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Cumulative live birth rate after GnRH agonist trigger and elective cryopreservation of all embryos in high responders

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KEY MESSAGE

Use of gonadotrophin-releasing hormone (GnRH) antagonist cycles and GnRH agonist triggering is effective in reducing the risk of developing ovarian hyperstimulation syndrome in high-responding patients. Patients can be reassured that high cumulative live birth rates can be expected when all embryos are cryopreserved and transferred in the subsequent menstrual cycles.

A B S T R A C T

Elective embryo cryopreservation after using gonadotrophin-releasing hormone (GnRH) antagonist protocols and GnRH agonist triggering is becoming an increasingly important part of medically assisted reproduction. We designed a single-centre retrospective study to assess the cumulative probability of achieving a live birth through consecutive transfers of vitrified-warmed blastocysts after elective embryo cryopreservation in high-responding patients. Hence, 123 women identified to be at high risk for developing ovarian hyperstimulation syndrome were included. They were stimulated using GnRH antagonist protocol, and GnRH agonist was used to trigger final oocyte maturation. All embryos were vitrified at the blastocyst stage and transferred in the subsequent menstrual cycles. Using the Kaplan–Meier survival analysis, a total of 65.9% (95% CI 57.5 to 74.3) women achieved a live birth after a maximum of six embryo transfer cycles using the 'conservative' approach. Applying the 'optimistic' approach, presuming that women who still had cryopreserved embryos and did not return for embryo transfer had the same chance of achieving a live birth as those returning for transfer, the cumulative live birth rate estimated in six embryo transfer cycles was 76.6% (95% CI 69.1 to 84.1). No cases of severe ovarian hyperstimulation syndrome were recorded.

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Introduction

The efforts to minimize complications of medically assisted reproduction have become an increasingly important part of reproductive medicine in the past decade. Today, ovarian hyperstimulation syndrome (OHSS) is the main potentially life-threatening complication of ovarian stimulation. In recent years, gonadotrophin-releasing hormone (GnRH) antagonist protocols have replaced GnRH agonist protocols as the most commonly used approach to ovarian stimulation. This is especially important when dealing with patients likely to have a high response to ovarian stimulation, as this approach has been associated with significant reduction in OHSS occurrence (Al-Inany et al., 2011; Papanikolaou et al., 2006; Youssef et al., 2011). However, GnRH antagonist protocols also allow for implementation of additional measures, most notably the replacement of HCG with GnRH agonist to induce final oocyte maturation. This approach practically eliminates the risk of developing OHSS (Griesinger et al., 2006; Kolibianakis et al., 2005; Youssef et al., 2010) and the success of oocyte retrieval is comparable in oocyte number and maturation rate to using HCG (Galindo et al., 2009; Hernandez et al., 2009). The drawback is hindered endometrial receptivity caused by rapid luteolysis and the associated luteal phase defect. This is probably caused by excessive negative steroid feedback mechanism that causes suppression at the pituitary level (Casper, 2015; Kol et al., 2015). Hence, early studies have shown significantly reduced pregnancy and live birth rates (Babayof et al., 2006; Griesinger et al., 2006; Humaidan et al., 2005). Intensified luteal support was considered, which can improve the success rate of the following embryo transfer in the same cycle (Humaidan et al., 2010; Iliodromiti et al., 2013) but this may come at a cost of increasing the incidence of OHSS development (Seyhan et al., 2013).

Elective cryopreservation of all embryos and transfer in subsequent menstrual cycles, therefore, presents as a rational and logical approach to the treatment of these women. This method was enabled by dramatic improvements in vitrification techniques and embryo survival rates in the past decade (Abdel Hafez et al., 2010). Today, the indications for elective cryopreservation of all embryos are broadening, and many more women, including those with abnormal late follicular progesterone levels and patients in oocyte donation programmes, are candidates for elective embryo cryopreservation. Indeed, frozen–thawed embryo transfer has numerous potential benefits compared with embryo transfer in a fresh cycle, most notably improved embryo–endometrial synchrony and the possibility of better workload organization in the clinic. Moreover, improved obstetrical and neonatal outcomes have also been suggested (Ishihara et al., 2014; Pelkonen et al., 2010; Wennerholm et al., 2013). Wider acceptance of elective cryopreservation of all embryos and transfer in a frozen–thawed cycle could dramatically change the way we will approach IVF in the future (Blockeel et al., 2016). In light of these facts, it is crucial to study the chances of the cycle outcome success after administering GnRH agonist and electively cryopreserving all embryos. We aimed to investigate the cumulative probability of achieving a live birth through consecutive transfers of vitrified-warmed blastocysts after applying the freeze-all strategy in high-responding patients.

Materials and methods

Study design

Women undergoing elective cryopreservation of all embryos in consecutive IVF and intracytoplasmic sperm injection (ICSI) cycles from January 2012 to July 2014 were included in the retrospectively designed study. All women were treated with GnRH antagonist protocol. Specifically, according to our clinical practice, only women identified as high risk for developing OHSS during ovarian stimulation were counselled about the possibility of using GnRH agonist to trigger the final oocyte maturation and electively cryopreserving all embryos.

Protocols

All cycles were synchronized using combined oral contraception. Ovarian stimulation was initiated on day 5 of the pill-free interval by administering a starting dose of 150 IU of recombinant FSH (Gonal-F, Merck Serono, Switzerland) or highly purified HMG (Menopur, Ferring, Switzerland) (Vlaisavljevic et al., 2003). On day 6 of the stimulation, 0.25 mg of cetrorelix (Cetrotide; Merck Serono, Switzerland) was started in a fixed protocol. The gonadotrophin dose could be adjusted on day 6 of the stimulation according to the level of the ovarian response as demonstrated by the ultrasound. Cycle monitoring was carried out using the combination of transvaginal ultrasound and serum oestradiol. Women with 19 or more developing follicles were counselled about the possibility of replacing HCG with GnRH agonist. All follicles measuring a mean diameter of 11 mm or wider were considered to be developing follicles. Ultrasound criteria have been shown to be more reliable than endocrinologic characteristics in predicting the possibility of OHSS and, hence, this was used as inclusion criterion (Griesinger et al., 2016; Papanikolaou et al., 2006; Reljic et al., 1999). Nonetheless, we routinely measure oestradiol levels before triggering final oocyte maturation in all patients according to our clinical practice. This means that some women with a high number of follicles and low oestradiol levels may not have decided on a freeze-all approach and still opted for routine triggering with HCG. If women decided to take this approach, the final oocyte maturation was achieved by administering 0.2 mg of triptorelin (Diphereline; Ipsen, France). The oocyte retrieval was planned 35 h after the GnRH agonist administration. An IVF or ICSI procedure was performed and successful fertilization of the oocytes was defined as the presence of two pronuclei 17–19 h after the procedure. All fertilized oocytes and embryos were cultured in the BlastAssist System sequential embryo culture media (Origio, Knardrupvej, Denmark) for 5 days. The blastocysts were graded according to our established grading system, previously described (Kovacic et al., 2004). In brief, a blastocyst was considered optimal if it was fully expanded, contained cohesive trophectoderm, compact inner cell mass and the blastocoel completely filled the embryo (Kovacic et al., 2004). The criteria for blastocysts available for cryopreservation were not very rigorous. Only expanded blastocysts were cryopreserved on day 5 or day 6. Also, blastocysts containing cytoplasmic fragments within trophectoderm or excluded blastomeres in their periviteline space were vitrified if at least a few of the inner-cell-mass cells were observed.

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