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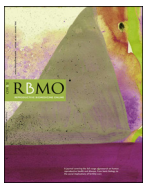

ARTICLE

# Random-start ovarian stimulation in an oocyte donation programme: a large, single-centre, experience

## BIOGRAPHY

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## KEY MESSAGE

The number of oocytes retrieved in oocyte donation cycles and live birth rates in recipients were similar after conventional and random-start ovarian stimulation. The implementation of random-start ovarian stimulation protocols in oocyte donation cycles does not negatively affect oocyte yield or clinical outcomes in recipients compared with conventional protocols.

## ABSTRACT

**Research question:** Do live birth rates differ between recipients matched with donors using conventional ovarian stimulation compared with those using random-start protocols?

**Design:** Retrospective analysis of 891 ovarian stimulations in egg donors (January–December 2018) and clinical outcomes in matched recipients ($n = 935$). Donors commenced ovarian stimulation on day 1–3 of the menstrual cycle ($n = 223$) or in the mid/late-follicular ($n = 388$) or luteal phase ($n = 280$) under a conventional antagonist protocol. Live birth rate of matched recipients was the main outcome.

**Results:** Duration of stimulation and total gonadotrophin dose were comparable between conventional versus random-start groups. The number of collected eggs were similar (17.6 ± 8.8 versus 17.2 ± 8.5, $P = 0.6$, respectively). Sub-group analysis showed that stimulation length (10.2 ± 1.8 versus 9.8 ± 1.7 versus 10.4 ± 1.7, $P < 0.001$) and gonadotrophin consumption (2041.5 ± 645.3 versus 2003.2 ± 647.3 versus 2158.2 ± 685.7 IU, $P = 0.01$) differed significantly between the conventional, mid/late follicular and luteal phase groups, respectively. In matched recipients receiving fresh oocytes and undergoing fresh embryo transfer, the biochemical pregnancy (63.8% and 63.3%; $P = 0.9$), clinical pregnancy (54.6% and 56.1%; $P = 0.8$) and live birth rates (47.7% and 46.6%; $P = 0.7$) per embryo-transfer were similar between conventional versus random groups. Similar results were obtained in recipients receiving vitrified eggs. Euploidy rate was also comparable.

**Conclusions:** No notable variations were found in clinical outcomes using oocytes obtained from random-start protocols and those proceeding from conventional ovarian stimulation in oocyte donation treatments. Luteal-phase stimulation seems to require longer stimulation and higher FSH consumption. Random-start stimulation strategy does not impair the potential of the oocyte yield or clinical outcomes in oocyte donation cycles.

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## KEYWORDS

ovarian stimulation
random-start IVF
oocyte donation cycles
follicular waves
live birth

## INTRODUCTION

Ovarian stimulation strategies have traditionally started in the early follicular phase, so that a receptive endometrium for fresh embryo transfer can be obtained. It is also widely believed to be the optimal time for follicular recruitment. The documentation of multiple follicular cohorts (or 'waves') during the menstrual cycle challenged the traditional theory that a single cohort of antral follicles grows only during the follicular phase of the menstrual cycle (*Baerwald et al., 2003*) and also that it provides the knowledge and physiological basis for the so-called 'non-conventional' ovarian stimulation approaches such as the 'random-start' protocol, i.e. initiation of the stimulation process irrespective of the phase of the menstrual cycle.

The bulk of existing research on random-start ovarian stimulation involves women referred to oncologic units for oocyte cryopreservation (*Cakmak and Rosen, 2015*). More recently, some studies have also evaluated the efficiency of this strategy in patients undergoing elective cryopreservation of oocytes or embryos, including those choosing planned preservation to mitigate the effect of age (*Pereira et al., 2017*) or infertile patients deferring the transfer owing to the nature of the treatment ('freeze-all' practice) where a receptive endometrium is not required (*Qin et al., 2016*). Data from these publications suggest no difference in the number of oocytes or embryos obtained regardless of the day of the cycle compared with those obtained with conventional protocols. Nonetheless, currently, it remains difficult to translate these preliminary studies to routine clinical practice because of the low number of patients studied (*Sighinolfi et al., 2018*).

To date, limited evidence is available on the use of this strategy in the context of another target of patients who could benefit: the egg donor. Being able to start donor ovarian stimulation at any time regardless of the day of their menstrual cycle, may provide an advantage in this population by allowing a more efficient synchronization between donor and recipient and a better adjustment of the availability window for both. Moreover, the oocyte donor model allows assessment of the unexplored scenario of the efficacy of random ovarian stimulation when fresh embryos are transferred.

The aim of the present study was to investigate whether the clinical outcomes in recipients receiving donated oocytes after random start are comparable to those obtained under conventional ovarian stimulation protocols.

## MATERIALS AND METHODS

### Study design

This retrospective observational cohort study reports data from the Oocyte Donation Programme at Instituto Bernabeu Alicante between January and December 2018. The data included in this study was framed in routine clinical activity. The study conformed to the Declaration of Helsinki for Medical Research about human subjects and was approved by the Institutional Review Board on 12 March 2019 (reference number MR-16/2019).

### Eligibility criteria and ovarian stimulation

All donors included in the study were voluntary, healthy women, aged younger than 32 years, with body mass index (BMI) between 18 and 28 kg/m$^2$, with regular menstrual cycles, i.e. between 26 and 35 days, recruited according to the clinical and legal requirements of the Spanish Assisted Human Reproduction act (RD 9/2014), which includes a psychological interview, gynaecological examination and a rigorous screening for infectious diseases and genetic abnormalities. As routine, contraceptive pills were not necessarily prescribed in the previous cycle; however, donors were asked about any unprotected intercourse on the previous days since last menses before starting ovarian stimulation and exhorted to prevent pregnancy during treatment.

Donor ovarian stimulation was started when contact was made by the clinic interested in carrying out the treatment irrespective of the day of menstrual cycle. Oocyte donor cycles starting stimulation on day 1–3 of the cycle (conventional group) were compared with oocyte donor cycles starting the ovarian stimulation independently of the menstrual cycle (from day 4 onwards [random-start group]). A further sub-group analysis was conducted after segregating the random-start group into mid-late follicular phase (day 4–14) and luteal phase (>day 14).

Donors started stimulation with an initial dose of 150–300 IU/day of FSH (Fostipur®), (Angelini Pharma, Barcelona, Spain) and Bemfola® (Gedeon Richter, Barcelona, Spain). The gonadotrophin starting dose was selected to balance follicular recruitment optimization and minimize the risk of high response. To summarize, the suggested optimal dose was 150 IU for donors with an antral follicle count (AFC) greater than 14, whereas a dose of 225 IU was deemed suitable for donors with 10–14 antral follicles. In cases in which fewer than 10 follicles were observed, a dose of 300 IU was determined. It is important to note that, in line with clinician discretion, these doses could be adjusted based on the donor's BMI. Donors were monitored from day 5–6 of stimulation by transvaginal ultrasound scans every 2–3 days and underwent a standard daily fixed antagonist protocol with a gonadotrophin releasing hormone (GnRH) antagonist (Cetrotide®) (Merck-Serono, Madrid, Spain) starting on day 5 of stimulation. Final oocyte maturation was induced with 0.2 mg of a GnRH agonist (Decapeptyl 0.1 mg®) (Ipsen Pharma, Barcelona, Spain) when at least three follicles wider than 17 mm were detected by ultrasound. Oocyte aspiration was carried out 36 h after induction by transvaginal ultrasound-guided needle-aspiration.

### Recipients and endometrial preparation

Recipients were women aged under 50 years with normal uterine cavity that attended the clinic to undergo IVF using donated oocytes. To assess the uterine cavity, transvaginal ultrasound was used. Any abnormal uterine findings detected during the ultrasound underwent further evaluation via three-dimensional scan, hysteroscopy, or both. Recipients with uterine distortion caused by uterine malformations or fibroids invading the cavity were subsequently excluded. In patients with regular ovarian function, a GnRH analogue (Gonapeptyl 3.75 mg®) (Ipsen-Pharma, Barcelona, Spain) was administered in the mid-luteal phase of the previous cycle for pituitary desensitization. Subsequently, for endometrial preparation, they were subjected to standard substitutive hormonal therapy with transdermal oestrogen (Evopad 50®) (Janssen-Pharmaceutica, Beerse, Belgium)

or oral oestradiol valerate (Progynova®) (Delpharm, Boulogne-Billancourt, France) at increasing doses for at least 12 days. Endometrial thickness measuring 7 mm or wider and trilaminar appearance at ultrasound were confirmed before oocyte allocation. Micronized progesterone supplementation started with intravaginal capsules 200 mg/8 h (Utrogestan®) (SEID, Barcelona, Spain) as soon as optimal fertilization was confirmed in the laboratory.

Recipients were carefully matched with donors, prioritizing shared phenotypes, blood groups and genetic compatibility for carrier screening tests, without the use of randomization.

The laboratory and clinical outcomes per embryo transfer were assessed. Circulating beta-HCG levels were determined 13 days after donation and, in case of a positive test result, the presence of a gestational sac was confirmed by ultrasound after 5 weeks. In pregnant women, the hormonal treatment was sustained for 12 weeks.

### Laboratory procedures

Retrieved oocytes were denuded and metaphase II (MII) oocytes were either anonymously assigned to their matched recipients or vitrified following the Cryotop protocol with Kitazato solutions for deferred donation.

In brief, oocytes were first equilibrated in a solution containing 7.5% (volume per volume) ethylene glycol, 7.5% (volume per volume) dimethylsulphoxide in M-199 medium. They were then transferred to vitrification solution containing 15% (volume per volume) EG, 15% (v/v) dimethylsulphoxide, and 0.5 M trehalose, washed thoroughly to eliminate leftover equilibration solution, and loaded in the tip of the Cryotop before plunging in liquid nitrogen. The procedure, from exposure of the oocytes to vitrification solution until the plunge in liquid nitrogen, is completed in 50–60 s.

For warming, the tip of the device was submerged in thawing solution (1M trehalose) at 37°C, as fast as possible. Oocytes were recovered from thawing solution in 1 min and transferred to dilution solution (0.5M trehalose, room temperature) for 3 min, followed by 5 min in washing solution (no osmotic agents, room temperature).

Oocytes were fertilized by intracytoplasmic sperm microinjection (ICSI). Sixteen to 18 h after insemination, oocytes showing two pronuclei and two polar bodies were considered correctly fertilized and were disposed individually in 30-$\mu$l micro drops of pre-equilibrated continuous culture media (Global Total®) (LifeGlobal, Guildford, CT, USA) in 5% $O_2$ 6% $CO_2$ at 37°C and cultured to day 5–6 blastocyst stage. Blastocyst were graded according to Istanbul consensus scoring on embryo assessment (*Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011*). Embryos of the highest quality were selected to be transferred and supernumerary good-quality blastocysts were cryopreserved. Embryo transfer was cancelled in the absence of viable embryos or in patients failing to reach adequate endometrium thickness, with the whole cohort of good-quality embryos being cryopreserved.

Where preimplantation genetic testing for aneuploidies (PGT-A) was indicated, e.g. recurrent pregnancy losses, implantation failure or abnormal FISH in spermatozoa), zona pellucida drilling was carried out on day 3 and laser-assisted (LYKOS, Hamilton Thorne, Beverly, MA, USA) trophectoderm biopsy of day 5–6 hatching blastocyst was carried out. Biopsied blastocysts were individually vitrified, and trophectoderm cells were processed for genetic analysis. Genetic analysis was carried out using Veriseq-NGS (Illumina, San Diego, CA, USA), with previous whole genome amplification using SurePlex DNA Amplification System (Illumina, San Diego, CA, USA), according to the manufacturer's protocols. In Veriseq protocol, the sequencing platform used was the MiSeq System (Illumina®, San Diego, USA). For chromosome analysis, the BlueFuse Multi software (Illumina®, San Diego, USA) was used for each corresponding technique. Embryos were reported as euploid if the analysed sample contained less than 25% of aneuploid cells, mosaic if it contained between 25% and 50% of aneuploid cells in one or more chromosomes, and aneuploid if the percentage of aneuploidy was over 50%. The detection limit for the segmental aneuploidies was 8 Mb.

### Study outcomes

The primary outcome of this study was the live birth rate (LBR), defined as deliveries with at least one live born infant after 23 weeks of gestation per embryo transfer cycle. Secondary outcomes analysed included fertilization, aneuploidy rate, survival rate after warming oocytes (number of surviving oocytes divided by the number of warmed oocytes), usable embryos (defined as the total number of embryos of the cohort: transferred plus cryopreserved) biochemical pregnancy (detection of circulating beta-HCG at 13 days after donation), clinical pregnancy (defined as the presence of a gestational sac confirmed by ultrasound after 5 weeks), implantation (number of gestational sacs observed divided by the number of embryos transferred), and early miscarriage (intrauterine pregnancy loss before 10 gestational weeks on ultrasound) (*Kolte et al., 2015*; *Zegers-Hochschild et al., 2017*). The following parameters of donor ovarian stimulation were explored: total gonadotrophin dose, stimulation length, cancellation rate, retrieved oocytes and metaphase II (MII).

### Statistical analysis

Continuous variables were presented as mean, SD and 95% confidence intervals. The Shapiro–Wilk test was used to assess whether the continuous variables were normally distributed. The Kruskal–Wallis test and Wilcoxon rank sum test were used for comparing continuous variables between groups, as appropriate. Categorical variables were expressed as percentage and were compared using the Pearson's chi-squared test or Fisher's exact test. In addition, multivariable binary logistic regression analysis was used to control for potential factors that may confound reproductive outcomes, namely donor age, BMI, smoking habit, parity, number of donated MII, number of embryos transferred, endometrial thickness and sperm source. Crude and adjusted odds ratios with 95% confidence intervals were calculated. $P < 0.05$ was considered statistically significant. R Statistical Software, version 4.2.0 and the Statistical Package for the Social Sciences, version 23.0 (SPSS, Chicago, IL, USA) were used for statistical analysis.

## RESULTS

The participant flow in the study is presented in FIGURE 1. Among the 891 egg donors included in the study, 223 started ovarian stimulation on day 1–3 of the menstrual cycle whereas 668 began in the mid to late-follicular phase ($n = 388$) or luteal phase ($n = 280$). The distribution of the ovarian stimulations according to the

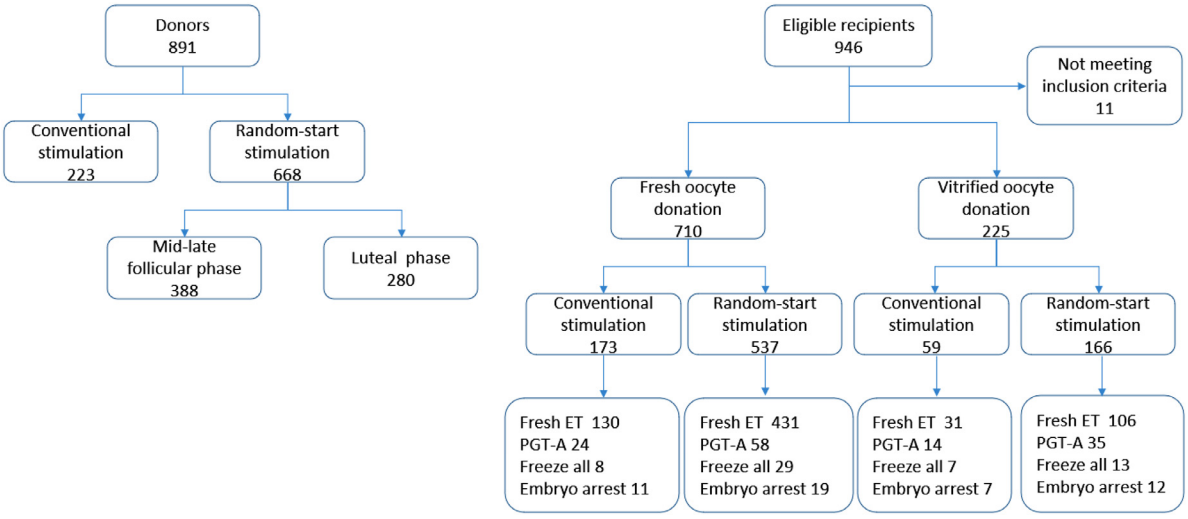


**FIGURE 1** The distribution of oocyte donors and matched recipients according to the start day of ovarian stimulation. ET, embryo transfer; PGT-A, preimplantation genetic testing for aneuploidy.

starting day of the menstrual cycle was plotted (FIGURE 2).

Donor age ranged from 18–32 years, average 25.6 ± 4.4 and 25.6 ± 4.1 for control and random-start group ($P = 0.8$), respectively. Regarding baseline characteristics (previous treatments, BMI, parity, antral follicle count and smoking habit) no significant differences between donors in both treatment groups were found (TABLE 1).

Overall, cycle characteristics were similar between conventional versus random-start stimulation cycles in total dose of gonadotrophins (2041.5 ± 645.3 and 2068.1 ± 667.5), and duration of stimulation (10.2 ± 1.8 and 10.1 ± 1.7), respectively. Additionally, the number of collected eggs were also comparable (17.6 ± 8.8 versus 17.2 ± 8.5, $P = 0.6$), as well as for MII (13.8 ± 7.1 versus 13.5 ± 7.0, $P = 0.6$). The treatment cancellation rates were similar between the groups (4% versus 3.5%, $P = 0.8$).

Within the study group, a sub-group analysis showed significant differences in the number of days of stimulation (10.2 ±

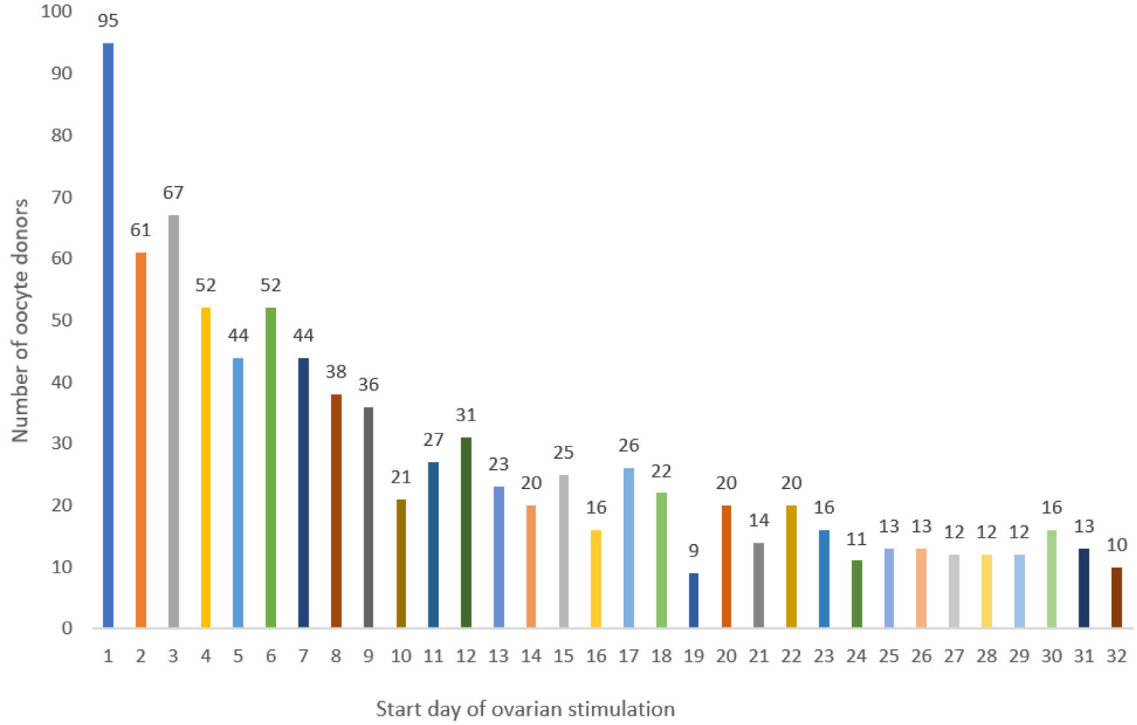


**FIGURE 2** Case distribution among oocyte donors categorized by the day the ovarian stimulation process is started.

**TABLE 1 DEMOGRAPHIC AND OVARIAN STIMULATION CYCLE CHARACTERISTICS OF OOCYTE DONORS**

| Characteristics | Conventional (*n* = 223) | 95% CI | Random start (*n* = 668) | 95% CI | Estimated difference (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Age, years | 25.6 (4.4) | 25 to 26 | 25.6 (4.1) | 25 to 26 | −0.07 (−0.73 to 0.58) | 0.8[a] |
| Previous cycles | 3.1 (2.2) | 2.8 to 3.4 | 3.0 (2.2) | 2.8 to 3.2 | 0.08 (−0.25 to 0.42) | 0.7[a] |
| Smoking habit | 92 (41.3%) | 35% to 48% | 309 (46.3%) | 43% to 50% | | 0.2[c] |
| Parity | 112 (50.2%) | 44% to 57% | 370 (55.4%) | 52% to 59% | | 0.2[c] |
| AFC | 17.0 (5.7) | 16 to 18 | 15.9 (4.8) | 16 to 16 | 1.1 (−0.08 to 1.69) | 0.070[a] |
| BMI, kg/m$^2$ | 22.2 (2.4) | 22 to 23 | 22.0 (2.6) | 22 to 22 | 0.19 (−0.19 to 0.56) | 0.3[a] |
| Gonadotrophin | | | | | | 0.5[c] |
| Fostipur | 105 (47.1%) | 40% to 54% | 296 (44.3%) | 41% to 48% | | |
| Bemfola | 118 (52.9%) | 46% to 60% | 372 (55.7%) | 52% to 59% | | |
| Starting dose of Gonadotrophin, IU | | | | | | 0.3[c] |
| 150 | 71 (31.8%) | 26% to 38% | 181 (27.1%) | 24% to 31% | | |
| 225 | 107 (48.0%) | 41% to 55% | 322 (48.2%) | 44% to 52% | | |
| 300 | 45 (20.2%) | 15% to 26% | 165 (24.7%) | 22% to 28% | | |
| Total dose of Gonadotrophin, IU | 2041.5 (645.3) | 1956 to 2127 | 2068.1 (667.5) | 2017 to 2119 | −27 (−126 to 73) | 0.5[a] |
| Duration of Stimulation, days | 10.2 (1.8) | 10 to 10 | 10.1 (1.7) | 9.9 to 10 | 0.18 (−0.09 to 0.45) | 0.3[a] |
| Cancellation rate | 9 (4.0%) | 1% to 7% | 24 (3.6%) | 2% to 5% | | 0.8[b] |
| Oocytes retrieved, *n* | 17.6 (8.8) | 16 to 19 | 17.2 (8.5) | 17 to 18 | 0.33 (−1.0 to 1.7) | 0.6[a] |
| Mature oocytes (MII), *n* | 13.8 (7.1) | 13 to 15 | 13.5 (7.0) | 13 to 14 | 0.18 (−0.79 to 1.4) | 0.6[a] |

Data presented as mean (SD) or number (%).

[a] Wilcoxon rank sum test.

[b] Fisher's exact test.

[c] Pearson's chi-squared test.

AFC, antral follicular count; BMI, body mass index; MII, metaphase II.

1.8 versus 9.8 ± 1.7 versus 10.4 ± 1.7, $P < 0.001$) and total dose of gonadotrophin (2041.5 ± 645.3 versus 2003.2 ± 647.3 versus 2158.2 ± 685.7, $P = 0.010$) when comparing the conventional, mid/late follicular and luteal phase groups, respectively (TABLE 2).

No adverse events were reported in conventional group, whereas one case of ovarian hyperstimulation syndrome was described in one donor who started stimulation in the luteal phase due to an unnoticed early pregnancy established concomitant with the beginning of ovarian stimulation. In this case, the patient requested termination of the pregnancy and was discharged 9 days later for additional outpatient follow-up, during which she showed complete resolution of her ovarian hyperstimulation syndrome.

A total of 946 matched recipients were initially evaluated. Of those, 11 patients were excluded owing to uterine cavity abnormalities, leaving 935 patients for analysis, 710 receiving fresh oocytes and 225 receiving vitrified oocytes (FIGURE 1). Laboratory and clinical outcomes for each group were collected.

In recipients receiving a fresh embryo transfer after synchronized fresh egg donation ($n = 561$), no differences were found between groups in recipient age, sperm source, endometrial thickness, or days of endometrial preparation. Number of donated eggs, fertilization rate and usable embryos were also comparable. The mean number of transferred embryos was slightly higher in random-start group (1.1 ± 0.3 versus 1.2 ± 0.4, $P = 0.048$), whereas the number of surplus blastocyst stage embryos suitable for cryopreservation was comparable (3.1 ± 2.1 versus 3.0 ± 2.0, $P = 0.5$). The between-group comparisons showed comparable biochemical pregnancy (63.8% and 63.3%, $P = 0.9$), clinical pregnancy (54.6% and 56.1%, $P = 0.8$), implantation (55.6% and 52.3%, $P = 0.5$), early miscarriage (11.3% and 16.5%, $P = 0.3$) and live birth rate (47.7% versus 46.6%, $P = 0.7$) per embryo-transfer (TABLE 3). After accounting for the confounding factors donor age, BMI, smoking habit, parity, number of donated MII, number of embryos transferred, endometrial thickness and sperm source in our adjusted analysis, pregnancy outcomes were found to be consist between the two groups. There were no statistically significant differences observed, with odds ratios and 95% confidence intervals as follows (OR 0.91, 95% CI 0.60 to 1.38, $P = 0.660$) for biochemical pregnancy (OR 0.99, 95% CI 0.66 to 1.48, $P = 0.950$) for clinical pregnancy, and (OR 0.88, 95% CI 0.48 to 1.58, $P = 0.681$) for live birth (TABLE 4).

As shown in TABLE 5, we also analysed 225 ICSI cycles of egg donation using oocytes vitrified after conventional ($n = 59$) or random-start ovarian stimulation ($n = 166$).

**TABLE 2 COMPARISON OF DEMOGRAPHIC AND OVARIAN STIMULATION CYCLE CHARACTERISTICS, SUB-GROUP ANALYSIS**

| Characteristics | Conventional, (*n* = 223) | 95% CI | Mid-late follicular (*n* = 388) | 95% CI | Luteal (*n* = 280) | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| Age, years | 25.6 (4.4) | 25 to 26 | 25.4 (4.1) | 25 to 26 | 25.9 (4.2) | 25 to 26 | 0.3[a] |
| Previous cycles | 3.1 (2.2) | 2.8 to 3.4 | 3.0 (2.2) | 2.8 to 3.2 | 3.0 (2.1) | 2.8 to 3.3 | 0.9[a] |
| Smoking habit | 92 (41.3%) | 35% to 48% | 184 (47.4%) | 42% to 53% | 125 (44.6%) | 39% to 51% | 0.3[c] |
| Parity | 112 (50.2%) | 44% to 57% | 205 (52.8%) | 48% to 58% | 165 (58.9%) | 53% to 65% | 0.12[c] |
| AFC | 17.0 (5.7) | 16 to 18 | 16.0 (5.1) | 16 to 17 | 15.7 (4.4) | 15 to 16 | 0.12[a] |
| BMI, kg/m$^2$ | 22.2 (2.4) | 22 to 23 | 22.0 (2.5) | 22 to 22 | 22.0 (2.6) | 22 to 22 | 0.5[a] |
| Gonadotrophin | | | | | | | 0.3[c] |
| Fostipur | 105 (47.1%) | 40% to 54% | 180 (46.4%) | 41% to 51% | 116 (41.4%) | 35% to 47% | |
| Bemfola | 118 (52.9%) | 46% to 60% | 208 (53.6%) | 49% to 59% | 164 (58.6%) | 53% to 65% | |
| Starting dose of Gonadotrophin, IU | | | | | | | 0.5[c] |
| 150 | 71 (31.8%) | 26% to 38% | 110 (28.4%) | 24% to 33% | 71 (25.4%) | 20% to 31% | |
| 225 | 107 (48.0%) | 41% to 55% | 185 (47.7%) | 43% to 53% | 137 (48.9%) | 43% to 55% | |
| 300 | 45 (20.2%) | 15% to 26% | 93(24.0%) | 20% to 29% | 72 (25.7%) | 21% to 31% | |
| Total dose of gonadotrophin, IU | 2041.5 (645.3) | 1956 to 2127 | 2003.2 (647.3) | 1939 to 2068 | 2,158.2 (685.7) | 2077 to 2239 | 0.010[a] |
| Duration of stimulation, days | 10.2 (1.8) | 10 to 10 | 9.8 (1.7) | 9.6 to 10.0 | 10.4 (1.7) | 10 to 11 | <0.001[a] |
| Cancellation rate | 9 (4.0%) | 1% to 7% | 14 (3.6%) | 2% to 5% | 10 (3.6%) | 1% to 6% | 0.9[b] |
| Oocytes retrieved, *n* | 17.6 (8.8) | 16 to 19 | 17.4 (8.9) | 17 to 18 | 17.0 (8.0) | 16 to 18 | 0.9[a] |
| Mature oocytes, MII | 13.8 (7.1j) | 13 to 15 | 13.5 (7.1) | 13 to 14 | 13.4 (6.7) | 13 to 14 | 0.8[a] |

Data presented as mean (SD) or *n* (%).

[a] Kruskal–Wallis rank sum test.

[b] Fisher's exact test.

[c] Pearson's chi-squared test.

AFC, antral follicular count; BMI, body mass index; MII, metaphase II.

No differences were observed in the average number of warmed oocytes (11.0 ± 2.2 and 11.2 ± 2.1, $P = 0.5$), survival rate (86.7% and 87.8%, $P = 0.6$), and fertilization rate (71.4% and 70.1%; $P = 0.4$). For recipients receiving a fresh embryo transfer (31 recipients in conventional and 106 recipients in random-start group), the number of embryos transferred (1.1 ± 0.3 and 1.1 ± 0.3; $P = 0.6$), biochemical pregnancy (61.3% and 59.4%; $P = 0.8$), clinical pregnancy (51.6% and 49.1%, $P = 0.8$), implantation (45.7% and 47.4%, $P = 0.9$), early miscarriage (18.8% and 21.2%, $P > 0.9$) and live birth rates (41.9% and 38.7%; $P = 0.7$) were also comparable. Likewise, these findings were consistent with the multivariable-adjusted pregnancy outcomes (TABLE 4).

In 131 treatments in which PGT-A was indicated, a total of 518 blastocysts were biopsied. The reported incidence of aneuploidy (25.3% versus 26.1%, $P = 0.8$) and mosaicism (17.1% versus 17.2%, $P = 0.9$) were comparable in embryos derived from oocytes coming from conventional versus random-start stimulations (TABLE 6).

## DISCUSSION

Our extensive observational study suggests that the likelihood of live birth in recipients who receive oocytes from random-start ovarian stimulation protocols, initiated at any point in the menstrual cycle, is comparable to that of recipients who receive oocytes from conventional ovarian stimulation protocols started on days 1–3 of the cycle. Importantly, a similar euploidy rate was demonstrated in embryos derived from the random approach compared with conventional controls.

Three separate theories of follicular recruitment have been proposed to explain the initiation of the stimulation process irrespective of the phase of menstrual cycle (*Baerwald et al., 2012*): the single recruitment episode suggests that a dominant ovulatory follicle is selected from a single follicular cohort that emerges during the mid-follicular phase following luteal regression; the follicular waves theory suggests that at least two cohorts of antral follicles emerge during the ovarian cycle, with a dominant ovulatory follicle developed in the final wave of the inter-ovulatory interval whereas preceding waves are anovulatory; finally, the theory of continuous recruitment suggests that small antral follicles (4–6 mm) grow and regress constantly throughout the inter-ovulatory interval and the dominant ovulatory follicle is selected, purely by chance, from the pool following luteal regression. Our findings, exploring random-start ovarian stimulation protocols in oocyte donors seem to support the continuous recruitment theory.

Most of the published research on random-start ovarian stimulation derives from women requiring urgent ovarian stimulation before gonadotoxic therapy for oncologic

**TABLE 3 CHARACTERISTICS OF RECIPIENTS, AND LABORATORY AND CLINICAL OUTCOMES AFTER DONATION OF FRESH OOCYTES**

| Characteristics | Conventional (*n* = 173) | 95% CI | Random start (*n* = 537) | 95% CI | Estimated difference (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Recipient age, years | 41.5 (4.2) | 41 to 42 | 41.4 (4.3) | 41 to 42 | 0.12 (−0.60 to 0.85) | 0.7[a] |
| Endometrial thickness, mm | 8.6 (1.7) | 7.9 to 9.2 | 7.9 (1.9) | 7.4 to 8.4 | 0.68 (−0.13 to 0.41) | 0.1[a] |
| Endometrial preparation, days | 18.1 (3.0) | 16.8 to 19.2 | 18.7 (2.6) | 18.0 to 19.4 | −0.18 (−0.39 to 0.76) | 0.3[a] |
| Sperm source | | | | | | 0.8[b] |
| Partner fresh spermatozoa | 130 (75%) | 68% to 81% | 380 (71%) | 67% to 75% | | |
| Partner frozen spermatozoa | 32 (18%) | 13% to 25% | 112 (21%) | 18% to 25% | | |
| Surgical sperm retrieval | 4 (2.3%) | 0.74% to 6.2% | 16 (3.0%) | 1.8% to 4.9% | | |
| Donor | 7 (4.0%) | 1.8% to 8.5% | 29 (5.4%) | 3.7% to 7.8% | | |
| Donated MII | 10.2 (1.8) | 9.9 to 10 | 10.0 (1.7) | 9.9 to 10 | 0.16 (−0.13 to 0.46) | 0.2[a] |
| 2PN | 7.2 (2.0) | 6.9 to 7.5 | 7.2 (2.0) | 7.0 to 7.3 | 0.07 (−0.28 to 0.42) | 0.4[a] |
| Fertilization rate | 70.9% | 68% to 74% | 71.3 % | 70% to 73% | | 0.9[c] |
| Usable embryos (transferred + vitrified) | 4.0 (2.1) | 3.6 to 4.3 | 4.0 (2.0) | 3.8 to 4.1 | 0.01 (−0.35 to 0.37) | 0.8[a] |
| Patients undergoing fresh embryo transfer, *n* | 130 | | 431 | | | |
| Transferred embryos | 1.1 (0.3) | 1.0 to 1.1 | 1.2 (0.4) | 1.1 to 1.2 | −0.07 (−0.13 to −0.01) | 0.048[a] |
| Vitrified embryos | 3.1 (2.1) | 2.8 to 3.5 | 3.0 (2.0) | 2.8 to 3.2 | 0.13 (−0.23 to 0.48) | 0.5[a] |
| Biochemical pregnancy rate | 83 (63.8%) | 55% to 72% | 273 (63.3%) | 58% to 68% | | 0.9[c] |
| Clinical pregnancy rate | 71 (54.6%) | 46% to 63% | 242 (56.1%) | 51% to 61% | | 0.8[c] |
| Implantation rate | 79/142 (55.6%) | 45% to 64% | 262/501 (52.3%) | 48% to 57% | | 0.5[c] |
| Early miscarriage rate | 8 (11.3%) | 5.3% to 22% | 40 (16.5%) | 12% to 22% | | 0.3[b] |
| Sacs | | | | | | 0.3[b] |
| 1 | 64 (90.1%) | 80% to 96% | 222 (91.7%) | 87% to 95% | | |
| 2 | 6 (8.5%) | 3.5% to 18% | 20 (8.3%) | 5.2% to 13% | | |
| 3 | 1(1.4%) | 0.07% to 8.7% | 0 (0%) | 0.00% to 1.9% | | |
| Live birth rate | 62 (47.7%) | 39% to 56% | 201 (46.6%) | 42% to 52% | | 0.7[c] |

Data presented as mean (SD) or *n* (%)

One late miscarriage occurred in each group.

[a] Wilcoxon rank sum test.

[b] Fisher's exact test.

[c] Pearson's chi-squared test

conditions (*von Wolff et al., 2016*). Additionally, smaller studies have also evaluated the efficiency of this strategy for elective fertility preservation (*Pereira et al., 2017*) and for infertile patients undergoing a freeze-all approach for logistic reasons (*Qin et al., 2016*). Our findings in the oocyte donor population starting ovarian stimulation on any day of the menstrual cycle allow a total disarticulation of menstrual cycle and ovarian stimulation with the generation of competent embryos. Today, oocyte donation makes up an increasingly large percentage of all assisted reproductive technology cycles worldwide (*European IVF-Monitoring Consortium for the European Society of Human Reproduction and Embryology et al., 2021*; *'ART Success Rates | CDC,' 2022*). Much of the current knowledge about the window of implantation, freeze-all and frozen embryo transfer protocols and trigger modalities has been learned through experience and investigations with donor egg cycles. In this way, oocyte donation rounds have played a pivotal role as a scientific tool in studying the menstrual cycle dynamics for improving ovarian stimulation protocols and implantation. The busy modern oocyte donation programmes face several challenges, including the synchronization of donor and recipient cycles. Therefore, starting donor ovarian stimulation irrespective of the phase of the menstrual cycle without adversely affecting oocyte yield or quality could facilitate schedules. Nonetheless, the optimization of ovarian stimulation protocols must invariably be accomplished while maximizing donor safety.

Overall, in terms of ovarian stimulation parameters, the present data showed a comparable consumption of gonadotrophins, GnRH antagonist and stimulation days in random-start cycles compared with conventional controls. The sub-group analysis within the random group showed a significant difference in the number of days of stimulation and gonadotropin consumption, with the highest values when ovarian stimulation was started in the luteal phase compared with the mid/late follicular and conventional groups. Our findings are concordant with previous publications showing the same pattern in oncologic patients undergoing urgent ovarian stimulation and in own-eggs IVF/ICSI cycles. A large analysis in the oncologic group (*von Wolff et al., 2016*) showed an

**TABLE 4 ASSOCIATION BETWEEN OVARIAN STIMULATION REGIMEN AND PREGNANCY OUTCOMES ON CRUDE AND ADJUSTED ANALYSIS**

| Oocytes | Crude OR (95% CI) | *P*-value | Adjusted OR[a] (95% CI) | *P*-value |
|---|---|---|---|---|
| Fresh | | | | |
| Biochemical pregnancy rate | 0.98 (0.65 to 1.47) | 0.917 | 0.91 (0.60 to 1.38) | 0.660 |
| Clinical pregnancy rate | 1.06 (0.72 to 1.58) | 0.758 | 0.99 (0.66 to 1.48) | 0.950 |
| Live birth rate | 0.91 (0.51 to 1.58) | 0.745 | 0.88 (0.48 to 1.58) | 0.681 |
| Vitrified | | | | |
| Biochemical pregnancy rate | 0.89 (0.38 to 2.00) | 0.780 | 0.81 (0.33 to 1.94) | 0.636 |
| Clinical pregnancy rate | 0.90 (0.40 to 2.02) | 0.802 | 0.74 (0.31 to 1.76) | 0.497 |
| Live birth rate | 0.90 (0.28 to 2.64) | 0.853 | 0.93 (0.26 to 3.03) | 0.903 |

[a] Adjusted for donor age, body mass index, smoking habit, parity, number of donated metaphase II cells, number of embryos transferred, endometrial thickness and sperm source.

**TABLE 5 CHARACTERISTICS OF RECIPIENTS, AND LABORATORY AND CLINICAL OUTCOMES AFTER DONATION OF VITRIFIED OOCYTES**

| Characteristics | Conventional (*n* = 59) | 95% CI | Random start (*n* = 166) | 95% CI | Estimated difference (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| Recipient age, years | 40.9 (4.3) | 40 to 42 | 41.6 (3.6) | 41 to 42 | −0.70 (−1.9 to 0.54) | 0.5[a] |
| Endometrial thickness, mm | 8.0 (1.5) | 7.7 to 8.2 | 8.7 (1.8) | 8.5 to 8.9 | −0.55 (−0.9 to 0.04) | 0.2[a] |
| Endometrial preparation, days | 13.1 (2.8) | 12.0 to 14.1 | 13.8 (3.0) | 12.6 to 14.5 | −0.75 (−1.6 to 0.13) | 0.5[a] |
| Sperm source | NA | NA | NA | NA | NA | >0.9[b] |
| Partner fresh spermatozoa | 38 (64.4%) | 51% to 76% | 107 (64.5%) | 57% to 72% | NA | NA |
| Partner frozen spermatozoa | 14 (23.7%) | 14% to 37% | 43 (25.9%) | 20% to 33% | NA | NA |
| Surgical sperm retrieval | 1 (1.7%) | 0.09% to 10% | 2 (1.2%) | 0.21% to 4.7% | NA | NA |
| Donor | 6 (10.2%) | 4.2% to 21% | 14 (8.4%) | 4.9% to 14% | NA | NA |
| Oocytes warmed | 11.0 (2.2) | 10 to 12 | 11.2 (2.1) | 11 to 12 | −0.20 (−0.85 to 0.45) | 0.5[a] |
| Oocytes injected | 9.5 (1.7) | 9.1 to 10 | 9.8 (1.8) | 9.6 to 10 | −0.29 (−0.82 to 0.24) | 0.2[a] |
| Survival rate | 86.7% | 85% to 91% | 87.8% | 87% to 91% | NA | 0.6[c] |
| 2PN | 6.8 (2.0) | 6.3 to 7.3 | 6.9 (1.9) | 6.6 to 7.2 | −0.08 (−0.68 to 0.52) | 0.7[a] |
| Fertilization rate | 71.4% | 67% to 76% | 70.1% | 68% to 72% | NA | 0.4[c] |
| Usable embryos (transferred + vitrified) | 3.1 (1.8) | 2.6 to 3.5 | 3.4 (2.0) | 3.1 to 3.7 | −0.38 (−0.95 to 0.19) | 0.3[a] |
| Patients undergoing fresh embryo transfer, *n* | 31 | NA | 106 | NA | NA | NA |
| Transferred embryos | 1.1 (0.3) | 1.00 to 1.25 | 1.1 (0.3) | 1.04 to 1.15 | −0.11 (−0.29 to 0.08) | 0.6[a] |
| Vitrified embryos | 2.7 (1.7) | 2.0 to 2.9 | 2.6 (2.0) | 2.4 to 3.0 | −0.27 (−0.81 to 0.27) | 0.9[a] |
| Biochemical pregnancy rate | 19 (61.3%) | 42% to 78% | 63 (59.4%) | 49% to 68% | NA | 0.8[c] |
| Clinical pregnancy rate | 16 (51.6%) | 33% to 70% | 52 (49.1%) | 39%,59% | NA | 0.8[c] |
| Implantation rate | 16/35 (45.7%) | 28 to 62 | 55/116 (47.4%) | 38 to 58 | NA | 0.9[c] |
| Early miscarriage rate | 3 (18.8%) | 5.0% to 46% | 11 (21.2%) | 12% to 35% | NA | >0.9[b] |
| Sacs | NA | NA | NA | NA | NA | >0.9[b] |
| 1 | 16 (100%) | 76% to 100% | 49 (94.2%) | 83% to 98% | NA | NA |
| 2 | 0 (0%) | 0.00% to 24% | 3 (5.8%) | 1.5% to 17% | NA | NA |
| 3 | 0 (0%) | 0.00% to 24% | 0 (0%) | 0.00% to 24% | NA | NA |
| Live birth rate | 13 (41.9%) | 24% to 60% | 41 (38.7%) | 30% to 49% | NA | 0.7[c] |

Data presented as mean (SD) or *n* %.

N.A., not applicable.

[a] Wilcoxon rank sum test.

[b] Fisher's exact test.

[c] Pearson's chi-squared test.

2PN, two pronuclei.

**TABLE 6 MOSAICISM AND ANEUPLOIDY RATES AFTER PREIMPLANTATION GENETIC TESTING**

| Characteristics | Conventional (*n* = 38) | Random start (*n* = 93) | *P*-value |
|---|---|---|---|
| Biopsied embryos | 146 | 372 | NA |
| Mean biopsied embryos | 3.8 (1.9) | 4.0 (1.5) | 0.1[a] |
| Mosaicism rate | 25 (17.1%) | 64 (17.2%) | 0.9[b] |
| Aneuploidy rate | 37 (25.3%) | 97 (26.1%) | 0.8[b] |

Data presented as mean (SD) or *n* %.
[a] Wilcoxon rank sum test.
[b] Pearson's Chi-squared test.
NA, not applicable.

increased number of days of gonadotrophin stimulation (11.5 ± 2.2 versus 10.6 ± 2.7 versus 10.8 ± 2.4), and total dose of gonadotrophins (2970 ± 1145 versus 2595 ± 980 versus 2496 ± 980) in the luteal phase group versus day 6–14 and day 1–5 groups, respectively; whereas a retrospective study (*Qin et al., 2016*) showed a similar trend in IVF/ICSI freeze-all cycles: longer ovarian stimulation (10.9 ± 3.4 versus 11.4 ± 3.1 versus 8.9 ± 1.4) and higher human menopausal gonadotrophin consumption per day (169.4 ± 28.1 versus 159.9 ± 11.9 versus 149.2 ± 14.6) in the luteal phase starting group versus late follicular and conventional groups, respectively. Apparently, whether an ovarian stimulation is initiated in a 'luteal/endogenous progestagenic environment' a longer stimulation and higher FSH consumption is expected, and even though the exact mechanisms explaining these findings are still a matter of research, they seem to be associated with a potent suppression of the hypophyseal activity induced by the elevated levels of progesterone in the luteal phase. In a safety note, the competence of embryos coming from oocytes generated during luteal phase stimulations have been demonstrated to be of good quality and performance in cohort followed up studies (*Jiang et al., 2022*). As an additional important remark, however, luteal phase stimulation in a (potentially fertile) population like oocyte donors carries another potential significant risk: the initiation of a stimulation process concomitantly with an inadvertent pregnancy. During the timeframe of our study, our group reported on the occurrence of OHSS after a GnRH agonist trigger in the random-start protocol in an egg-donor owing to the concomitant presence of an undetectable pregnancy during ovarian stimulation (*Castillo et al., 2020*). All in all, these findings suggest that luteal phase stimulation should be withheld in oocyte donors, perhaps with the exception of specific groups in which the probability of pregnancy becomes negligible, i.e. tubal blockage, carriers of intra-uterine device, implant contraceptive and same-sex or azoospermic partners. The same recommendations could be extrapolated to the group of women seeking for planned fertility preservation. On the contrary, initiating an ovarian stimulation process at any moment during the follicular phase up to the pre-ovulatory period, i.e. below day 14, seems to be safe, efficient and convenient for egg donors with the additional advantages of facilitating scheduling and synchronizing with the recipient, and avoiding the use of oral contraceptives for this purpose.

Our study has some limitations. Foremost among these is its retrospective nature, which opens the possibility of inadvertently including confounding factors, introducing selection bias and challenges in maintaining precise experimental controls. Consequently, it is important to exercise caution when interpreting the data. Moreover, certain variables, such as the anti-Müllerian hormone levels of donors, were unavailable for our analysis and merit investigation in prospective trials. Additionally, we must acknowledge that our donor classification relied on the commencement of menstruation. Unfortunately, the ovulation status in the luteal phase subgroup was not consistently documented, implying that an indeterminate number of donors in this category may not have been in a genuine luteal phase.

In matched recipients, while acknowledging some variations in the stimulation protocols across trials, our data provide additional support for the viability of oocytes obtained from random-start protocols, as previously described in oncologic patients (*von Wolff et al., 2016*) and in the freeze-all IVF/ICSI population (*Qin et al., 2016*). In recipients receiving fresh embryos for transfer after a fresh oocyte donation, the inter-group comparisons showed similar biochemical pregnancy, clinical pregnancy and live birth rates per embryo-transfer in the conventional versus random-start group. After adjusting for confounding factors, the odds of pregnancy outcomes were not significantly different, suggesting that random start protocols had no discernible effect on oocyte competence. Of note, the number of surplus good-quality blastocyst stage embryos suitable for cryopreservation was also similar. In a further note of reassurance, the yield of cryopreserved eggs derived from random-start protocols showed comparable results to those generated after a conventional ovarian stimulation in post-warming tolerance, fertilization rate and reproductive outcomes in recipients. Furthermore, the reproductive outcomes from cryopreserved eggs, compared with fresh eggs derived from random-start protocols, were also similar. In contrast to previous studies in which oocytes and embryos were cryopreserved after random start, the present study is, to our knowledge, the first to provide data on the performance after the transfer of fresh embryos derived from random-start protocols. Finally, when analysing PGT-A cycles derived from random-start protocols, our data showed a similar rate of euploid embryos compared with conventional protocols. Taken altogether, and even acknowledging the inherent limitations associated with a retrospective data analysis, our findings provide reassurance of a comparable reproductive outcome of oocytes derived from random-start protocols and support the notion that the cohort of follicles recruited after exogenous FSH exposure demonstrate optimal competence, finally providing a rationale for the notion that ovarian stimulation treatment can be started at different times during the menstrual cycle. Long-term studies, however, need to be conducted in the future to assess peri- and post-natal outcomes to confirm the safety of random-start protocols.

In conclusion, in this large observational study, no significant differences were observed in clinical outcomes using

oocytes coming from random-start protocols compared with those proceeding from conventional ovarian stimulation in oocyte donation treatments. Because of longer stimulation, higher FSH consumption and implicit potential risk, however, caution should be exercised for luteal-phase stimulation in egg donors.

## DATA AVAILABILITY

Data will be made available on request.

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## AUTHORS' ROLES

JG, JC, and RB: study conception and design; JG, JC and JT: collection of data; JG, JC, JT, JO, AB: statistical analysis and interpretation of data; JG: wrote the first draft of the manuscript; JC, JT and BL wrote sections of the manuscript; JC, JT, JO, BL, DO, FQ, AB and RB: critical review of the article. All authors agree on the submission of the manuscript.

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