ARTICLE IN PRESS
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Journal of the Formosan Medical Association (2018) xx, 1–9

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.jfma-online.com

Original Article

Advantages of cumulative pregnancy outcomes in freeze-all strategy in high responders — A case-control matching analysis of a large cohort

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Received 12 September 2017; received in revised form 11 May 2018; accepted 14 May 2018

KEYWORDS
Assisted reproductive technology;
Embryo transfer;
Freeze-all;
Ongoing pregnancy rate;
Vitrification

Background/Purpose: The freeze-all strategy in high responders is considered to be a safe and effective strategy for *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment; however, the cumulative pregnancy outcomes have not been established.
Methods: A retrospective, single-center cohort study was conducted and 1311 high-responder patients (>20 oocytes retrieved and/or a serum estradiol level > 3000 pg/ml on the triggering day) were recruited from 2006 to 2015. The study group (n = 351) underwent the freeze-all strategy with subsequent thawed embryo transfer (ET), and the control group (n = 960) received fresh-cycle ET and subsequent thawed ET if needed. A case-control matching analysis was performed to match the two groups for the number of retrieved oocytes. The primary outcomes were the ongoing pregnancy rate (OPR) of the first ET cycle and the cumulative OPR.
Results: After matching, there was a significantly higher OPR in the first ET cycle (49.5% vs. 32.2%, $p < 0.0001$; n = 301 in each group) and the cumulative OPR (69.4% vs. 55.1%, $p < 0.0001$) in the study group, with significantly fewer total transferred embryos and cycles. The advantages of the freeze-all strategy for the OPR in the first ET cycle (OR: 1.97, $p < 0.0001$) and the cumulative OPR (OR: 1.49, $p = 0.032$) remained statistically significant

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https://doi.org/10.1016/j.jfma.2018.05.011

Please cite this article in press as: Wu M-Y, et al., Advantages of cumulative pregnancy outcomes in freeze-all strategy in high responders — A case-control matching analysis of a large cohort, Journal of the Formosan Medical Association (2018), https://doi.org/10.1016/j.jfma.2018.05.011

after adjusting for other possible confounding factors in multivariate logistic regression analysis.
Conclusion: For high responders, the freeze-all strategy with thawed ET achieved a significantly higher OPR in the first ET cycle and a higher cumulative OPR than the fresh ET strategy.

Introduction

The number of thawed embryo transfer (ET) cycles performed has increased significantly in recent years. There are three main reasons for the growing popularity of thawed ET cycles: the increased efficiency and security of freezing technology for human embryos[1–3] and gametes which facilitate various clinical applications;[4,5] the freeze-all strategy and transferring embryos in a natural or an artificial endometrial preparation cycle, with the aim of reducing the risk of ovarian hyperstimulation syndrome (OHSS)[6–9]; and superior embryo-endometrium synchrony and possible lower ectopic pregnancy rates, as well as increased health of childbirth compared to controlled ovarian stimulation (COS) cycles with fresh ET.[10–12]

The freeze-all strategy and elective thawed ET with better endometrial status and the best embryos from cohort freezing rather than supernumerary embryos following failed fresh ET might improve the safety and effectiveness of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI).[13,14] This hypothesis is supported by one small randomized controlled study that showed higher ongoing pregnancy rates (OPRs) were achieved with the freeze-all strategy and thawed ET than the fresh ET strategy;[15] however, all available embryos in that study were transferred at the blastocyst stage and frozen at the 2 pronuclei (2PN) stage of development, which is not commonly performed in many centers. In addition, the cumulative pregnancy rates were not further explored in the study, thus further clarification is needed.

In the past, the fresh ET strategy was the norm in assisted reproductive technology (ART) procedures because of previous concerns of cryo-damage, as well as reduced procedure-related cost and time.[16] Presently, the available evidence does not justify a change in practice, but strongly supports the need to evaluate the clinical- and cost-effectiveness of the freeze-all strategy versus the fresh ET strategy.[13,17]

Limited data exists from which to evaluate the cumulative pregnancy outcomes over a number of thawed ET cycles in ART. Therefore, the aim of this study was to compare the cumulative OPR and the OPR of the first ET cycle between the freeze-all and fresh ET strategies.

Materials and methods

Study population

The current study was approved by the Ethics Committee of National Taiwan University Hospital (201407010RINA). This was a retrospective, single-center cohort study that was conducted between January 2006 and December 2015.

The inclusion criteria were as follows: women <40 years of age; high responder (the number of retrieved oocytes was >20 and/or the serum estradiol [E2] concentration was >3000 pg/ml on the day of oocyte triggering)[18,19]; and the first IVF/ICSI cycle was at our hospital. All patients received ETs cycle-by-cycle until an ongoing pregnancy (≥12 weeks gestation) was achieved. The exclusion criteria included oocyte cryopreservation, embryo biopsy, oocyte donor-recipient program, and a chromosomal anomaly detected in either the female or male patient.

Patient characteristics were evaluated, including age, body mass index (BMI), gravidity, parity, causes of infertility, basal follicle-stimulating hormone (FSH) level, and hormone levels on the day of oocyte triggering. Other measured parameters included the duration of COS, the number of retrieved oocytes, the number of fertilized embryos, the number of transferred embryos, and the number of cryopreserved embryos. The major end points were the OPR in the first ET cycle (the fresh ET in the control group and the first thawed ET in the study group) and the cumulative OPR (the OPR after a number of ET cycles until all the embryos were used).

Protocols for controlled ovulation stimulation

All patients received COS to achieve multiple follicular development. A gonadotropin-releasing hormone (GnRH) agonist (Supremon® [buserelin acetate]; Hoechst AG, Frankfurt, Germany) was used in long and short protocols, and a GnRH antagonist (Cetrotide® [cetrorelix acetate]; Merck-Serono, Geneva, Switzerland) was used in an antagonist protocol. The starting dose of recombinant FSH ([rFSH], Gonal-F®; Merck-Serono or Puregon®; Organon Espanola S.A., Barcelona, Spain) or highly-purified human menopausal gonadotropin ([hp-hMG], Menopur®; Ferring Pharmaceuticals, Geneva, Switzerland) was 150–300 IU/day according to patient age, baseline FSH level, BMI, and physician preference. The dose of gonadotropin was adjusted according to the ovarian response, as determined by ultrasonography and serum E2 levels.

Oocyte retrieval and fertilization

When 2 follicles reached a mean diameter of 18 mm or 3 follicles reached a mean diameter of 17 mm, final oocyte maturation was triggered with 250–500 mcg of recombinant human chorionic gonadotropin ([hCG], Ovidrel®; Merck Serono, Darmstadt, Germany), which was equivalent

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