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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

and non-parametric variables were expressed as number of cases (*n*) with percentage of occurrence (%) and median (interquartile range [IQR]), respectively. Independent *t*-tests, Wilcoxon signed-rank tests, McNemar's chi-squared tests, and Kruskal–Wallis tests were used as required for the aforementioned variables. All women undergoing conventional CD 2/3 ovarian stimulation start with oestradiol <75 pg/ml on the day of ovarian stimulation start were considered the control cohort. Those undergoing random-start ovarian stimulation were considered the study cohort and were further subdivided based on which phase of the menstrual cycle that ovarian stimulation began. All ovarian stimulation starts between CD 4 and CD 7, with a lead follicle <12 mm and oestradiol ≥75 pg/ml were considered early follicular starts. Ovarian stimulation starts >CD 7 and a lead follicle ≥13 mm, but with a serum progesterone (ng/ml) < 2 ng/ml were considered late follicular starts, while ovarian stimulation initiated with a corpus luteum cyst visible on transvaginal pelvic ultrasonography or a serum progesterone ≥3 ng/ml were considered luteal starts (Cakmak et al., 2013). GnRH-antagonist injections were started from the first day of gonadotrophin injections in the late follicular group. Analysis of variance (ANOVA) with Bonferroni multiple comparisons was used to compare outcome variables between the controls and three random-start ovarian stimulation groups. Furthermore, odds ratios (OR) with 95% confidence intervals (CI) for cycle cancellation and percentage of mature oocytes were calculated for early follicular, late follicular and luteal starts and compared with conventional CD 2/3 ovarian stimulation starts. These odds were adjusted for age, total stimulation days and total gonadotrophins administered. While the Cakmak et al. (2013) study showed no difference in oocyte yield, a difference in the total gonadotrophins administered was noted between the conventional CD 2/3 (3404 IU) and luteal (4344 IU) ovarian stimulation starts. A sample size of at least 11 patients per group was estimated with an assumed α error of 5% and a power of 80% to detect this difference. Statistical significance was set at $P < 0.05$, and all statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, TX, USA).

Results

A total of 1308 women presented to our centre for elective cryopreservation of oocytes during the study period. Of these, six women did not initiate ovarian stimulation for medical (*n* = 3) or personal (*n* = 3) reasons. Of the remaining 1302 women, 859 (66.0%) underwent conventional CD 2/3 ovarian stimulation start and 443 (34.0%) underwent random-start ovarian stimulation. The random-start group was subdivided as follows: 342 (26.3%) early follicular starts, 42 (3.2%) late follicular starts and 59 (4.5%) luteal starts. Of the 859 women undergoing conventional CD 2/3 ovarian stimulation, 94 (10.9%) used oral contraceptive pills for pretreatment in the preceding menstrual cycle. **Figure 1** summarizes the selection of the study cohort.

Table 1 compares the demographics and baseline characteristics of all women included, stratified by ovarian stimulation start type. There was no difference in the mean age of women undergoing conventional CD 2/3 or random-start ovarian stimulation. As evident in **Table 1**, there was no difference in the mean age, BMI or gravidity of women in all ovarian stimulation groups. Furthermore, the basal FSH, LH and AMH levels, and AFC were within normal limits, without any statistical difference between the ovarian stimulation groups.

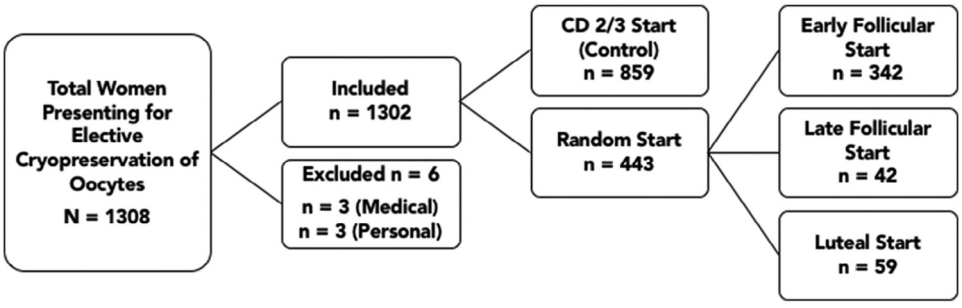

Figure 1 – Selection of the study cohort.

Table 1 – Comparison of demographics and baseline controlled ovarian stimulation characteristics of women undergoing elective cryopreservation of oocytes (*n* = 1302).

Parameter	Control (*n* = 859)	Early follicular (*n* = 342)	Late follicular (*n* = 42)	Luteal (*n* = 59)
Age (years)	36.9 (±3.7)	37.1 (±3.3)	37.1 (±3.4)	37.2 (±3.1)
BMI (kg/m^2)	22.6 (±5.3)	22.5 (±4.6)	22.4 (±4.9)	22.3 (±4.6)
Gravidity	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Basal FSH (mIU/ml)	5.7 (3.2–7.7)	5.4 (3.1–7.4)	5.6 (3.2–7.8)	5.4 (2.6–7.6)
Basal LH (mIU/ml)	3.5 (1.6–4.9)	3.3 (1.7–5.1)	3.6 (2.5–4.9)	3.4 (2.5–5.3)
Basal AMH (ng/ml)	2.2 (±1.1)	2.1 (±1.4)	2.3 (±0.9)	2.2 (±1.3)
AFC	13.2 (±2.6)	12.9 (±3.6)	13.1 (±3.1)	13.3 (±3.7)

Data are presented as mean ± standard deviation, *n* (%) and median (interquartile range).
There were no statistically significant differences between the groups.
AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index.

Table 2 – Comparison of controlled ovarian stimulation outcomes stratified by type (*n* = 1302).

Parameter	Control (*n* = 859)	Early follicular (*n* = 342)	Late follicular (*n* = 42)	Luteal (*n* = 59)
Protocol *n* (%)				
GnRH-agonist based	93 (10.8)	55 (16.1)	6 (14.3)	9 (15.3)
GnRH-antagonist based	766 (89.2)	287 (83.9)	36 (85.7)	50 (84.7)
Total stimulation days*	9.5 (8–11)	9.5 (8.5–12)	11.5 (7.5–13.5)	11 (8–12)
Total gonadotrophin dose (IU)*	3155 (2100–4500)	3280 (2180–4700)	4665.5 (3300–5975)	4345 (3100–5650)
Gonadotrophin dose/day (IU/day)*	332.1	345.3	405.7	395.0
Trigger type *n* (%)				
i.m. HCG	197 (22.9)	94 (27.5)	9 (21.4)	15 (25.4)
subcutaneous HCG	449 (52.3)	192 (56.1)	20 (47.6)	29 (49.2)
Dual leuprolide and HCG	152 (17.7)	37 (10.8)	8 (19.1)	11 (18.6)
Pure leuprolide	61 (7.1)	19 (5.6)	5 (11.9)	4 (6.8)
Oestradiol on day of trigger (pg/ml)	1796 (1189–2540)	1781 (1045.5–2583.5)	1804 (1058.5–2661)	1789 (1052–2504)
Oestradiol after day of trigger (pg/ml)	2509 (1619.5–3372.5)	2495.5 (1442.5–3298.5)	2488 (1674–3174.5)	2465 (1309–3174.5)
Cancellation rate *n* (%)	31 (3.6)	12 (3.5)	3 (7.1)	2 (3.4)

Data are presented as *n* (%) and median (interquartile range).
GnRH = gonadotrophin-releasing hormone; HCG = human chorionic gonadotrophin.
* $P < 0.001$.

Table 2 compares the outcomes of the control and random-start ovarian stimulation subgroups. There was no difference in the distribution of GnRH-antagonist versus GnRH-agonist ovarian stimulation protocols, distribution of ovulatory trigger types, oestradiol levels on the day of and after trigger, or the cycle cancellation rate. Overall, the total days of ovarian stimulation (11 versus 9 days), total dosage of gonadotrophins administered (4095.5 versus 3155 IU; $P < 0.001$) and gonadotrophin dosage per day (381.9 versus 332.1 IU/day), were higher in the random-start ovarian stimulation group compared with the conventional CD 2/3 ovarian stimulation group ($P < 0.001$). Upon applying the Bonferroni multiple comparisons, no difference was found in total dosage of gonadotrophins when comparing the control and early follicular start groups. However, the total dosage of gonadotrophins administered was significantly higher in the late follicular start group (4665.5 IU) compared with the control (3155 IU), early follicular (3280 IU) and luteal start (4345 IU) groups ($P < 0.001$). Similar statistical trends were noted for the gonadotrophin dosage per day when comparing the late follicular start group to the remaining ovarian stimulation groups ($P < 0.001$). When comparing the total stimulation days with Bonferroni multiple comparisons, no difference was noted between either the control and early follicular groups and the late follicular and luteal groups. Women in the latter two groups, however, underwent a longer duration of ovarian stimulation compared with the former two groups. Notably, a non-significant trend towards increased cycle cancellation was observed in the late follicular start group (7.1%) compared with the other ovarian stimulation groups.

Table 3 lists the oocyte yield of the various ovarian stimulation groups. No difference was noted in the total number of MII oocytes retrieved. Furthermore, there was no difference in the percentage of MII oocytes or the ratio of MII oocytes to AFC across all ovarian stimulation groups. The odds of MII oocytes in the control group compared with the early follicular, late follicular and luteal ovarian stimulation groups were OR 1.01, 95% CI 0.33–3.14; OR 0.98, 95% CI 0.32–3.06; OR 1.01, 95% CI 0.33–3.13; respectively. These odds remained non-significant when adjusted for age, total stimulation days and total gonadotrophins administered.

Discussion

Oocyte cryopreservation has now become an established assisted reproductive technique (Argyle et al., 2016) and its popularity can be attributed to the standardization, reproducibility and efficacy of oocyte vitrification (Cobo et al., 2013). Within the field of fertility preservation, elective cryopreservation of oocytes has been heralded as a breakthrough for reproductive autonomy (Harwood, 2009). Several studies have suggested that a significant proportion of single women who choose to cryopreserve their oocytes are highly satisfied (Stoop et al., 2015), and may choose to pursue treatment even at younger ages to safeguard their reproductive potential (Stoop et al., 2011). Latest research has therefore focused on maximizing the yield of good-quality oocytes in such women by proposing various technical

Table 3 – Yield of total and metaphase II oocytes stratified by controlled ovarian stimulation type (*n* = 1302).

Parameter	Control (*n* = 859)	Early follicular (*n* = 342)	Late follicular (*n* = 42)	Luteal (*n* = 59)
Total oocytes retrieved	13.1 (±2.3)	12.7 (±2.7)	13.0 (±3.1)	13.2 (±2.9)
MII oocytes retrieved	11.0 (±3.1)	10.8 (±2.7)	11.1 (±3.0)	10.9 (±3.2)
MII oocytes (%)	84.0	85.0	85.4	82.6
MII oocytes/AFC	0.83	0.84	0.85	0.82

Data are presented as mean ± standard deviation and *n* (%).
AFC = antral follicle count; MII = metaphase II.
There were no statistically significant differences between the groups.

(Dominguez et al., 2013; Martínez-Burgos et al., 2011) and clinical strategies (Garcia-Velasco et al., 2013), as well as identifying the optimal timing for oocyte cryopreservation (Mesen et al., 2015).

There is currently a shortage of evidence regarding optimal ovarian stimulation protocols or timing of such protocols within the menstrual cycle to maximize oocyte yield in women pursuing oocyte cryopreservation. While a conventional CD 2/3 ovarian stimulation start has been used in most oocyte cryopreservation cycles (Cobo et al., 2013, 2016; Garcia-Velasco et al., 2013), current evidence also suggests that random-start ovarian stimulation may yield an equal number of oocytes (Cakmak et al., 2013; Kim et al., 2015; Pereira et al., 2016; von Wolff et al., 2016), which have similar early developmental competence as those retrieved from conventional CD 2/3 ovarian stimulation. These results are obtained from studies in cancer patients, where random-start ovarian stimulation is frequently used to minimize the delay between ovarian stimulation and chemotherapy or radiation. However, retrieval of MII oocytes during any phase of the menstrual cycle also suggests that folliculogenesis occurs continually throughout the menstrual cycle and not just in a single wave (Kuang et al., 2014).

Much of our understanding of folliculogenesis arises from histological and endocrinological studies in non-human primates (Baerwald et al., 2012). Ultrasonographic studies in humans have further corroborated, or in some instances have challenged, these findings. Three main theories of folliculogenesis exist currently – the single recruitment theory, the continuous recruitment theory and the follicular wave theory (Baerwald et al., 2012). The single recruitment theory posits that once during every menstrual cycle, a cohort of 2–5 mm follicles is recruited during the preceding late luteal phase or early follicular phase (Baerwald et al., 2003a). The timing of recruitment corresponds to the regression of the corpus luteum (CL), resulting in oestradiol and inhibin levels falling and FSH levels rising (Baerwald et al., 2003a). Then, a single dominant follicle is selected from this cohort during the mid-follicular phase, which continues to develop and ultimately ovulates (Hodgen, 1982). The remaining follicles regress and undergo atresia. Almost all conventional CD 2/3 ovarian stimulation protocols for ovulation induction utilize early follicular starts in an effort to maximally stimulate optimal follicle development as well as to synchronize oocytes to a receptive endometrium. In contrast, the continuous recruitment theory suggests that small antral follicles measuring 4–6 mm grow and regress continuously during the inter-ovulatory interval (Baerwald et al., 2012). The dominant follicle destined for ovulation arises purely by chance from this pool of antral follicles following regression of the CL. Finally, the follicular wave theory proposes that multiple 'waves' of antral follicles develop during the menstrual cycle (de Mello Bianchi et al., 2010). This theory has been seen in bovine (Jaiswal et al., 2004) and non-human primate species (Bishop et al., 2009). Also, 2–3 follicular waves have been described in healthy women during the inter-ovulatory interval using endocrinological and ultrasonographic measurements (Baerwald et al., 2003b). Thus, the findings of random-start ovarian stimulation protocols appear to support the follicular wave or continuous recruitment theories.

Based on the aforementioned findings and existing data in cancer patients, this study sought to investigate the utility of random-start ovarian stimulation protocols in women desiring elective cryopreservation of oocytes, at least on a preliminary basis. The overall results suggest that the yields of total and MII oocytes are similar in conventional CD 2/3 start or random-start ovarian stimulation protocols. Furthermore, the number of total and MII oocytes retrieved during the early follicular, late follicular and luteal phase of the menstrual cycle are comparable. These findings are reassuringly consistent with the clinical results of random-start ovarian stimulation in patients with cancer (Cakmak et al., 2013; Kim et al., 2015; Pereira et al., 2016; von Wolff et al., 2016). The current study also noted longer duration of ovarian stimulation and higher gonadotrophin utilization in patients initiating ovarian stimulation in the late follicular or luteal phase compared with the other groups. These findings were also noted by Cakmak et al. (2013), von Wolff et al. (2016) and Kim et al. (2015) in their retrospective studies of 128, 684 and 22 patients, respectively. The increased ovarian stimulation duration and gonadotrophin utilization may be explained by the local inhibitory effects on early follicular recruitment exerted by the CL, which arises after ovulation of the dominant follicle in the late follicular ovarian stimulation group or is pre-existing in the luteal ovarian stimulation group (McNatty et al., 1983). We also observed a non-significant trend towards increased cycle cancellation in the late follicular ovarian stimulation group. However, only three ovarian stimulation cycles were cancelled; two of these patients had a lead follicle of 13 mm on the day of ovarian stimulation start.

While the current study uniquely assesses the utility and efficacy of random-start ovarian stimulation protocols in a large cohort of women desiring elective oocyte cryopreservation, it is not without shortcomings. A major limitation of the study is that it did not evaluate the developmental competence of the oocytes obtained via random-start ovarian stimulation. Thus, we remain uncertain about the effects, if any, of elevated P4 levels on oocyte quality and competence. A more thorough assessment of oocyte quality after late follicular or luteal phase stimulation in terms of gene expression, metabolism and dynamic developmental parameters is still needed. In addition, detailed neonatal outcomes as well as cost-effectiveness need to be evaluated. A recent prospective paired non-inferiority observational study compared the rates of euploid blastocyst formation after follicular phase or luteal phase stimulation in the same menstrual cycle of 43 patients (Ubaldi et al., 2016). The authors reported no significant differences in the number of cumulus–oocyte complexes, MII oocytes, blastocysts biopsied or euploid blastocyst rate in follicular phase or luteal phase stimulation. Furthermore, at least two case reports have also reported pregnancies after retrieval of oocytes from variations from random-start ovarian stimulation protocols (Bentov et al., 2010; Hatırnaz et al., 2015). Also, published studies have shown that similar numbers of oocytes and embryos are available for cryopreservation in both conventional and luteal phase ovarian stimulation cycles (Demirtas et al., 2008; Maman et al., 2012). The current study was powered to detect a dosage difference of 940 IU between conventional CD 2/3 and luteal ovarian stimulation starts (Cakmak et al., 2013). However, larger sample sizes would be required to detect differences in ovarian stimulation duration or oocyte yield. Finally, the study's retrospective design also represents a limitation.

In conclusion, the findings from this study indicate that 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 ovarian stimulation start in women desiring elective cryopreservation of oocytes. Prospective studies are required to confirm the long-term developmental competence of oocytes retrieved from random-start ovarian stimulation, and whether the trends of both increased ovarian stimulation duration and increased gonadotrophin utilization associated with these protocols outweigh its observed benefits.

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REFERENCES

Argyle, C.E., Harper, J.C., Davies, M.C., 2016. Oocyte cryopreservation: where are we now? Hum. Reprod. Update 22, 440–449.
Baerwald, A.R., Adams, G.P., Pierson, R.A., 2003a. A new model for ovarian follicular development during the human menstrual cycle. Fertil. Steril. 80, 116–122.
Baerwald, A.R., Adams, G.P., Pierson, R.A., 2003b. Characterization of ovarian follicular wave dynamics in women. Biol. Reprod. 69, 1023–1031.
Baerwald, A.R., Adams, G.P., Pierson, R.A., 2012. Ovarian antral folliculogenesis during the human menstrual cycle: a review. Hum. Reprod. Update 18, 73–91.
Bentov, Y., Esfandiari, N., Gokturk, A., Burstein, E., Fainaru, O., Casper, R.F., 2010. An ongoing pregnancy from two waves of follicles developing during a long follicular phase of the same cycle. Fertil. Steril. 94, 350, e8–11.
Bishop, C.V., Sparman, M.L., Stanley, J.E., Bahar, A., Zelinski, M.B., Stouffer, R.L., 2009. Evaluation of antral follicle growth in the macaque ovary during the menstrual cycle and controlled ovarian stimulation by high-resolution ultrasonography. Am. J. Primatol. 71, 384–392.
Cakmak, H., Rosen, M.P., 2015. Random-start ovarian stimulation in patients with cancer. Curr. Opin. Obstet. Gynecol. 27, 215–221.
Cakmak, H., Katz, A., Cedars, M.I., Rosen, M.P., 2013. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil. Steril. 100, 1673–1680.
Chen, C., 1986. Pregnancy after human oocyte cryopreservation. Lancet 1, 884–886.
Cobo, A., García-Velasco, J.A., 2016. Why all women should freeze their eggs. Curr. Opin. Obstet. Gynecol. 28, 206–210.
Cobo, A., Garcia-Velasco, J.A., Domingo, J., Remohí, J., Pellicer, A., 2013. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil. Steril. 99, 1485–1495.
Cobo, A., García-Velasco, J.A., Coello, A., Domingo, J., Pellicer, A., Remohí, J., 2016. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil. Steril. 105, 755–764.
de Mello Bianchi, P.H., Serafini, P., Monteiro da Rocha, A., Assad Hassun, P., Alves da Motta, E.L., Sampaio Baruselli, P., Chada Baracat, E., 2010. Review: follicular waves in the human ovary: a new physiological paradigm for novel ovarian stimulation protocols. Reprod. Sci. 17, 1067–1076.
Demirtas, E., Elizur, S.E., Holzer, H., Gidoni, Y., Son, W.Y., Chian, R.C., Tan, S.L., 2008. Immature oocyte retrieval in the luteal phase to preserve fertility in cancer patients. Reprod. Biomed. Online 17, 520–523.
Dominguez, F., Castello, D., Remohí, J., Simón, C., Cobo, A., 2013. Effect of vitrification on human oocytes: a metabolic profiling study. Fertil. Steril. 99, 565–572.
Doyle, J.O., Richter, K.S., Lim, J., Stillman, R.J., Graham, J.R., Tucker, M.J., 2016. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. Fertil. Steril. 105, 459–466, e2.
Garcia-Velasco, J.A., Domingo, J., Cobo, A., Martínez, M., Carmona, L., Pellicer, A., 2013. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. Fertil. Steril. 99, 1994–1999.
Gook, D.A., 2011. History of oocyte cryopreservation. Reprod. Biomed. Online 23, 281–289.
Harwood, K., 2009. Egg freezing: a breakthrough for reproductive autonomy? Bioethics 23, 39–46.
Hatırnaz, S., Hatırnaz, E., Ata, B., 2015. Live birth following early follicular phase oocyte collection and vitrified-warmed embryo transfer 8 days later. Reprod. Biomed. Online 31, 819–822.
Hodgen, G.D., 1982. The dominant ovarian follicle. Fertil. Steril. 38, 281–300.
Huang, J.Y., Rosenwaks, Z., 2014. Assisted reproductive techniques. Methods Mol. Biol. 1154, 171–231.
Jaiswal, R.S., Singh, J., Adams, G.P., 2004. Developmental pattern of small antral follicles in the bovine ovary. Biol. Reprod. 71, 1244–1251.
Kawwass, J.F., Monsour, M., Crawford, S., Kissin, D.M., Session, D.R., Kulkarni, A.D., Jamieson, D.J., National ART Surveillance System (NASS) Group, 2013. Trends and outcomes for donor oocyte cycles in the United States, 2000–2010. JAMA 310, 2426–2434.
Kim, J.H., Kim, S.K., Lee, H.J., Lee, J.R., Jee, B.C., Suh, C.S., Kim, S.H., 2015. Efficacy of random-start controlled ovarian stimulation in cancer patients. J. Korean Med. Sci. 30, 290–295.
Kuang, Y., Hong, Q., Chen, Q., Lyu, Q., Ai, A., Fu, Y., Shoham, Z., 2014. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. Fertil. Steril. 101, 105–111.
Kuwayama, M., Vajta, G., Kato, O., Leibo, S.P., 2005. Highly efficient vitrification method for cryopreservation of human oocytes. Reprod. Biomed. Online 11, 300–308.
Maman, E., Meirow, D., Brengauz, M., Raanani, H., Dor, J., Hourvitz, A., 2012. Luteal phase oocyte retrieval and in vitro maturation is an optional procedure for urgent fertility preservation. Fertil. Steril. 95, 64–67.
Martínez-Burgos, M., Herrero, L., Megías, D., Salvanes, R., Montoya, M.C., Cobo, A.C., Garcia-Velasco, J.A., 2011. Vitrification versus slow freezing of oocytes: effects on morphologic appearance, meiotic spindle configuration, and DNA damage. Fertil. Steril. 95, 374–377.
McNatty, K.P., Hillier, S.G., van den Boogaard, A.M., Trimbos-Kemper, T.C., Reichert, L.E., Jr., van Hall, E.V., 1983. Follicular development during the luteal phase of the human menstrual cycle. J. Clin. Endocrinol. Metab. 56, 1022–1031.
Mesen, T.B., Mersereau, J.E., Kane, J.B., Steiner, A.Z., 2015. Optimal timing for elective egg freezing. Fertil. Steril. 103, 1551–1556.
Palermo, G.D., Cohen, J., Alikani, M., Adler, A., Rosenwaks, Z., 1995. Intracytoplasmic sperm injection: a novel treatment for all forms of male factor infertility. Fertil. Steril. 63, 1231–1240.
Pereira, N., Hancock, K., Cordeiro, C.N., Lekovich, J.P., Schattman, G.L., Rosenwaks, Z., 2016. Comparison of ovarian stimulation response in patients with breast cancer undergoing ovarian stimulation with letrozole and gonadotropins to patients undergoing ovarian stimulation with gonadotropins alone for elective cryopreservation of oocytes. Gynecol. Endocrinol. 32, 823–826.

Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, 2013. Mature oocyte cryopreservation: a guideline. Fertil. Steril. 99, 37–43.

Schattman, G.L., 2015. CLINICAL PRACTICE. Cryopreservation of oocytes. N. Engl. J. Med. 373, 1755–1760.

Schattman, G.L., 2016. A healthy dose of reality for the egg-freezing party. Fertil. Steril. 105, 307.

Stoop, D., Nekkebroeck, J., Devroey, P., 2011. A survey on the intentions and attitudes towards oocyte cryopreservation for non-medical reasons among women of reproductive age. Hum. Reprod. 26, 655–661.

Stoop, D., Cobo, A., Silber, S., 2014. Fertility preservation for age-related fertility decline. Lancet 384, 1311–1319.

Stoop, D., Maes, E., Polyzos, N.P., Verheyen, G., Tournaye, H., Nekkebroeck, J., 2015. Does oocyte banking for anticipated gamete exhaustion influence future relational and reproductive choices? A follow-up of bankers and non-bankers. Hum. Reprod. 30, 338–344.

Ubaldi, F.M., Capalbo, A., Vaiarelli, A., Cimadomo, D., Colamaria, S., Alviggi, C., Trabucco, E., Venturella, R., Vajta, G., Rienzi, L., 2016. Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation. Fertil. Steril. 105, 1488–1495, e1.

von Wolff, M., Capp, E., Jauckus, J., Strowitzki, T., Germeyer, A., FertiPROTEKT Study Group, 2016. Timing of ovarian stimulation in patients prior to gonadotoxic therapy: an analysis of 684 stimulations. Eur. J. Obstet. Gynecol. Reprod. Biol. 199, 146–149.