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Original article

Elective frozen-thawed embryo transfer (FET) in women at risk for ovarian hyperstimulation syndrome

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ABSTRACT

Elective cryopreservation of cultured embryos has become a treatment option for women at risk for ovarian hyperstimulation syndrome (OHSS). The aim of our study was to investigate the outcome of elective cryopreservation and consecutive frozen-thawed embryo transfer (FET) in a large IVF clinic in Austria. A total of 6104 controlled ovarian hyperstimulation cycles (COH) were performed on 2998 patients including 200 patients (6.7%) who were undergoing elective cryopreservation and FET due to high risk of OHSS. We estimated the cumulative live birth rate using the Kaplan-Meier method and evaluated independent predictors for successful live births with a Cox model. A total of 270 frozen-thawed embryo transfers were performed on 200 patients with up to 4 transfers per patient. The first embryo transfer showed a live birth rate of 42.0%, the second transfer showed a cumulative rate of 58.5%. After a total of 4 FETs from the same COH cycle, a cumulative live birth rate of 61.0% per COH cycle could be achieved. Four cases of OHSS occurred amongst these patients (2.0%), all of them of moderate severity. Multivariate analysis identified maternal age, the use of assisted hatching and the number of embryos transferred at the blastocyst stage as independent predictors for cumulative live birth. Our study clearly suggests that elective FET is safe and shows excellent cumulative live birth rates. This concept can, therefore, be used to avoid the severe adverse events caused by COH and the inefficient use of cultured embryos.

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is a known iatrogenic complication of ovarian stimulation during assisted reproductive technology (ART). The relatively low incidence of OHSS among patients undergoing ovarian stimulation often leads to an underestimation of the importance of this syndrome and the impact it can have.

Previous reports have shown a statistically significant increase in pregnancy–related complications in women who suffer from OHSS compared with in vitro fertilization (IVF) controls [1,2]. As a result, several strategies have been implemented clinically in order to reduce the risk of OHSS through controlled ovarian hyperstimulation (COH). Although the incidence of severe OHSS is now low (1–2%), several reports indicate an increase in this form of the syndrome and in the percentage of patients requiring hospitalization [1,3–5]. The most worrying consequence of OHSS is that it poses a serious threat to patient welfare, as it remains a significant source of morbidity and mortality in ART [6–9]. Several treatment options have focused on overcoming the risk of OHSS but full prevention has never been achieved. Cancelling a cycle before human chorionic gonadotropin (hCG) administration or early oocyte retrieval still remains the most widely applied method of prevention but this can be frustrating and costly for the patient concerned [5,10].

It has been suggested that triggering final oocyte maturation using Gonadotropin releasing hormone (GnRH) agonist administration may lower the risk of OHSS in patients without previous down-regulation of the pituitary gland. However, several studies and a meta-analysis have shown GnRH agonists to be associated with significantly lower clinical pregnancies and higher rates of miscarriage compared to standard hCG treatment if the ET is performed during the COH cycle [11–13]. Furthermore, as pituitary desensitizing GnRH agonist protocols have become the most widely used standard in COH, GnRH agonist induction of ovulation has attained little clinical interest.

Elective cryopreservation of embryos after ART is another effective method of preventing conception within an overstimulated cycle and thus reducing the risk of severe OHSS. Several studies have reported the outcome of elective FET in patients at risk of OHSS [14,15].

However, a recent and updated evaluation of embryo freezing by the Cochrane collaboration group identified a lack of reliable data and studies and therefore concluded insufficient evidence to support routine

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cryopreservation in women at risk of OHSS [16]. Moreover, another study including 117 treatment cycles showed that elective cryopreservation does not reliably protect against the development of OHSS but that it is associated with a significantly lower clinical pregnancy and live birth rate compared to fresh embryo transfer [17].

These studies, reported in the Cochrane publication, were performed at the beginning of the 1990s and thus lacked modern cryopreservation methods such as vitrification, blastocyst transfer, assisted hatching and endometrial preparation in hormone replacement cycles [18–21]. In addition, these studies were of limited sample size and reported pregnancy rates rather than live birth rates.

The aim of our recent study was to investigate cumulative live birth rates among patients at high risk of OHSS who were treated with elective frozen-thawed embryo transfer (FET) and to evaluate this strategy in a modern era of embryo cryopreservation.

2. Materials and methods

2.1. Patients

We performed a retrospective cohort study evaluating 2998 patients who underwent a total of 6104 COH cycles with autologous oocyte retrieval between March 2000 and December 2012. Due to increased risk of OHSS, elective cryopreservation of all good quality embryos was conducted at the Private Kinderwunsch-Clinic Dr. J. Zech GmbH in Innsbruck, Austria. During the same period, a total of 1685 FET cycles were also performed, the majority of which were hormonally induced. Within the reported 6104 COH cycles, 61 episodes of OHSS requiring subsequent hospital admission were observed (1%).

A total of 200 patients analyzed in this study were at risk of OHSS, defined as elevated peak estradiol (E2) levels of more than 3500 pg/ml and/or more than 25 follicles (greater than 17 mm) evaluated by ultrasound assessment. Patients at high risk of OHSS or those displaying symptoms indicative of OHSS before embryo transfer were informed about the option of bypassing a fresh embryo transfer, cryopreserving all embryos, if possible at the blastocyst stage (day 5 or 6), and doing an elective FET in a later cycle than oocyte retrieval.

Patients were followed for at least 1 year, until treatment was either discontinued or a live infant was delivered. In addition, a questionnaire was returned to our clinic 3 months after delivery to assess obstetric complications during pregnancy, preterm delivery, caesarean delivery, birth defects, small for gestational age (SGA) and perinatal mortality.

All patients gave informed consent. Institutional review board (IRB) was not obtained. In Austria, there is no legal obligation to obtain IRB approval for retrospective, non-interventional studies.

2.2. Controlled ovarian hyperstimulation and elective cryopreservation policy

According to pre-existing pathology, most patients received COH in long or short protocols with GnRH agonists (Decapeptyl®, Ferring, Germany) and recombinant follicle-stimulating hormone (FSH) (Puregon®, Organon, Netherlands). FSH dosage was adjusted according to ovarian response as assessed by frequently performed ultrasound assessment. For final maturation of oocytes and induction of ovulation, 5000 to 10,000 units of human chorionic gonadotropin (hCG, Pregnyl®, Saint-Prex, Switzerland) or GnRH analogon *(Decapeptyl®, Ferring, Germany)* were administered. Transvaginal, ultrasound-guided follicular aspiration was performed 35–36 h after induction of ovulation. Oocytes were identified, washed in culture medium and incubated in groups with 800 µL of culture medium per well in humidified benchtop incubators (K-MINC-1000 Mini-incubator, COOK, Australia) set at 37 ° Celsius, 6.6% carbon dioxide, 5% oxygen and 88.4% nitrogen. Fertilization of oocytes was performed either with conventional IVF, intra cytoplasmatic sperm injection (ICSI) or intracytoplasmic morphologically-selected sperm injection (IMSI). The choice of fertilization method was dependent on the quality of oocytes and the presence, or absence, of substantial male factor infertility. Fertilization status was assessed at day 1 (16–18 h after insemination) and embryo imaging was applied during culture. Embryonic development was evaluated on day 3 using a scoring system that focusses on the number and regularity of blastomeres, as well as the percentage of fragmentation [22]. Embryos cultured until day 5 or 6, the blastocyst stage, were scored according to a numerical morphology grading system similar to the criteria established by Gardner and Schoolcraft.

Day 3 embryos with eight cells and < 15% fragmentation were considered good. Depending on the patient's medical history, top quality embryos were either frozen on day 2 or 3 (Cryopreservation/Thawing Kit, COOK®, Sydney, Australia) or cultured until day 5/6 for blastocyst cryopreservation. Expanded blastocysts with an inner cell mass of at least grade B and trophectoderm of at least grade C were considered suitable for cryopreservation (Blastocyst cryopreservation/Thawing Kit, Sydney, Australia). Embryos from day 3 to 6 were vitrified using the VitriFreeze™ Media Kit and warmed with VitriThaw™ Media Kit (FertiPro, Belgium). All samples were stored in liquid nitrogen. The loss of embryos during freezing and thawing processes was not documented.

Assisted hatching through a three-dimensional partial zona dissection was introduced at our center in March 2001 *and* was applied according to the thickness of the zona pellucida [23]. In November 2005, laser assisted hatching was implemented (Octax, MTG, Germany); this procedure was conducted shortly after warming according to a similar method used by Mantoudis [24]. From June 2007, embryos or blastocysts were moved from culture medium to EmbryoGlue (Vitrolife, Gothenburg, Sweden) approximately 30 min–3 h prior to embryo transfer.

In later exogenous hormone replacement cycles, estrogen (Progynova mite® 1 mg, Bayer, Vienna, Austria) and progesterone (Utrogestan® 100 mg, Meda Pharma, Vienna, Austria) were administered orally, transdermally and vaginally, in order to achieve exact synchronization between endometrial maturation and embryo development. During hormonal substitution, frequent ultrasound scans were performed to monitor endometrial thickness and secretory state and to determine the optimal time for FET. Embryo transfers were performed with a full bladder and under transabdominal ultrasound guidance. The embryo(s) were placed 1 cm from the most distal fundal region of the uterine cavity using a catheter attached to a microinjector (Narishige, Tokyo, Japan). Emptying of the bladder and then 20–30 min of bed rest followed. In the case of pregnancy, luteal support was continued until the 8th–12th week of gestation.

2.3. Statistical analysis

Systematic and routine documentation at the IVF clinic provided the data basis for this retrospective study. Sample size was not pre-specified. Baseline information included patient characteristics, details of IVF techniques and treatment outcomes. The primary outcome of this study was defined as the delivery of one or more live infants following elective FET. The secondary outcome was the occurrence of OHSS. The cumulative probability of the first live birth per woman was estimated using the Kaplan-Meier method, according to the number of FET attempts. Analyses were stratified by maternal age and performed for both an optimistic and a conservative scenario as reported previously in the setting of ART [25]. The optimistic scenario assumed that patients who did not return for a subsequent FET would have the same chance of a pregnancy resulting in a live birth as patients who continued treatment. The conservative scenario assumed no live births among patients who did not return for further treatment.

A Cox proportional hazards model was used to evaluate independent predictors for a successful live birth. Hazard ratios (HR) and their 95% confidence intervals (95%CI) were assigned to indicate the prognostic relevance of covariates such as age, the use of reproductive