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Luteal phase support does not improve the clinical pregnancy rate of natural cycle frozen-thawed embryo transfer: a retrospective analysis

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ABSTRACT

Objective: To evaluate pregnancy outcomes with and without use of luteal phase support (LPS) in frozen-thawed embryo transfer (FET) performed in natural cycles (NC).
Study design: Retrospective analysis. Before 1st July 2009, two doses of 1500 IU intramuscular human chorionic gonadotrophin were given on the day of FET and 6 days after the transfer. Such practice was stopped after 1st July 2009. The pregnancy outcomes of NC FET with and without LPS were compared.
Results: A total of 408 NC FET cycles were analysed. Demographic data, embryo quality, clinical pregnancy rates and miscarriage rates were comparable with and without LPS. By univariate logistic regression, the only significant factors predicting the clinical pregnancy rate were the women's age, the number of embryos transferred, the number of top quality embryos before and after cryopreservation, and the average number of blastomeres after thawing. Only the women's age (OR 0.944, 95%C.I. 0.893–0.998, $p = 0.044$) remained to be a significant predictor of clinical pregnancy rate by multivariate logistic regression.
Conclusion: The pregnancy outcomes of NC FET were similar with or without LPS. The women's age was the significant factor affecting the clinical pregnancy rate. A randomised trial should be carried out to confirm the results.

1. Introduction

The use of luteal phase support (LPS) is well proven to be associated with a significantly higher live birth rate in *in vitro* fertilisation (IVF) treatment cycles involving ovarian stimulation [1] due to the use of GnRH agonist for down-regulation and the removal of the granulosa cells during oocyte retrieval. When given for LPS, the efficacy of progesterone and human chorionic gonadotrophin (hCG) in improving the live-birth rates was comparable [1,2]. However, hCG was associated with a significantly higher risk for ovarian hyperstimulation syndrome, and progesterone should be the drug of choice as suggested by the latest Cochrane review [1].

For frozen-thawed embryo transfer (FET) performed in natural cycles (NC) where ovulation is documented and there is corpus luteum formation, there is no physiological basis for the use of luteal phase support, and evidence for its benefit in FET cycles is scarce. One retrospective study showed no improvement in the pregnancy rate following vaginal progesterone administration in hCG-induced NC FET cycles [3], whereas a randomised trial revealed a significantly higher live birth rate when vaginal progesterone was given in NC FET cycles [4].

In our centre, we used to give hCG for LPS in NC FET, despite the lack of scientific evidence. After reviewing the literature, we decided to stop the use of LPS in NC FET cycles from 1st July 2009. In view of the above conflicting evidence, we performed this retrospective analysis to evaluate the effect of LPS on the pregnancy outcomes of NC FET cycles.

2. Materials and methods

2.1. Study population

This is a retrospective analysis of FET cycles carried out in the Centre of Assisted Reproduction and Embryology, The University of Hong Kong – Queen Mary Hospital, Hong Kong. The practice of giving LPS in NC FET was stopped on 1st July 2009. Medical records of all FET cycles performed between 1st July 2008 and 30th June 2010 were retrieved. Each patient was included in this study once only. The University of Hong Kong/Hospital Authority Hong Kong West Cluster Institutional Review Board approved this retrospective study.

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2.2. Treatment regimens

The details of the long protocol of the ovarian stimulation regimen, gamete handling, cryopreservation of embryos and FET were as previously described [5]. In the fresh stimulated cycle, patients were allowed to have a maximum of two embryos replaced into the uterine cavity 2 days after the retrieval and surplus good quality embryos were frozen on day 2. Those who did not get pregnant in the stimulated IVF cycle and had at least one frozen embryo would undergo either NC, clomiphene citrate-induced or hormonal replacement FET, at least 2 months after the stimulated cycle.

Patients having regular ovulatory cycles would undergo NC FET. They attended the clinic daily from 18 days before the next expected period for the determination of serum E2 and LH concentrations until the LH surge, which was defined as the day on which the LH level was above 20 IU/L and more than double the average of the LH levels over the past 3 days. FET was performed on the third day after the LH surge. Both clomiphene citrate-induced and hormonal replacement FET were excluded from this study.

All embryos were transferred or cryopreserved on day 2 after oocyte retrieval. They were graded by our embryologists as grade one to grade six according to the size evenness of the cells and the percentage of fragmentation [6]. Embryos of 4 cells with grades one and two were regarded as top quality embryos in this study. No grading would be awarded after thawing if some of the blastomeres lysed. Only embryos with more than 50% of blastomeres present after thawing would be transferred. As routine practice in our centre, two embryos would be stored in one straw for cryopreservation and up to two embryos would be transferred in one treatment cycle.

LPS before 30th June 2009 was given as two intramuscular injections of 1500 IU hCG, one on the day of FET and one 6 days after the transfer. A urine pregnancy test was done 16 days after ET. If it was positive, ultrasound examination was performed 10–14 days later to confirm intrauterine pregnancy and viability and to determine the number of gestational sacs present. Patients were referred out for antenatal care at 8–10 gestational weeks.

2.3. Outcome measures

The primary outcome measure of the study was the clinical pregnancy rate, defined as positive fetal pulsation at 8–10 gestational weeks per transfer. The secondary outcome measure was the positive pregnancy test rate and the miscarriage rate.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Results of continuous variables were given as mean ± standard deviation (SD) if normally distributed, and as median (range) if not normally distributed. Statistical comparison was carried out by Student's *t*-test, Mann–Whitney *U*-test, Wilcoxon signed ranks test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, where appropriate. Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS Inc., Version 17.0, Chicago, USA). The two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

A total of 935 FET cycles were performed during the study period. As hormonal replacement cycles ($n = 78$) and clomiphene citrate-induced cycles ($n = 84$) were excluded and only the first cycle of FET of each subject during the study period was included, 408 NC FET cycles were available for analysis.

3.2. Outcomes

The demographic data are shown in Table 1. There were no significant differences in the age of the women, cause of infertility, duration of infertility, total dosage of gonadotrophins used, serum oestradiol concentration on the day of ovulation trigger, the number of follicles ≥16 mm and the endometrial thickness between the groups with or without LPS.

The clinical outcomes of the FET cycles are shown in Table 2. There were no significant differences in the positive pregnancy test rates, clinical pregnancy rates and miscarriage rates between the groups with or without LPS (Table 2). The embryo quality, the number of top quality embryos transferred and the average number of blastomeres in the transferred embryos were not different between the groups with and without LPS (Table 3).

By univariate logistic regression, women's age (OR 0.930, 95%C.I. 0. 870–0.930, $p = 0.032$), the number of embryos transferred (OR 2.539, 95%C.I. 1.249–5.161, $p = 0.010$), the number of top quality embryos before (OR 1.948, 95%C.I. 1.460–2.598, $p < 0.001$) and after cryopreservation (OR 1.962, 95%C.I. 1.449–2.659, $p < 0.001$), and the average number of blastomeres after thawing (OR 1.320, 95%C.I. 1.041–1.674, $p = 0.022$) were the significant factors on the clinical pregnancy rates, while the use of LPS (OR 0.851, 95%C.I. 0.551–1.315, $p = 0.468$), the average number of blastomeres before cryopreservation (OR 1.204, 95%C.I. 0.945–1.532, $p = 0.132$) and the number of lysed embryos not suitable for transferred (OR 1.032, 95%C.I. 0.586–1.817, $p = 0.913$) were not significant factors. Multivariate logistic regression with the significant factors was performed to show the effect of various

Table 1
Demographic and clinical data in subjects undergoing natural cycles frozen-thawed embryo transfer.

	With LPS ($n = 205$)	Without LPS ($n = 203$)	*p*-Value
Age	36.9 (25–45)	36.6 (28–45)	0.650
Duration of infertility (year)	4.5 (1–16)	4.5 (1–14)	0.453
Indications of infertility			0.123
Tubal	44 (21.5%)	26 (12.8%)	
Endometriosis	13 (6.3%)	12 (5.9%)	
Male	102 (49.8%)	115 (56.7%)	
Unexplained	11 (5.4%)	18 (8.9%)	
Others	35 (17.1%)	32 (15.8%)	
Clinical data in the stimulated cycles			
Total dosage of gonadotrophin used (IU)	2316 (1150–7350)	2231 (900–4500)	0.290
Oestradiol concentration on hCG day (pmol/L)	12,563 (1887–39,514)	13,754 (934–54,868)	0.092
Number of follicles ≥16 mm	7.0 (1–15)	6.9 (1–16)	0.976
Endometrial thickness (mm)	12.4 (6.6–22.2)	12.6 (7.5–20.4)	0.486

Data presented as median (range) or number of subjects (percentage).
Chi-square test was used for categorical data, while for non-parametric data, Mann–Whitney *U*-test was used.