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ORIGINAL ARTICLE *Reproductive endocrinology*

Medroxyprogesterone acetate versus ganirelix in oocyte donation: a randomized controlled trial

R. Beguería, D. García, R. Vassena*, and A. Rodríguez

Clínica EUGIN, Travessera de les Corts 322, 08029 Barcelona, Spain

*Correspondence address. Clínica EUGIN, Travessera de les Corts 322, 08029 Barcelona, Spain. E-mail: rvassena@eugin.es

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STUDY QUESTION: Is oral medroxiprogesterone acetate (MPA) non-inferior compared to ganirelix with respect to the number of mature oocytes (MII) retrieved at ovum pick-up (OPU) in oocyte donation cycles?

SUMMARY ANSWER: MPA is comparable to ganirelix in terms of number of MII retrieved at OPU in oocyte donation cycles.

WHAT IS KNOWN ALREADY: Oral treatment with MPA inhibits the pituitary LH surge during ovarian stimulation in infertile patients. Because of its negative effect on the endometrium, MPA suppression is combined with freeze-all. Published reports indicate that both the number of MII retrieved and pregnancy rates from these oocytes are comparable to short protocol of GnRH agonists during IVF cycles with freeze-all. MPA might allow for more comfortable and cost-effective ovarian stimulation.

STUDY DESIGN, SIZE, DURATION: Randomized clinical trial, open-label, single center, to assess the non-inferiority of MPA (10 mg/day) versus ganirelix (0.25 mg/day) from Day 7, in ovarian stimulation cycles triggered with triptoreline acetate. Trigger criterion was ≥3 follicles of diameter >18 mm.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Overall, 252 oocyte donors were selected (eligible), 216 were randomized and 173 reached OPU: 86 under MPA and 87 under ganirelix. The main outcome was the number of MII retrieved at OPU. Secondary outcomes were embryological laboratory outcomes and reproductive outcomes in recipients. The study was powered to test that the lower limit of the 95% confidence interval of the difference in retrieved MII between groups will be above the non-inferiority limit of −3. Differences were tested using a two-sided Student's *t*-test or a Pearson's Chi^2 test, as appropriate.

MAIN RESULTS AND THE ROLE OF CHANCE: All participants were in their first cycle of oocyte donation. On average, donors were 24 (SD 4.5) years old and with a BMI of 23 (SD 2.9) kg/m^2. Duration of stimulation was similar in both groups (11.2 days), as well as the total gonadotropin dose up to trigger (2162 IU in MPA and 2163 IU in ganirelix). The number of MII retrieved was no different: 15.1 (SD 8.3) with MPA and 14.6 (SD 7.0), 95% CI of the difference −2.78, −1.83 excluding the pre-defined non-inferiority limit (−3). Recipients and embryo transfer (ET) characteristics were also similar between groups. The average age of recipients was 42 (SD 4.8) years and the BMI was 24 (SD 4.4) kg/m^2. The mean number of MII assigned to each recipients was 6.7 (SD 1.2) in MPA and 6.6 (SD 1.2) in ganirelix ($P = 0.58$). MII were fertilized with partner sperm in 84% cycles overall and fertilization rate was 76% in MPA versus 74% in ganirelix ($P = 0.34$). Overall, there was 54% of double ET and 46% of single ET, with 40% of ETs were performed in D5. In spite of similar recipients and cycle characteristics, reproductive outcomes were unexpectedly lower with MPA. Biochemical pregnancy rate was 44 versus 57% ($P = 0.023$); clinical pregnancy rate 31 versus 46% ($P = 0.006$); ongoing pregnancy rate 27 versus 40%, ($P = 0.015$) and live birth rate 22 versus 31%, ($P = 0.10$).

LIMITATIONS, REASONS FOR CAUTION: Although oocyte recipient and ET characteristics are similar among groups, this RCT has been designed under a hypothesis of non-inferiority in the number of MII obtained and recipients were not randomized; therefore, the reproductive outcomes in recipients should be evaluated with extreme caution.

WIDER IMPLICATION OF THE FINDINGS: Ovarian stimulation using MPA for prevention of LH surge yields comparable number of MII oocytes compared to ganirelix in oocyte donation cycles. The unexpected finding in reproductive outcomes should be further investigated.

STUDY FUNDING/COMPETING INTEREST(S): None to report.

TRIAL REGISTRATION NUMBER: EudraCT number: 2015-004328-73; ClinicalTrials.gov Identifier: NCT02796105.

TRIAL REGISTRATION DATE: 29 September 2015 (EudraCT); 9 June 2016 (ClinicalTrials.gov).

DATE OF FIRST PATIENT'S ENROLLMENT: The date of enrollment of the first participant was 07 July 2016, and the last participant last visit in the study was on 10 July 2017.

Key words: oocyte donation / medroxyprogesterone acetate / ganirelix / MII oocytes / RCT / controlled ovarian stimulation / live birth rate

Introduction

Controlled ovarian stimulation protocols combining GnRH antagonist with GnRH agonist have been shown to all but eliminate the risk of ovarian hyperstimulation syndrome (OHSS) (Bodri *et al.*, 2009; Fatemi and Garcia-Velasco, 2015). GnRH antagonists suppress the endogenous LH surge while the GnRH agonist induces the final oocyte maturation, with comparable results to HCG triggering in terms of mature oocytes (MII) retrieved at ovum pick-up (OPU) (Bodri *et al.*, 2010). This protocol is extensively used in oocyte donation (OD) cycles, and, combined with frozen embryo transfer (ET), in IVF or ICSI cycles using the patient's own oocytes (Griesinger *et al.*, 2011).

Estradiol and progesterone regulate hypothalamus function (Messinis, 2006); progesterone secreted by the corpus luteum inhibits GnRH pulsatility and LH secretion (Richter *et al.*, 2002); medroxyprogesterone 17-acetate (MPA) is a synthetic progestin structurally related to progesterone, with high progestational activity and antigonadotropic action. MPA seems to be effective in preventing premature LH surges during controlled ovarian hyperstimulation (Kuang *et al.*, 2015). MPA peak concentration in blood occurs 3 h after oral administration; it has the highest bioavailability (>90%) of all progestins and a half-life of 24 h (Stanczyk *et al.*, 2013). A recent randomized controlled trial (RCT) indicated that MPA was sufficient to prevent the LH rise in women undergoing IVF/ICSI treatment (Dong *et al.*, 2017); moreover, the number of MII retrieved from IVF/ICSI patients treated with MPA, and their reproductive outcomes were comparable to those obtained with short protocol of GnRH agonists during IVF cycles with freeze-all embryos. If further confirmed, these results would lead to the development of more comfortable and user-friendly stimulation regimens, as MPA is administered orally, and to a decrease in stimulation costs which should in turn increase patients' access to assisted reproduction treatments.

The aim of this study is to evaluate the efficacy of medroxyprogesterone acetate in OD cycles compared to ganirelix (GnRH antagonist protocol) in terms of MII collected at OPU.

Materials and Methods

Study oversight

This is a phase IV randomized clinical trial, open-label, comparing MPA 10 mg/day versus ganirelix 0.25 mg/day, in ovarian stimulation of OD cycles triggered with triptoreline 0.3 mg. The study was performed in a fertility clinic between June 2016 and June 2017, after approval from the local Ethics Committee for Clinical Research (CEIC EUGIN, approval code CEUGIN-2015-12) and authorization from the National Authority (Agencia Española de Medicamentos y Productos Sanitarios, approval code 2015-004328-73). The study was registered with EudraCT Number 2015-004328-73 and under the ClinicalTrials.gov Identifier: NCT02796105, and it was completely intramurally funded, with no commercial sponsorship or external support of any kind. The study design fulfilled Consolidated Standards of Reporting Trials (CONSORT) quality standard criteria for randomized trials. The study was conducted in accordance with the principles of the Declaration on Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization.

Study participants

Women between 18 and 35 years old attending the clinic for their first cycle to donate oocytes, who had normally appearing ovaries at transvaginal ultrasound and an antral follicular count >8 were eligible for the study and were invited to participate during the donation screening visit by any of the physicians of the center. All participants gave written informed consent.

Women with irregular menstrual cycles or those that reported taking any type of hormonal treatment in the previous 3 months were excluded. Similarly, participants were withdrawn from the trial if they presented estradiol levels in blood >70 pg/ml on Day 2 of menstrual cycle, suggestive of ovarian follicular cyst with estrogenic activity (Kuang *et al.*, 2015) or if during the stimulation they took any drug that is metabolized in the liver and could interact with MPA metabolism.

Randomization

Participants were randomly allocated in a 1:1 ratio to receive MPA 10 mg/day or ganirelix 0.25 mg/day during the length of the ovarian stimulation. A computer-generated sequence of blocks of 10 subjects to ensure balanced distributions within the study arms was used. Allocation was performed by the pharmacist of the center using a password-protected program. Participants and physicians were not blinded to group assignment due to the different administration route of the drugs in study; however, the main investigator (R.B.) and those involved in data compilation and statistics (D.G., F.F., S.B.) were blinded during the outcomes assessment and statistical analysis, respectively.

Drug regimen and monitoring

Controlled ovarian stimulation started on the second day of the menstrual cycle, with an initial dose of recombinant follicle stimulating hormone (rFSH) (Gonal-F®, Merck, Madrid, Spain) chosen according to age, antral follicle count and BMI (La Marca and Sunkara, 2014; Grisendi and La Marca, 2017). In addition to rFSH, participants received either MPA (Progevera® 10 mg, Pfizer, Spain) or ganirelix (Orgalutran® 0.25 mg/50 ml, Merck Sharp & Dohme Limited, UK). MPA was administered orally

in a single dose each day every evening of the stimulation period until the day of the triptorelin acetate administration (trigger day). The prescribed dose has been used in previous publications to ensure pituitary inhibition (10 mg/day) (Kuang et al., 2015). Ganirelix was administered by subcutaneous daily injections (0.25 mg/day) in the evening, from the seventh day of hormonal stimulation until trigger day.

Monitoring of ovarian stimulation was carried out by 3D-ultrasound (Voluson S6 RIC 5-9W-RS transducer, GE Healthcare Austria) on the seventh day of stimulation and every 2–4 days afterwards. When ≥3 follicles with >18 mm diameter were observed, 0.3 mg of triptorelin acetate (Decapeptyl®, Merck, Madrid-Spain) was administered to trigger ovulation. Ganirelix was administered on the day of trigger only if the time between the last dose of ganirelix and triptorelin acetate exceeded 26 h. OPU was carried out strictly 36 h after triggering in both groups.

Serum FSH, LH, estradiol and progesterone were measured by immunoluminescence (mini VIDAS®, Biomérieux, Spain) just before beginning the ovarian stimulation on the second day of the menstrual cycle on and at each control thereafter until the OPU day.

Participants ended their participation in the study 72 h after OPU, when a routine follow-up call was performed.

Oocytes fertilization and ET

Oocytes were denuded of cumulus cells (Hyase-10 X—Vitrolife®, Göteborg, Sweden) and MII were allocated to recipients (hereafter MPA recipients and ganirelix recipients). Sperm were selected by swim-up. Oocytes were inseminated by ICSI. Injected oocytes were checked 18–20 h post-ICSI for signs of fertilization. Oocytes exhibiting two pronuclei and the extrusion of the second polar body were cultured for 2–5 days before ET (Sage 1-Step—Origio®, Màlov Denmark). Morphological embryo quality was assessed on D2 and D3 by considering aspects like number of cells, symmetry and fragmentation rates, giving them a score between 4 and 10 (Coroleu et al., 2006). The highest quality embryos were chosen for ET and the remaining good quality embryos were cryopreserved.

Oocyte recipients were women under 51 years of age with different indications to receive donor oocytes: advanced maternal age, failed IVF cycles with own oocytes, failed insemination cycles, low ovarian reserve, endometriosis, recurrent miscarriage, genetic or chromosomal abnormalities transmissible to offspring and spontaneous or iatrogenic menopause. In cases of residual ovarian function, the recipient hypophysis was suppressed with GnRH agonists (Triptoreline, 3.75 mg, Decapeptyl 3.75 mg, Ipsen Pharma). Endometrial estrogenic preparation (constant dose) and luteal phase support of recipients has been described previously (Madero et al., 2017).

ET was performed either on D2–3 or D5 of development, with fresh or frozen embryos. If at least five 2PN embryos were available on D1, culture to D5 was proposed. The score system for embryos on D2-D3 was based on: number of cells, cell symmetry, blastomere fragmentation, presence/absence of vacuoles, presence/absence of cytoplasmic ring and embryo shape. The scoring system assigns a default score of 10 to each embryo, and then deducts points depending on the abovementioned factors (Solé et al., 2011). Blastocysts were scored according to Gardner and Lane (1997).

Reproductive outcomes of the recipients' first ET were recorded, namely biochemical, clinical and ongoing pregnancy, and live birth.

Outcome measures

The primary outcome was the number of MII collected at OPU. Secondary outcomes related to donors were as follows: length of stimulation, total dose of rFSH to reach trigger criterion, hormonal profile during controlled ovarian stimulation, and LH surge. The criterion for detection of the LH surge was described as an LH rise of 180% above the last value available for the patient (Testart et al., 1981). Secondary outcomes related to recipients were: fertilization rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate and live birth rate in oocyte recipients.

Statistical analysis

In total, 86 subjects per arm were estimated necessary, i.e. $n = 172$ subjects, to reject a null hypothesis (MPA is inferior to ganirelix by at least three MII at OPU; non-inferiority design) with a 80% power and a 5% error (Julious, 2004). The common standard deviation was assumed to be 7.7, based on the center experience. It was anticipated a drop-out rate of 4.6%, based in the previous experience of the center.

The 95% CI for the differences in MII between groups was calculated by assuming a Student's *t*-distribution. Secondary outcomes were tested for differences by Pearson's Chi^2 or Student's *t*-tests, as appropriate. We used a 'per protocol approach' for the main analysis; the per protocol population included all the donors who received the allocated intervention and reached OPU with no protocol deviation. A further 'intention to treat' analysis, which included the donors who arrived to OPU with some protocol deviation, was performed to corroborate the results.

A per protocol analysis using a multilevel regression was performed to investigate the effect of MPA versus ganirelix on the reproductive outcomes (biochemical, clinical, ongoing pregnancy; and live birth). This analysis included all recipients who arrived to ET. Multilevel analysis allows addressing hierarchical data structures where each donor has several recipients, by decomposing the variance into two levels: cycles (Level 1) nested within donors (Level 2). The models were constrained to be equal across all dyads (donor-recipient), i.e. they included only fixed effects. A model with the main effect of MPA versus ganirelix was constructed; and, additionally the following covariates were added to the main effect: recipient age, fresh versus frozen semen, fresh versus frozen embryo, ET D2–3 versus D5, number of transferred embryos >1 versus 1, recipient smoking status and patches versus oral endometrial preparation. A similar analysis was performed in an intention-to-treat approach where outcome failure included either cycle cancelation or negative reproductive outcome.

All analyses were performed using SPSS version 22.0 and MLwiN 2.31 (Rasbash et al., 2011). A *P*-value <0.05 was set as statistically significant.

Results

Study participants

In total, 252 eligible oocyte donors were selected for the study. Of them, 216 were finally included and randomized to the two study groups and 194 received the allocated treatment, 97 in each group. There were seven cycle cancellations after treatment start: five due low response to ovarian stimulation (two in MPA and three in ganirelix), one due to early ovulation in ganirelix, and one due to an ovarian cyst in MPA. At the end, 173 participants reached OPU, 86 in MPA and in 87 ganirelix, and constituted the per protocol population of donors for the main analysis, while the intention to treat population included 187 participants, 94 in MPA and 93 in Ganirelix. Details of selected, included, excluded and withdrawn participants before OPU are provided in Fig. 1.

The collected oocytes were attributed according to clinical needs to 324 recipients: 161 MPA recipients and 163 ganirelix recipients. Of them, 308 proceeded to ET, constituting the per protocol population of recipients, while 16 cycles were canceled. The reasons for ET cancellation were as follows: vitrification of all embryos ($n = 11$), no

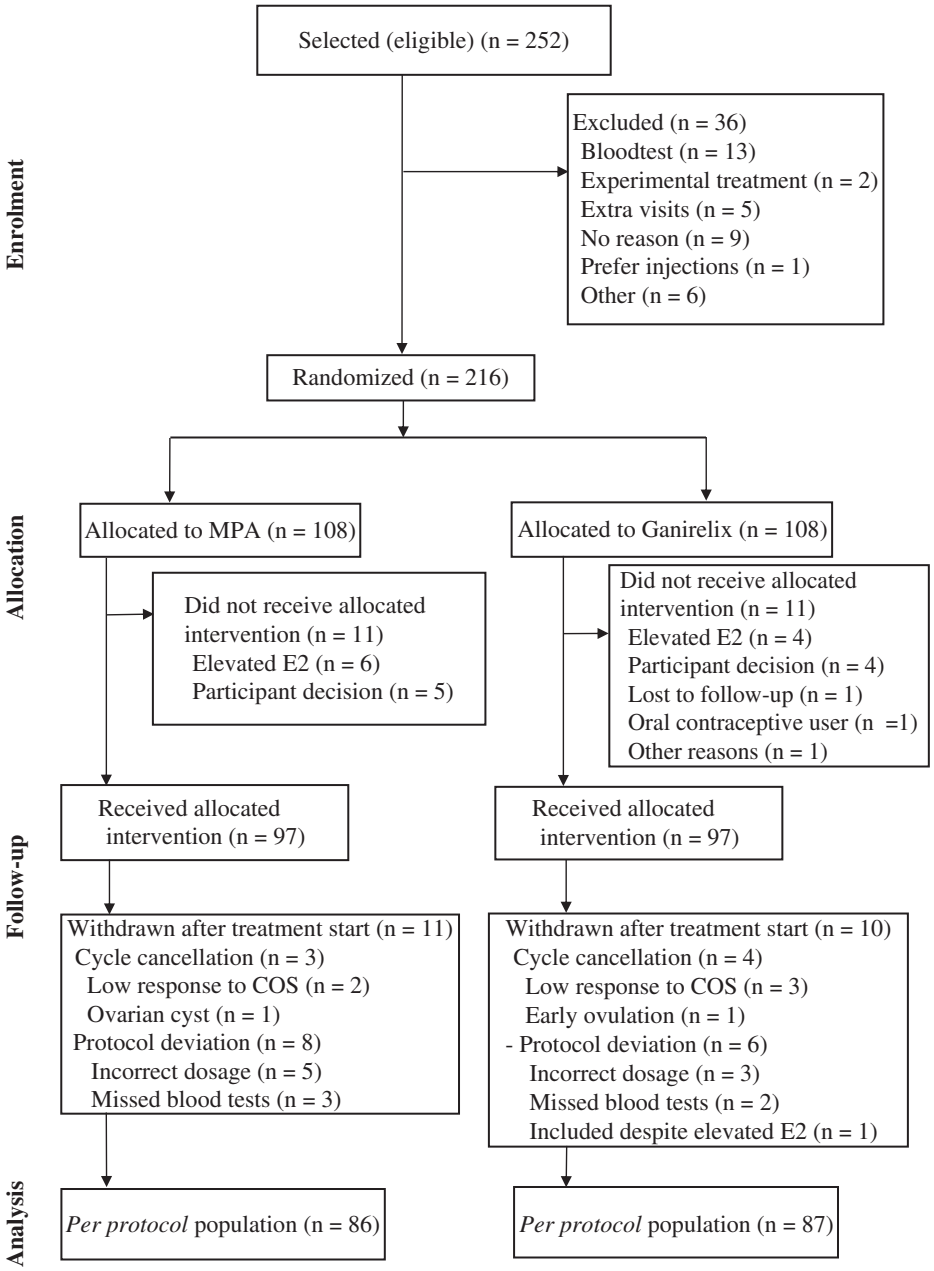

Figure 1 CONSORT flowchart. E2 = Estradiol; COS = controlled ovarian stimulation.

transferrable embryos ($n = 3$), fertilization failure ($n = 1$) and personal reasons ($n = 1$).

The characteristics of oocyte donors and recipients at baseline were well-balanced (Tables I and II). The main indications for which patients underwent treatment with oocytes from donors were advanced maternal age (99, 33%); ovarian failure (95, 29%); and failed IVF cycles with own oocytes (46, 16%).

Outcomes

The number of MII obtained at OPU was similar in the two groups: 15.1 in MPA and 14.7 in ganirelix (difference 0.473 [95% CI: −1.83, 2.78]) in the per protocol main analysis (Fig. 2). These results were corroborated by the intention to treat analysis: 15.0 in MPA and 14.6 in ganirelix (difference 0.344 [95% CI: −1.90, 2.58]).

Table III shows the differences in controlled ovarian stimulation between study groups. The required days of treatment and total dose of rFSH were the 11.20 days on average in both groups. As expected, the time of pituitary inhibition was longer in the study group, as MPA was administered from the beginning of the stimulation (11.9 versus 5.8 days, $P < 0.001$). There were no differences in the number of monitoring controls needed to achieve ovulatory trigger criteria (2.9 controls, on average). The number of follicles with diameters larger than 14 mm was not statistically different (14.7 versus 13.6 follicles, respectively, $P = 0.29$).

Table I Demographic characteristics of oocyte donors overall and by study group.

	Overall *n* = 173	MPA *n* = 86	Ganirelix *n* = 87
Age (y), mean (SD)	24.4 (4.5)	24.7 (4.7)	24.1 (4.3)
Antral follicle count, mean (SD)	21 (8.0)	21.2 (8.2)	20.8 (7.9)
BMI (kg/m^2), mean (SD)	23.0 (2.9)	22.9 (2.9)	23.1 (2.9)
With children, *n* (%)	44 (25.4)	25 (29)	19 (22)
Smoker, *n* (%)	71 (41.0)	36 (42)	35 (40)

MPA = Medroxiprogesterone acetate.

Table II Demographic characteristics of recipients overall and by study group.

	Overall *n* = 308	MPA *n* = 153	Ganirelix *n* = 155
Age (y), mean (SD)	42.0 (4.7)	42.3 (4.5)	41.7 (4.9)
BMI (kg/m^2), mean (SD)	23.9 (4.4)	23.8 (4.4)	24.0 (4.4)
Childless, *n* (%)	216 (70.1)	103 (67.3)	113 (72.9)
Menopausal, *n* (%)	8 (2.6)	6 (3.9)	2 (1.3)
Smoker, *n* (%)	41 (13.8)	25 (17.1)	16 (10.6)
First reception cycle, *n* (%)	296 (94.9)	145 (93.6)	151 (96.2)
History of miscarriage, *n* (%)	81 (28.5)	46 (30.8)	35 (25.9)
Endometrial thickness (mm), mean (SD)	9.9 (1.6)	9.8 (1.6)	9.9 (1.6)

MPA = Medroxiprogesterone acetate.

Progesterone, estradiol, FSH and LH levels determined during all monitoring visits are presented in Fig. 3. The maximum LH value on the day of trigger found in the MPA group was 8.2 IU/ml and the mean value for progesterone on the same day was 1.4 ng/ml. Estradiol mean level on trigger day in the MPA group was 2726 pg/ml and in the ganirelix group was 2336 pg/ml ($P = 0.23$). The hormonal profile of the participants was equivalent in both treatment groups; however, we observe higher levels of hormones on the OPU day in the MPA group. Also, there is a different progression in LH levels; while in the MPA group this hormone is progressively slowed down from the beginning of treatment, in the ganirelix group the descent is more pronounced. No LH surge was detected in either group.

All oocytes were inseminated by ICSI. Donor sperm was used in 16% of cycles. Partner sperm could be fresh or frozen, while donor's was always frozen. The fertilization rate was similar in both groups: 76.0 versus 73.8% ($P = 0.34$). The morphological score of the resulting embryos at Days 2–3 in the cohort was 7.3 versus 7.5, $P = 0.46$. The score of the transferred embryos (8.2 versus 8.0, $P = 0.51$), and the proportion of top quality blastocysts obtained (56.1 versus 55.3%, $P = 0.60$) were similar between groups. Embryos could be transferred fresh or after cryopreservation (40.4%). Embryos were mostly transferred at Days 2–3 of embryo development in both groups (60.4%). Two embryos were transferred in half of the cycles, being DET slightly more common in the MPA group: 58.2 versus 50.3% ($P = 0.17$). Cycles characteristics are detailed in Table IV.

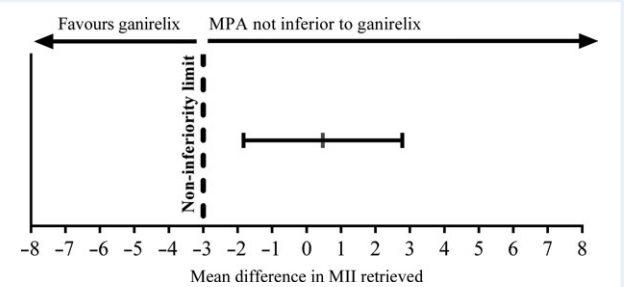

Figure 2 Differences in MII obtained in each group.

Regarding reproductive outcomes in oocyte recipients, we observed significantly worse pregnancy rates in women recipient of oocytes from the MPA group (Table V). Biochemical pregnancy, clinical pregnancy and ongoing pregnancy were, respectively, 13, 15.1 and 13.2% lower in the MPA group. Live birth was 8.7% lower, but this difference was not statistically significant.

The per protocol multilevel analysis confirmed the previous results on pregnancy rated and revealed significance on live birth. Comparing ganirelix versus MPA, the univariate multilevel analysis provided an unadjusted OR [95% CI] of 1.65 [1.05, 4.3] for biochemical pregnancy ($P = 0.032$), 1.86 [1.17, 2.97] for clinical pregnancy ($P = 0.010$), 1.78 [1.09, 2.89] for ongoing pregnancy ($P = 0.022$), and 1.55 [0.91, 2.67] for live birth ($P = 0.11$). The multivariate multilevel analysis provided an adjusted OR [95% CI] of 1.86 [1.15, 3.01] for biochemical pregnancy ($P = 0.012$), 2.29 [1.38, 3.80] for clinical pregnancy ($P = 0.002$), 2.19 [1.31, 3.67] for ongoing pregnancy ($P = 0.004$), and 1.98 [1.10, 3.54] for live birth ($P = 0.023$). Adjusted and unadjusted ORs are displayed in Fig. 4, where we can appreciate the statistical significance of all reproductive outcomes from biochemical pregnancy to live birth at adjusted analysis.

The intention-to-treat multilevel analyses, where the 16 canceled ETs were considered as negative outcomes, provided the following results. Comparing ganirelix versus MPA, the univariate multilevel analysis provided an unadjusted OR [95% CI] of 1.50 [0.87, 3.91] for biochemical pregnancy ($P = 0.14$), 1.74 [1.01, 2.98] for clinical pregnancy ($P = 0.046$), 1.71 [1.00, 2.93] for ongoing pregnancy ($P = 0.05$), and 1.46 [0.81, 2.65] for live birth ($P = 0.21$). The multivariate multilevel analysis provided an adjusted OR [95% CI] of 1.71 [0.96, 3.07] for biochemical pregnancy ($P = 0.07$), 2.17 [1.21, 3.89] for clinical pregnancy ($P = 0.010$), 2.13 [1.19, 3.79] for ongoing pregnancy ($P = 0.011$), and 1.89 [1.00, 3.58] for live birth ($P = 0.05$).

Safety

No serious adverse events were reported by the participants in any of the groups.

Discussion

MPA has shown no significant difference in the number of MII ensuing ovarian stimulation of OD cycles, compared to ganirelix. In agreement with previous studies performed in IVF patients, the number of MII

Table III Controlled ovarian stimulation of oocyte donors overall and by study group. Data are mean (SD).

	Overall *n* = 173	MPA *n* = 86	Ganirelix *n* = 87	*P*-value[a]
Number of control visits,	2.9 (0.9)	2.8 (0.9)	2.9 (1.0)	0.46
Days of stimulation,	11.2 (2.1)	11.2 (1.8)	11.2 (2.4)	0.98
Initial stimulation dose (IU)	194 (31.6)	195 (33.8)	193.1 (29.5)	0.72
Total stimulation dose (IU)	2162.8 (524.6)	2162 (495.2)	2163 (555)	0.99
Follicles ≥14 mm at trigger	14.2 (6.7)	14.7 (7.3)	13.6 (6.0)	0.29

[a]Student's *t*-test.
IU = International units; MPA = Medroxiprogesterone acetate.

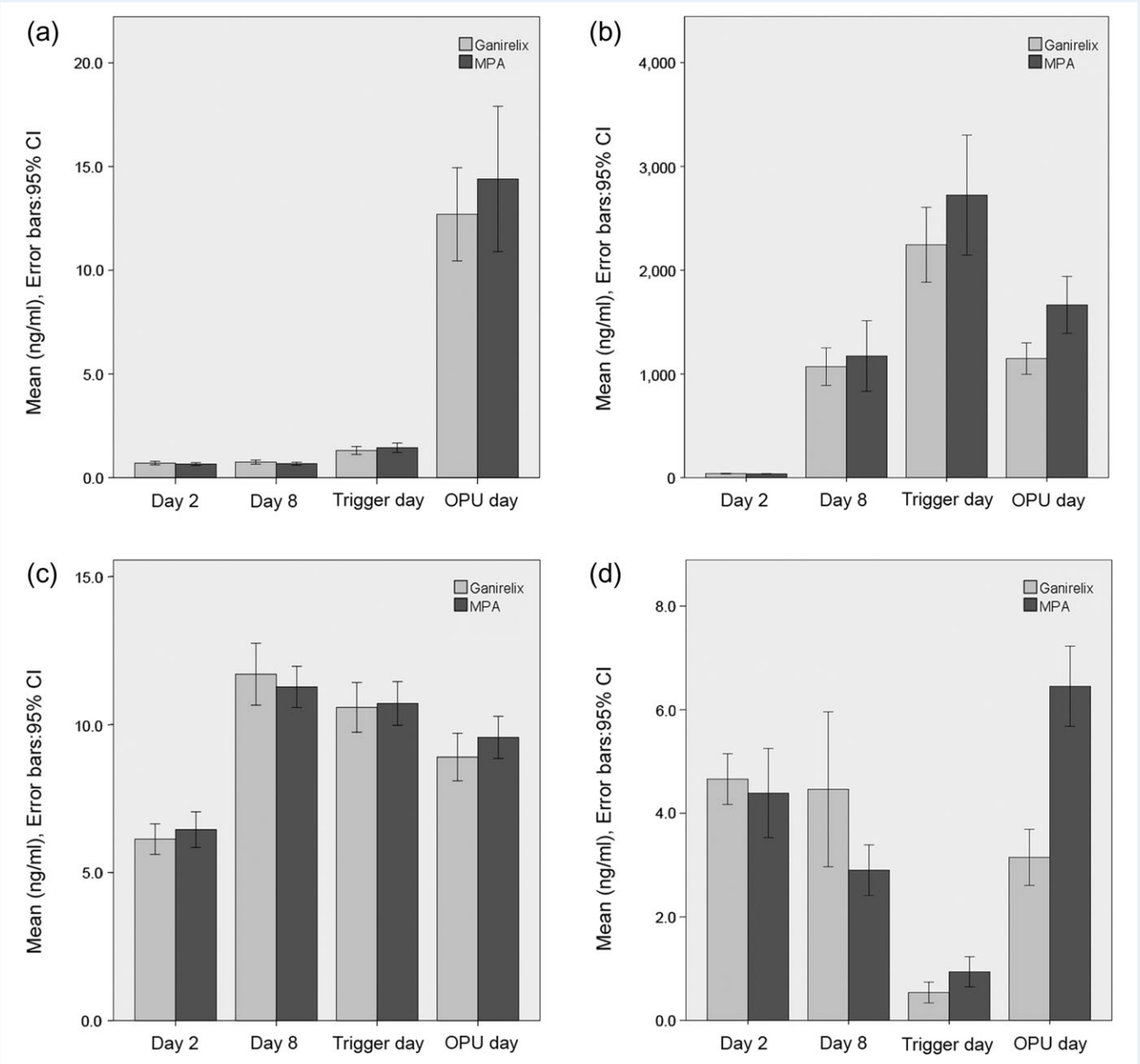

Figure 3 Hormonal profile of oocytes donors from selection day (D2) to oocytes pick-up day (OPU), for medroxiprogesterone acetate (MPA) and ganirelix. (**a**) Progesterone. (**b**) Estradiol. (**c**) FSH. (**d**) LH.

Table IV Characteristics of the recipient cycles by study groups.

	Overall *n* = 307	MPA *n* = 153	Ganirelix *n* = 155	*P*-value[a]
Donor sperm, *n* (%)	48 (15.7)	26 (17.1)	22 (14.3)	0.50
Frozen sperm, *n* (%)	275 (90.2)	136 (89.5)	139 (90.8)	0.69
Allocted MII, mean (SD)	6.7 (1.2)	6.7 (1.2)	6.6 (1.2)	0.58
Number of fertilized oocytes (2PN), mean (SD)	5.0 (1.5)	5.1 (1.4)	4.9 (1.7)	0.27
Fertilization rate %, mean (SD)	74.9 (20.0)	76.0 (18.9)	73.8 (21.0)	0.34
Morphological score of D2–3 embryo cohort, mean (SD)	7.4 (1.0)	7.3 (1.1)	7.5 (1.0)	0.46
Morphological score of D2–3 transferred embryos, mean (SD)	8.1 (1.3)	8.2 (1.3)	8.0 (1.3)	0.51
Top quality blastocysts, *n* (%)	158 (56.0)	74 (56.1)	84 (55.3)	0.60
Day of transfer				
2–3, *n* (%)	186 (60.4)	92 (60.1)	94 (60.6)	0.93
5, *n* (%)	122 (39.6)	61 (39.9)	61 (39.4)	
Embryos transferred				
1, *n* (%)	141 (45.8)	64 (41.8)	77 (49.7)	0.17
2, *n* (%)	167 (54.2)	89 (58.2)	78 (50.3)	
Frozen oocytes cycles, *n* (%)	23 (7.6)	10 (6.8)	13 (8.5)	0.57
Frozen embryos cycles, *n* (%)	122 (40.4)	60 (40.5)	62 (40.3)	0.96
Endometrial preparation				
Patches, *n* (%)	236 (77.9)	122 (81.3)	114 (74.5)	0.30
Oral, *n* (%)	61 (20.1)	25 (16.7)	36 (23.5)	
Natural cycle, *n* (%)	6 (2.0)	3 (2.0)	3 (2.0)	
Contraceptives, *n* (%)	4 (2.6)	0 (0.0)	4 (2.6)	0.05

[a]Student's *t*-test or Pearson's Chi^2 test, as appropriate.
MPA = Medroxiprogesterone acetate.

Table V Reproductive outcomes in recipients overall and by study group. Data are *n*(%).

	Overall *n* = 308	MPA *n* = 153	Ganirelix *n* = 155	*P*-value[a]
Biochemical pregnancy	155 (50.3)	67 (43.8)	88 (56.8)	0.023
Clinical pregnancy	118 (38.3)	47 (30.7)	71 (45.8)	0.006
Ongoing pregnancy	101 (33.3)	40 (26.7)	61 (39.9)	0.015
Live birth	73 (26.3)	31 (22.0)	42 (30.7)	0.10

[a]Pearsons' Chi^2 test.
MPA = Medroxiprogesterone acetate.

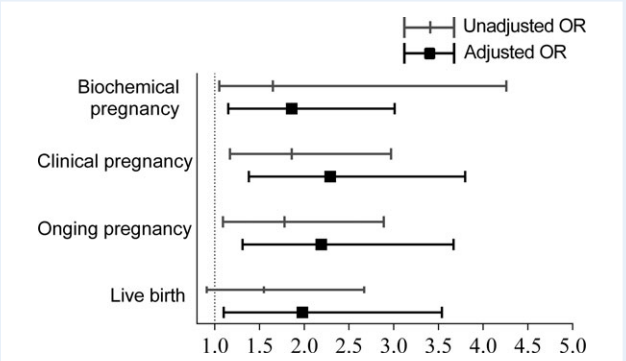

Figure 4 Adjusted and unadjusted odds ratios (OR) for reproductive outcomes. Ganirelix versus medroxiprogesterone acetate (MPA; reference).

retrieved at OPU was similar in MPA and the comparison group (Kuang *et al.*, 2015; Dong *et al.*, 2017; Crha *et al.*, 2018). Moreover, the length of ovarian stimulation and doses of gonadotropins used were equivalent. However, these previous published studies were observational, while this RCT is the first to evaluate MPA for pituitary inhibition in ovarian stimulation of OD cycles.

Higher patient comfort and lower cost of MPA compared to GnRH antagonist would make MPA attractive for controlled ovarian stimulation, where complaints about frequent injections and high costs are common. However, we found worse reproductive outcomes when MPA was used for this purpose.

This RCT was designed and powered to detect non-inferiority between MPA and GnRH antagonist in the number of MII collected as main outcome. One limitation of this RCT is that treatment could not be blinded, due to the different administration route of the drugs in

study. Another limitation is that recipients were not randomized; hence, reproductive results should be interpreted with caution since they might be due to chance. Nevertheless, demographic and cycle characteristics in oocyte recipients' groups were comparable; etiology of infertility and proportion of first donation were also similar between groups, as well as the number of MII assigned to each woman. Our results suggest a possible impairment of oocyte competence that should be confirmed in further studies focused on recipients or patients using their own oocytes, perhaps a more appropriate model for these outcomes, and controlling for all potential confounding factors.

To evaluate the reproductive results, one should consider that, in most studies, MPA has been compared to other pituitary suppressors in a short GnRH agonist protocol, rather than a GnRH antagonist protocol (Kuang *et al.*, 2015; Dong *et al.*, 2017). We, however, used MDA in a GnRH antagonist protocol, as recommended in OD cycles, to reduce the incidence of OHSS (Al-Inany *et al.*, 2007; Bodri *et al.*, 2010). While pituitary inhibition happens within a few hours from the first administration in the GnRH antagonist protocol, pituitary inhibition is preceded by a flare-up in the short GnRH agonist protocol (Kumar and Sharma, 2014). Secondly, rFSH was administered in our work and in a previous study (Crha *et al.*, 2018), while hMG, which contains a small amount of urinary hCG, was used by others (Kuang *et al.*, 2015; Dong *et al.*, 2017). Third, our donors were all triggered with GnRH agonist to minimize the risk of OHSS (Orvieto, 2005; Griesinger *et al.*, 2006) while in the above studies the trigger was performed with hCG (Kuang *et al.*, 2015) or by hCG and triptorelin (Dong *et al.*, 2017).

Importantly, a recent study (Crha *et al.*, 2018) followed the same treatment protocol that we used, comparing MPA versus the antagonist protocol in a small group of 13 oocyte donors that were stimulated with rFSH and the number of collected oocytes and the quality of obtained embryos were not affected. While most research indicates that elevated progesterone levels on trigger day do not have a negative impact on the results of stimulated cycles with MPA after frozen ET (Lu *et al.*, 2016), there are some reports of a negative effect of elevated progesterone on oocyte quality (Requena *et al.*, 2014; Vanni *et al.*, 2017).

Conclusion

In conclusion, MPA in OD cycles triggered with GnRH agonist yields comparable numbers of MII to those obtained using ganirelix in a GnRH antagonist protocol. Reproductive outcomes might be affected by this treatment, and studies powered to detect these outcomes designed studies should clarify this further.

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Authors' roles

R.B: involved in study design, data collection and article preparation. D.G.: involved in study design, coordination, data collection, statistical analysis and article preparation. R.V.: involved in study design, implementation and supervision, expert knowledge and article preparation. A.R. involved in study design, article revision and expert knowledge.

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Conflict of interest

The authors have no conflict of interest to declare.

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