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Random-start ovarian stimulation in women desiring elective cryopreservation of oocytes

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KEY MESSAGE

The number of total and MII oocytes derived from random-start ovarian stimulation protocols initiated during any phase of the menstrual cycle are similar to conventional CD 2/3 ovarian stimulation start protocols. Thus, random-start ovarian stimulation can be a valuable alternative to conventional start in women desiring elective cryopreservation of oocytes.

A B S T R A C T

The current study investigates the utility of random-start ovarian stimulation in women desiring elective oocyte cryopreservation. Women in the study cohort underwent random-start ovarian stimulation, and were subdivided based on the phase of the menstrual cycle that ovarian stimulation began, i.e. early follicular, late follicular or luteal phase. Women undergoing conventional cycle day (CD) 2/3 ovarian stimulation start were controls. A total of 1302 women were included – 859 (66.0%) conventional CD 2/3, 342 (26.3%) early follicular, 42 (3.2%) late follicular and 59 (4.5%) luteal ovarian stimulation starts. There was no difference in the demographics or baseline ovarian stimulation characteristics. The duration of ovarian stimulation (11 versus 9 days; $P < 0.001$) and total dosage of gonadotrophins administered (4095.5 versus 3155 IU; $P < 0.001$) was higher in the random-start group. The number of total and MII oocytes in the control and random-start groups was similar. A non-significant trend towards increased cycle cancellation was noted in the late follicular start group (7.1%). Study findings indicate the number of total and MII oocytes derived from random-start protocols initiated during any phase of the menstrual cycle is similar to conventional CD 2/3 ovarian stimulation start protocols in women desiring elective oocyte cryopreservation.

Introduction

Oocyte cryopreservation has advanced rapidly since the first live birth from cryopreserved oocytes was achieved in 1986 (Chen, 1986; Gook, 2011). Advances in the technical aspects of oocyte cryopreservation, specifically vitrification (Practice Committees of American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, 2013), have successfully facilitated the application of this technique to a myriad of clinical settings (Schattman, 2015). Notably,

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a rising trend in the proportion of donor oocyte cycles using cryopreserved oocytes was observed between 2000 and 2010 (Kawwass et al., 2013). In addition, cryopreservation of oocytes has become an integral part of fertility preservation in reproductive-age women with cancer or other medical conditions facing imminent gonadotoxic chemo-, radio- or immunotherapy (Argyle et al., 2016; Schattman, 2015). Also, oocyte cryopreservation is used by an increasing number of women who wish to delay motherhood for personal or professional reasons (Cobo and García-Velasco, 2016; Schattman, 2015), as well as by those wanting to protect against age-related fertility decline (Cobo et al., 2013; Stoop et al., 2014). Optimization of ovarian stimulation protocols aimed at maximizing oocyte yield in such women is therefore of utmost importance (Doyle et al., 2016; Schattman, 2016). In women undergoing ovarian stimulation to cryopreserve oocytes and not attempting to conceive a pregnancy in that cycle, endometrial development does not need to be synchronized with the oocytes (Schattman, 2015). Thus, ovarian stimulation can be initiated irrespective of the phase of the menstrual cycle without adversely impacting oocyte yield or quality, thereby facilitating schedules and reducing delays (Schattman, 2015). While this approach, of cryopreserving oocytes with random-start ovarian stimulation protocols, has been well studied in women with cancer (Cakmak and Rosen, 2015; Cakmak et al., 2013; Pereira et al., 2016), its utility in elective settings has not been reported. In this context, the primary objective of the current study is to investigate the utility of random-start ovarian stimulation protocols in women who desire elective cryopreservation of oocytes.

Materials and methods

Inclusion and exclusion criteria

All women undergoing ovarian stimulation for cryopreservation of oocytes during a 6-year period were evaluated for potential inclusion in the current study. Only women desiring oocyte cryopreservation for elective reasons, without any underlying medical or gynaecological diseases, were included in this analysis. Women undergoing ovarian stimulation for cancer-related indications, utilizing letrozole-based protocols, or those recently treated with chemotherapy or radiation were excluded. Elective cryopreservation of oocytes has previously been described as 'elective egg freezing', 'social egg freezing' or 'non-medical egg freezing' (Argyle et al., 2016; Cobo and García-Velasco, 2016; Schattman, 2015). We consider all such definitions synonymous with elective cryopreservation of oocytes for the purpose of the study. Women presenting for their initial consultation were offered the choice of a conventional cycle day (CD) 2/3 ovarian stimulation start or a random ovarian stimulation start, and were counselled based on previous studies (Cakmak and Rosen, 2015; Cakmak et al., 2013; Pereira et al., 2016) showing no difference in oocyte yield when comparing the two ovarian stimulation strategies. This study protocol was approved by the Institutional Review Board (protocol number 1307014154).

Clinical and laboratory protocols

Ovarian stimulation, human chorionic gonadotrophin (HCG) trigger and oocyte retrieval were performed according to previously described protocols (Huang and Rosenwaks, 2014). A subset of women in the conventional CD 2/3 group were prescribed combination monophasic oral contraceptive (OC) pills for 10–14 days for pre-ovarian stimulation treatment. Women undergoing ovarian stimulation with conventional CD 2/3 start or random-start protocols were stimulated with recombinant gonadotrophins (Follistim; Merck, Kenilworth, NJ, USA or Gonal-F; EMD-Serono Inc., Rockland, MA, USA). In the majority of cycles (1139/1302, 87.5%), ovulation was suppressed with once daily 0.25 mg gonadotrophin-releasing hormone (GnRH) antagonist injections (Ganirelix Acetate; Merck, Kenilworth, NJ, USA) based on a previously described flexible protocol (Huang and Rosenwaks, 2014). Urinary gonadotrophins (Menopur; Ferring Pharmaceuticals Inc., Parsippany, NJ, USA) were generally started at the time of GnRH antagonist injections in such ovarian stimulation protocols. GnRH-agonist based flare protocols were used in the remaining patients (163/1302, 12.5%). In general, the decision to use a GnRH-antagonist or GnRH-agonist based ovarian stimulation protocol was based on physician preference; however, all patients in the random-start group underwent ovarian stimulation with GnRH-antagonist based ovarian stimulation protocols.

Oocyte maturation was induced with one of four different regimens depending on the patient's response to stimulation: (i) subcutaneous HCG 250 µg (Ovidrel; EMD-Serono Inc., Rockland, MA, USA); (ii) i.m. 10,000 IU HCG; (iii) leuprolide acetate 4 mg (Lupron; AbbVie, Lake Bluff, IL, USA) in women considered to be at high risk for ovarian hyperstimulation syndrome (OHSS); or (iv) a dual trigger with 2 mg leuprolide acetate and 1500 IU HCG. The ovulatory triggers were administered when the two lead follicles attained a mean diameter >17 mm. Oocyte retrieval was performed under conscious sedation and transvaginal ultrasound guidance with a 30 cm 16 G oocyte aspiration needle (Cook Medical, Bloomington, IN, USA) 34–35 h after the ovulatory trigger. The retrieved oocytes were then exposed to 40 IU recombinant hyaluronidase (Cumulase™; Halozyme Therapeutics, Inc., San Diego, CA, USA) to remove the cumulus–corona complex (Palermo et al., 1995), and then vitrified using the Cryotop method (Kuwayama et al., 2005). None of the aforementioned clinical or laboratory protocols changed during the study period.

Outcome variables

Baseline demographics recorded were age, body mass index (BMI, kg/m^2) and gravidity. Also, baseline characteristics were recorded when appropriate and included basal FSH (mIU/ml), basal LH (mIU/ml), basal anti-Müllerian hormone (AMH, ng/ml) and antral follicle count (AFC). Ovarian stimulation outcomes recorded were as follows: protocol type (GnRH-antagonist versus GnRH-agonist), total days of ovarian stimulation, total dosage of gonadotrophins administered (IU), gonadotrophin dosage per day (IU/day), ovulatory trigger type (subcutaneous HCG versus i.m. HCG versus dual leuprolide acetate and HCG versus pure leuprolide acetate), oestradiol (pg/ml) on the day of and after trigger, and cancellation rate (%). The total number of oocytes, total number of mature (metaphase II [MII]) oocytes, percentage of MII oocytes, and the ratio of MII oocytes to AFC were also recorded, as well as the number of cycle cancellations. Cycle cancellations occurred most often due to poor ovarian response or a dominant follicle; self-cancellations occurred in a few cases.

Statistical analysis

Continuous variables were checked for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD). Categorical

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