







Original Research

Does the Transfer of a Poor-Quality Embryo alongside a Good-Quality Embryo at the Cleavage or Blastocyst Stage Affect Pregnancy Rates? A Retrospective Cohort Study

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Abstract

Background: Embryo quality is a critical determinant of success in assisted reproductive technology (ART). A strong and positive correlation between embryo quality and clinical pregnancy rate (CPR) has been reported. The aim of this study was to evaluate the effect of transferring one good-quality embryo (GQE) alongside one poor-quality embryo (PQE) on CPR and live birth rate (LBR) in fresh ART cycles. **Methods:** This retrospective cohort study included a total of 1631 women who underwent an *in vitro* fertilization–intracytoplasmic sperm injection (IVF-ICSI) cycle. The study was conducted at T.C. Ministry of Health, Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, İstanbul, Türkiye. Patient data were obtained from medical records. Patients were assigned to 5 different groups according to the number and quality of embryos transferred: Group 1 for 1 GQE transferred; Group 2 for 2 GQEs transferred; Group 3 for 2 embryos transferred with 1 GQE along with 1 PQE; Group 4 for 1 PQE transferred; and Group 5 for 2 PQEs transferred. Age, number of retrieved oocytes, number of captured metaphase II (MII) oocytes, number of formed embryos, number of transferred embryos, and number of GQEs were assessed. **Results:** In 891 cases in which a single GQE was transferred, the LBR was 26.3%, whereas in 126 cases in which a GQE with a PQE was transferred, the LBR was 16.7% ($p < 0.001$). Statistically significant differences were observed for age ($p < 0.001$), number of oocytes retrieved ($p < 0.001$), total number of embryos obtained ($p < 0.001$), number of MII oocyte numbers ($p < 0.001$), CPR ($p < 0.01$), and LBR ($p < 0.001$) between groups classified according to the number and quality of the transferred embryos. The study group was also analyzed as two separate age groupings: <35 years and ≥ 35 years. Using a regression analysis, day 5 embryo transfer (ET) was found to improve CPRs in both age groups [relative risk (RR), 95% confidence interval (CI): 1.875, 1.267–2.775, $p = 0.002$ and RR, 95% CI: 2.973 1.277–6.918, $p = 0.011$]. Day 5 ET improved LBR only in <35 years age group (RR, 95% CI: 1.760, 1.174–2.639, $p = 0.006$). 2 GQE ETs were found to be more effective than other transfer options in both age groups, when considering CPRs (RR, 95% CI: 2.962, 1.463–6.000, $p = 0.003$; and RR, 95% CI: 2.001, 1.062–3.773, $p = 0.032$). **Conclusions:** This study indicated that the transfer of an additional PQE alongside a top-quality embryo does not have a favorable effect on clinical pregnancy and LBR. On the contrary, the transfer of an additional PQE negatively affects LBR.

Keywords: clinical pregnancy rate; embryo transfer; good-quality embryo; poor-quality embryo

1. Introduction

An increasing number of couples are being treated with assisted reproductive techniques (ART) for biological and social reasons. Strong and positive relationship between embryo quality and clinical pregnancy rate (CPR) has been reported. Even though transferring good-quality embryos (GQEs) is preferable, for a large number of patients without GQEs, the transfer of poor-quality embryos (PQEs) is unavoidable [1,2].

A study comparing outcomes in patients undergoing single embryo transfer and double embryo transfer have conflicting results including both an improvement or no benefit on live birth rate [3]. A systematic review and meta-

analysis of 85 studies concluded that, in women under 40 years old or in the presence of GQE, single embryo transfer (SET) should be implemented. In the absence of GQEs, double embryo transfer (DET) may be preferable [4]. A retrospective study reported that live birth rate (LBR) were significantly higher with SET than with DET [5]. Although SET has become a suggested approach over time, multiple embryo transfers are still common in clinical practice [6]. Some *in vitro* fertilization (IVF) clinics are supporting multiple embryo transfers, as it has been previously reported that DET transfer increases pregnancy and LBR [7,8]. In a systematic review and meta-analysis of 5 randomized controlled trials, single blastocyst stage transfer was associated



with a higher ongoing pregnancy rate and birth rate than single cleavage stage transfer [9].

Advanced age, poor ovarian reserve, and a history of previous failed ART cycles are predictors of poor prognosis. Multiple embryo transfer is often considered in this patient group [10]. However, this patient group has a limited number of embryos, with good quality embryos either absent or few. Therefore, the clinician may decide to transfer PQE in addition to GQE to improve IVF success.

There are limited studies evaluating the negative impact of PQE transfer with GQE on pregnancy rates in fresh *in vitro* fertilization–intracytoplasmic sperm injection (IVF-ICSI) cycles. Thus, the aim of the current study was to evaluate the effect of transferring 1 GQE plus 1 PQE on clinical pregnancy and LBR in fresh ART cycles. This information may provide guidance for the management of residual PQEs that are not suitable for cryopreservation.

2. Materials and Methods

2.1 Study Design

This retrospective cohort study evaluated women who underwent IVF-ICSI at the IVF clinic at Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, Istanbul, Türkiye. The study protocol was approved by the Zeynep Kamil Women's and Children's Diseases Training and Research Hospital Institutional Review Board (Date: 17.04.2019; Number: 47). Data of 1631 cases treated at the IVF clinic between January 2013–December 2014 were obtained from medical printed and electronic records.

Women between 20–40 years old who submitted to controlled ovarian stimulation (COS) for ICSI were considered eligible. Only cases undergoing fresh embryo transfer were included in the study. In all cases, transferred embryos were day 3 embryo and/or day 5 embryo. Patients in whom oocytes could not be obtained through oocyte retrieval, whose sperm could not be found despite surgical methods, who had pronucleus (PN) arrest and 3 PN development and who had fertilization failure were excluded from the study. In our clinic, 2 PN control is performed at 8 am and recorded.

All cases received antagonist protocol treatment with either human menopausal gonadotropin or recombinant follicle stimulant hormone starting from the 3rd day of menstruation. Cetorelix acetate was added to the treatment when the leading follicle reached 12 to 14 mm in diameter. When the dominant follicle reached ≥ 18 mm in the presence of at least two 16 mm follicles, choriogonadotropin-alfa 250 micrograms was given to trigger ovulation. Oocyte retrieval was performed 35 to 36 hours after the human chorionic gonadotropin injection, using a 17-gauge needle under transvaginal ultrasound guidance.

The mature oocytes were selected for ICSI and then cultured separately. Fertilization was confirmed by the presence of 2 pronuclei and 2 polar bodies. Embryo qual-

ity was assessed at 43–45 hours after ICSI according to the number, degree of the fragmentation in percentage of blastomeres and the presence or absence of multiple nuclei. On day 2, embryo quality was assessed at 67–69 hours and for a day 2 embryo, GQE was defined as an embryo with 4 symmetrical blastomeres, normal size, <10% fragmentation, and no multiple nuclei [10]. Embryos on the day 3 of development with 8 symmetrical blastomeres, normal sized, with <10% of fragmentation, and without multinucleation were also considered GQE [11]. We included patients who had day 3 or 5 embryo transfers.

Patients were assigned to 5 different groups according to the number and quality of embryos transferred. Group 1 for 1 GQE transferred; Group 2 for 2 GQEs transferred; Group 3 for 2 embryos transferred with 1 GQE along with 1 PQE; Group 4 for 1 PQE transferred; and Group 5 for 2 PQEs transferred. Single embryo transfer was performed in the first 2 attempts in patients under 35 years of age. At 24 hours after oocyte retrieval, patients began receiving luteal phase supplementation.

In patients under the age of 35 years, a single embryo transfer was performed in the first 2 IVF cycles, and 2 embryos were transferred when 2 consecutive IVF cycles failed. In patients aged 35 years and over, 2 embryos were transferred in accordance with Turkish legislation, regardless of previous treatment success.

The presence of a gestational sac by ultrasound after 5 weeks was defined as clinical pregnancy. Live birth was defined as at least 1 live baby born after 28 weeks of gestation. Clinical pregnancy per embryo transfer (ET) was defined as CPR and live birth per ET as LBR. Age, number of retrieved oocytes, number of captured metaphase II (MII) oocytes, number of formed embryos, number of transferred embryos and of GQEs were assessed.

There was no change in culture conditions during the study period. The embryology team consisted of the same people. Transfers were performed by 4 clinicians using the same technique.

2.2 Statistical Analyses

Statistical analyses were performed using the IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) program. In addition to descriptive statistical methods (mean, standard deviation), the one-way analysis of variance (ANOVA) test was used to compare normally distributed parameters in quantitative data, and the post-hoc Tukey's Honest Significant Difference test was used to determine the group that caused the difference. The Kruskal-Wallis test was used to compare parameters that did not follow a normal distribution, and the Mann-Whitney U test was used to establish which group produced the discrepancy. A Chi-square test was employed to compare qualitative data. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into logistic regression analysis to determine independent

Table 1. Demographic characteristics, controlled ovarian stimulation cycle related laboratory, oocyte and embryo results for transferred embryo quality groups.

	Transferred embryo quality groups					<i>P</i>
	Group 1: 1 GQE; n = 891	Group 2: 2 GQEs; n = 109	Group 3: 1 GQE + 1 PQE; n = 126	Group 4: 1 PQE; n = 450	Group 5: 2 PQE; n = 55	
Age (years) mean \pm SD	30.7 \pm 4.0	34.6 \pm 4.7	35.5 \pm 3.5	31.4 \pm 4.2	35.8 \pm 3.4	¹ <0.001
Age groups, n (%)						² <0.001
20–34 years	732 (82.2)	36 (33.0)	36 (28.6)	332 (73.8)	12 (21.8)	
35–40 years	159 (17.8)	73 (67.0)	90 (71.4)	118 (26.2)	43 (78.2)	
Etiology of infertility, n (%)						² 0.436
Unexplained	309 (34.7)	35 (32.1)	49 (38.9)	164 (36.4)	20 (36.4)	
Male factor	379 (42.5)	48 (44.0)	41 (32.5)	196 (43.6)	21 (38.2)	
Tubal factor	203 (22.8)	26 (23.9)	36 (28.6)	90 (20.0)	14 (25.5)	
Day 2 E ₂ (ng/L) median; (IQR)	44; (34–57)	48; (37–61)	44; (35–63)	46; (35–59)	44; (34–61)	³ 0.136
Number of oocytes retrieved, median; (IQR)	8; (5–12) ^a	8; (6–13) ^a	6; (3–10) ^b	6; (2–10) ^b	6; (3–10) ^b	³ <0.001
Number of MII oocytes, median; (IQR)	6; (3–9) ^a	7; (4–10) ^a	5; (3–8) ^b	4; (2–7) ^c	4; (3–6) ^{b,c}	³ <0.001
Number of formed embryos, median; (IQR)	2; (1–5) ^b	3; (2–5) ^c	3; (2–4) ^c	1; (1–3) ^a	2; (2–4) ^{b,c}	³ <0.001
Transfer day, median; (IQR)	9; (8–10)	9; (8–9)	9; (8–9)	9; (8–9)	8; (7–9)	³ 0.556
Embryo day, n (%)						² <0.001
Day 3 embryo	775 (87.0)	90 (82.6)	123 (97.6)	434 (96.4)	54 (98.2)	
Day 5 embryo	116 (13.0)	19 (17.4)	3 (2.4)	16 (3.6)	1 (1.8)	

¹One-way analysis of variance (ANOVA) test; ²Chi-square test; ³Kruskall Wallis test. GQE, good-quality embryo; PQE, poor-quality embryo; MII, metaphase II; E₂, estradiol; IQR, inter quartil range (25%–75%); SD, standard deviation. ^{a,b,c}Groups with statistically significant differences are marked with superscript letters.

Table 2. Clinical pregnancy rate and live birth rate results for transferred embryo quality groups.

	Transferred embryo quality groups					<i>P</i>
	Group 1: 1 GQE; n = 891	Group 2: 2 GQEs; n = 109	Group 3: 1 GQE + 1 PQE; n = 126	Group 4: 1 PQE; n = 450	Group 5: 2 PQE; n = 55	
Clinical pregnancy rate, n (%)	300 (33.7) ^a	53 (48.6) ^b	33 (26.2) ^a	76 (16.9) ^c	9 (16.4) ^c	<0.001
Live birth rate, n (%)	234 (26.3) ^a	40 (36.7) ^b	21 (16.7) ^c	58 (12.9) ^c	7 (12.7) ^c	<0.001

Kruskall Wallis test. ^{a,b,c} Groups with statistically significant differences are marked with superscript letters.

predictors of patient outcome. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. p -values less than 0.05 were considered significant.

3. Results

The study included 1631 cases aged 20 to 40 years. Age data were examined categorically in 2 groups as <35 years and ≥ 35 years. Table 1 presents demographic characteristics, infertility etiology, menstrual cycle day 2 estradiol (E_2) values, the number of oocytes retrieved, the number of embryos obtained, and the day of the transferred embryo results according to the groups. The groups were found to be statistically similar in terms of infertility etiology, menstrual cycle day 2 E_2 values, and the day of the treatment when the transfer was made ($p > 0.05$) (Table 1).

The ages differed significantly based on the quality of the transferred embryos ($p < 0.01$). The number of oocytes retrieved in the 1 GQE group and 2 GQEs group were statistically similar and the number of oocytes retrieved was statistically higher than in groups 3, 4 and 5. Group 1 and Group 2 were statistically similar in terms of MII oocyte numbers. Groups with statistically different MII oocyte numbers were identified by post-hoc analysis. The number of embryos obtained from Group 1 cases was statistically significantly lower than the number of embryos obtained from Groups 2 and 3. The number of embryos obtained from Group 4 cases was found to be significantly lower than all groups.

CPR and LBT for the 5 groups are presented in Table 2. CPR for cases where 2 GQEs were transferred (Group 2) were found to be significantly higher than those for cases where 1 GQE and 1 PQE were transferred (Group 3) (48.6% vs. 26.2%, respectively, $p < 0.05$). CPR were statistically similar between single embryo transfer (Group 1) and 1 GQE + 1 PQE transfer (Group 3) groups (33.7% vs. 26.2%, respectively, $p > 0.05$). LBR were statistically similar among the groups in which at least 1 PQE was transferred (Group 3, 4 and 5). LBR for Group 3 in which 1 PQE with 1 GQE was transferred were found to be significantly lower than Group 1 and Group 2 (16.7% vs. 26.3%–36.7%, $p < 0.05$). There was no statistical evidence that transferring a PQE over a GQE affected pregnancy rates. Transfer of a PQE together with a GQE resulted in a statistically significant lower live birth rate compared to transfer of a single GQE or 2 GQEs ($p < 0.001$).

The cases included in the study were between 20–40 years of age. The study group was divided into 2 categories as <35 years of age and ≥ 35 years of age. The regression analysis results to determine independent predictors of CPRs and LBRs for each age category are presented in Tables 3,4. Day 5 ET improved the CPRs in both age groups (relative risk (RR), 95% confidence interval (CI): 1.875, 1.267–2.775, $p = 0.002$ and RR, 95% CI: 2.973, 1.277–6.918, $p = 0.011$). Day 5 embryo transfer improved LBRs only in <35 years old cases. Two GQE embryo transfer was

found to be effective than other transfer options for CPRs. Two GQE ET was found to be decisive in improving LBRs only for cases under 35 years of age. Regression analysis demonstrated that 2 GQE embryo transfers had a statistically significant effect on LBRs only in cases under 35 years of age (RR, 95% CI: 2.314, 1.164–4.601) (Tables 3,4).

4. Discussion

Based on the results of our study, we determined that GQE transfer combined with a PQE transfer did not have a positive effect on CPR. On the contrary, an additional PQE negatively affects LBR.

The benefit of 2 embryo transfers is debatable in cases where a GQE is transferred with a PQE in IVF-ICSI cycles. The importance of the interaction between the embryo and the endometrium in the implantation process has been demonstrated. Poor quality embryo transfer may negatively affect endometrial receptivity and may also prevent implantation of a GQE [12,13]. The effect of transferring a PQE as a second embryo in fresh IVF-ICSI cycles on pregnancy rates has been studied. Some studies have reported that PQE has no negative effect on GQE [14,15]. A study reported that the transfer of a PQE accompanied by a GQE compared to a single GQE and double GQE transfer did not show a difference in LBR [14]. Pregnancy rates and LBR have been reported to be similar when the second embryo transferred alongside a GQE is either a GQE or a PQE [15]. In contrast, transfer of 1 GQE and 2 GQEs has been reported to be associated with higher implantation and pregnancy rates than transfer of 1 GQE with 1 PQE [16]. In the group of patients with poor prognosis, it has been found that an additional PQE to GQE does not negatively affect implantation rates, but increases live births and multiple pregnancies [17]. In a meta-analysis, it has been reported that DET including GQEs and PQEs does not lead to an increase or decrease in CPR and LBR compared to a single GQE transfer, but is associated with a higher multiple pregnancy rate [18]. Similarly, Hill *et al.* [19] reported that a concomitant PQE transfer does not have a negative effect on good quality blastocyte transfer and causes a significant increase in the risk of multiple pregnancies. It has been stated that single GQE embryo transfer is beneficial if GQE is obtained in women under the age of 40 years. It has been added that DET can be planned if GQE is not obtained. The same study emphasized that there is insufficient evidence for women over 40 years of age [5]. In a group of patients who underwent frozen-thawed embryo transfer, no improvement in LBRs was observed with the addition of PQE; but in patients who underwent embryo transfer at the blastocyst stage, an increase in LBR was reported with GQE + PQE double embryo transfer [20].

Our study demonstrated that an additional PQE transfer together with GQE did not have a positive effect on CPR and LBR. On the contrary, it was concluded that an additional PQE negatively affected LBR.

Table 3. Logistic regression analysis of independent predictors of pregnancy outcome for 2 different age categories.

Risk factors	Cases <35 years old (n = 1148)		Cases ≥35 years old (n = 483)	
	RR (95% CI)	<i>p</i>	RR (95% CI)	<i>p</i>
Age (years)	0.962 (0.921–1.005)	0.085	0.915 (0.803–1.043)	0.185
Number of MII oocytes	1.016 (0.983–1.050)	0.338	1.000 (0.934–1.070)	0.998
Embryo day (day 3 vs. day 5)	1.875 (1.267–2.775)	0.002	2.973 (1.277–6.918)	0.011
Group 2 (2 GQEs)	2.962 (1.463–6.000)	0.003	2.001 (1.062–3.773)	0.032
Group 3 (1 GQE+1 PQE)	0.586 (0.261–1.319)	0.197	1.203 (0.662–2.185)	0.544
Group 4 (1 PQE)	0.473 (0.343–0.652)	0.001	0.366 (0.185–0.725)	0.004
Group 5 (2 PQEs)	0.198 (0.025–1.544)	0.122	0.701 (0.298–6.918)	0.415

95% CI, 95% confidence interval; RR, relative risk.

Table 4. Logistic regression analysis of independent predictors of live birth rate outcome for 2 different age categories.

Risk factors	Cases <35 years old (n = 1148)		Cases ≥35 years old (n = 483)	
	RR (95% CI)	<i>p</i>	RR (95% CI)	<i>p</i>
Age (years)	0.919 (0.877–0.964)	0.000	0.914 (0.787–1.061)	0.237
Number of MII oocytes	1.024 (0.988–1.061)	0.192	1.049 (0.975–1.129)	0.196
Embryo day (day 3 vs. day 5)	1.760 (1.174–2.639)	0.006	1.405 (0.554–3.567)	0.474
Group 2 (2 GQEs)	2.314 (1.164–4.601)	0.017	1.644 (0.828–3.265)	0.156
Group 3 (1 GQE+1 PQE)	0.614 (0.248–1.520)	0.292	0.851 (0.424–1.704)	0.648
Group 4 (1 PQE)	0.524 (0.370–0.743)	0.000	0.270 (0.114–0.640)	0.003
Group 5 (2 PQEs)	1.760 (1.174–2.639)	0.999	0.832 (0.335–2.065)	0.691

The retrospective nature of our study may be a limitation. Patients were followed up with a telephone survey, which is less reliable than medical records. We did not record any data to evaluate endometrial receptivity. It would be a more valuable study if we could discuss endometrial receptivity and pregnancy success with the data of our cases. There may be bias in the embryo evaluation process. In one review, the overall median distribution of artificial intelligence models was reported as 74% (range 64%–98%, inter quartil range (IQR) = 68.5–83.5) while the distribution of embryologists was 64% (range 53%–76%, IQR = 55.5–69.5). Studies conducted with the results of processes involving artificial intelligence models may change these results over time. However, the strength of our study can be stated as being performed in a single center and by the same competent embryologists [21].

5. Conclusions

In conclusion, our results demonstrated that an additional PQE transfer in fresh embryo transfer cycles did not have a positive effect on CPRs and LBRs. On the contrary, an additional PQE negatively affected LBRs with GQE transferred together. Evaluating the issue in different infertile patient groups and frozen embryo transfer cycles may provide more accurate and different results.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BEB, İŞ and NUT designed the research study. BEB, ÇYA, Gİ and HTK performed the research. BEB, HTK and NUT analyzed the data. All authors contributed to writing and editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Zeynep Kamil Women's and Children's Diseases Training and Research Hospital Institutional Review Board (Date: 17.04.2019; Number: 47). Since the study was retrospective, informed consent was not obtained. Patients' personal data were shared only with the study team.

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Conflict of Interest

The authors declare no conflict of interest.

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