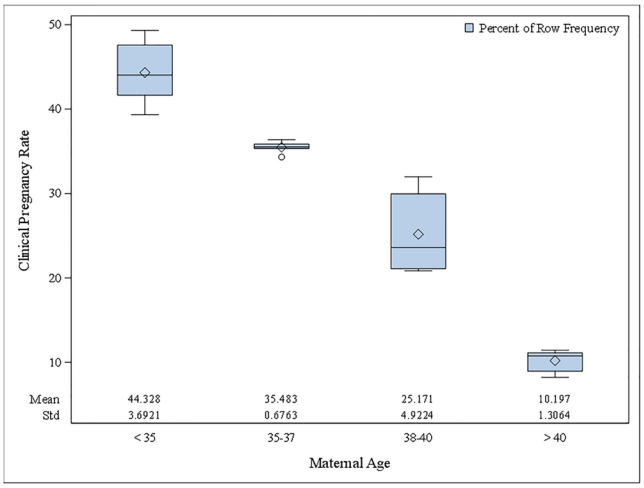

Fig. 1. Relationship between maternal age and clinical pregnancy rate.

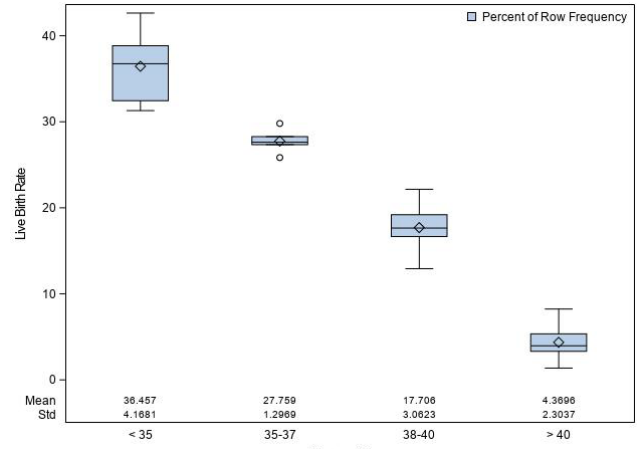

Fig. 2. Relationship between maternal age and live birth rate.

every year increase in age (Table 4). This is consistent with previous publications demonstrating the negative effect of maternal age on LBRs in ART.[7] Age is the single most important factor in determining success rates after IVF,[8] with success rates diminishing greatly after the age of 40.[9] In our study, there was a significant decrease in CPR with age. CPR decreased from 44.3% before 35 years of age to 10.2% after 40 years of age (Fig. 1). Similarly, LBR decreased from 36.5% before the age of 35 years to 4.4% after 40 years of age (Fig. 2).

We did not find any significant effects on the number of oocytes retrieved on CPR (OR 1.002, 0.995-1.01, *P* = 0.60) and LBR (OR 1.003, 0.996-1.01, *P* = 0.40) after adjusting for age (Table 4). Prior studies looking at the relationship between the number of eggs retrieved and LBR demonstrated a strong association (15 eggs retrieved being the optimal number).[10] However, such a relationship was not apparent in our study. This disparity in findings may have arisen from the exclusion of cancelled embryo transfers, which would have occurred more in those with lower number of oocytes retrieved.

Table 4. Effect of Age and Number of Oocytes Retrieved on Clinical Pregnancy Rate and Live Birth Rate (Adjusted for Age Using Multivariate Logistic Regression Analysis)

Effect	Clinical Pregnancy Rate		Live Birth Rate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.91 (0.90, 0.93)	<0.0001	0.91 (0.89, 0.92)	<0.0001
Number of oocytes obtained	1.002 (0.995, 1.01)	0.6011	1.003 (0.996, 1.01)	0.4030

CI: Confidence interval; OR: Odds ratio

Based on our data, the LBR and CPR were significantly different among all 4 groups (P <0.001). Patients in the SET group were older patients with poorer ovarian response with a correspondingly lower number of oocytes retrieved, hence contributing to the significantly lower LBR and CPR. However, the LBR and CPR were not significantly different when we compare only the DET, single blastocysts stage embryo transfer and double blastocysts stage embryo transfer group (LBR: $P = 0.64$, CPR: $P = 0.48$). This is contrary to a previous study by Papanikolaou et al which demonstrated that blastocyst transfers have a higher LBR and CPR than cleavage-stage embryo transfers when the same number of embryos were transferred.[4] However, this result was not reproducible in other studies which also demonstrated no significant difference in pregnancy outcomes between blastocyst transfers and cleavage-stage embryo transfers.[11] We did not find any significant differences in CPR and LBR between DET and DBT groups despite the same number of embryos transferred. Moreover, we also noticed no difference in LBR and CPR in the single blastocysts stage embryo transfer group.

Previous studies pertaining to comparison between cleavage-stage embryo transfers and blastocyst transfers have yielded mixed results. The study by Schwarzler et al[12] showed that blastocyst transfers result in higher MPR with a significantly higher CPR, however, the study did not differentiate between double and SBTs. Based on our data, the patients who underwent SBT had a similar LBR as DBT, albeit with significantly fewer multiple pregnancies.

Conclusion

This retrospective review suggests that single blastocysts stage embryo transfer in a fresh IVF cycle has similar CPR and LBR as compared to DET and double blastocysts stage embryo transfer, without the complication of multiple pregnancies. The SET group had the poorest outcome, presumably due to the poor ovarian response and the lack of embryos to choose from for embryo transfer. However, our population of patients who underwent single blastocysts stage embryo transfer were younger and hence may inherently have a confounding effect on LBR. Hence, our data support the use of single blastocysts stage embryo transfer where patients are candidates for blastocyst culture to achieve an acceptable LBR and CPR while eliminating the risk of MPR and its attendant morbidities.

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