

ARTICLE

Clinical outcomes in oocyte donation cycles: GnRH-antagonists versus progesterone-primed ovarian stimulation with micronized progesterone



BIOGRAPHY

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KEY MESSAGE

Oral natural micronized progesterone (NMP) is a viable alternative to gonadotrophin releasing hormone antagonists in oocyte donation cycles. It is linked to improved fertilization and more usable embryos, with comparable live birth rates. These findings suggest NMP could simplify ovarian stimulation while maintaining clinical outcomes in donor cycles.

ABSTRACT

Research question: In oocyte donation cycles, does the use of oral natural micronized progesterone (NMP) result in comparable clinical outcomes, compared with gonadotrophin releasing hormone (GnRH) antagonist treatment?

Design: Retrospective analysis of 1368 oocyte donation cycles (January 2018 to December 2022), and laboratory ($n = 793$) and clinical outcomes ($n = 645$) in matched recipients. Donors initiated ovarian stimulation in early follicular phase. To prevent a premature LH peak, the study group received natural micronized progesterone orally concurrently with FSH administration, whereas the control group began GnRH antagonist treatment in a flexible protocol. Live birth rate was the primary outcome.

Results: Duration of stimulation and total gonadotrophins dose were comparable between groups. The NMP group yielded significantly higher retrieved oocytes (15.9 ± 8.5 versus 13.1 ± 7.9 ; $P < 0.001$) and mature oocytes (12.8 ± 7.3 versus 11.7 ± 7.3 ; $P = 0.003$), and a lower maturation rate ($80.89 \pm 16.78\%$ versus $89.49 \pm 14.48\%$; $P < 0.001$). These donors had higher fertilization rates (81.3% versus 74.3% ; $P < 0.001$) and number of usable embryos (4.6 ± 2.0 versus 4.1 ± 2.0 ; $P < 0.001$) compared with those treated with a GnRH antagonist. In matched recipients undergoing fresh embryo transfer, reproductive outcomes, including live birth rates, were similar in the GnRH antagonist and NMP groups (47.2% and 44.6%).

Conclusions: Comparable live birth rates were found in fresh embryo transfers for recipients across both groups. The NMP protocol was associated with a higher number of mature oocytes but lower oocyte maturation rate, higher fertilization rates and number of usable blastocysts. Progesterone priming may positively influence oocyte donation cycles.

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KEYWORDS

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Live birth rate

INTRODUCTION

Traditional ovarian stimulation protocols in assisted reproduction techniques typically involve the use of gonadotrophin-releasing hormone (GnRH) analogues to prevent early luteinization, a common cause of cycle cancellation caused by endogenous LH surges (Van Uem *et al.*, 1986). These surges can trigger premature ovulation, leading to elevated serum progesterone levels and hindering the necessary oocyte retrieval for IVF. The third generation of GnRH antagonists, such as cetrorelix and ganirelix, allow for rapid and reversible suppression of pituitary gonadotrophin production. This advancement enables shorter stimulation periods, lower doses of exogenous gonadotrophins and the use of GnRH agonists with a flare-up effect for oocyte trigger, resulting in a significant decrease in overall rates of ovarian hyperstimulation syndrome. This protocol is widely used in oocyte donation cycles (Bodri *et al.*, 2010).

Alternatively, a novel approach called progesterone-primed ovarian stimulation (PPOS) has been developed, focusing on manipulating ovarian function by using progestins (medroxyprogesterone acetate [MPA], dydrogesterone and similars) or natural micronized progesterone (NMP) for pituitary suppression. This method simplifies the process by transitioning from subcutaneously administered antagonists to orally administered medications. Progestins administered in the follicular phase have shown success in various infertility scenarios (Kuang *et al.*, 2015; Wang *et al.*, 2016; Chen *et al.*, 2017; Zhu *et al.*, 2017; Guo *et al.*, 2020). Initially, oral natural progesterone was considered ineffective owing to its high hepatic metabolism (over 80%) and poor absorption. Advances in micronization, however, reducing particle size and delivering it in a gelatin capsule with an oily vehicle, have significantly improved its bioavailability. Micronized progesterone reaches peak concentrations about 4 h after ingestion, remains in the bloodstream for up to 24 h and its absorption is enhanced when taken with food (Simon *et al.*, 1993). Synthetic progestins, however, do not fully replicate the complex biological activities of natural progesterone (Perone, 1993).

In oocyte donation cycles, orally taken progestins in the follicular phase eliminate the need for injecting a GnRH analogue,

offering greater patient comfort, a patient-friendly approach and lower costs.

Another advantage is the avoidance of embryo vitrification, as the woman undergoing stimulation is not the recipient of the transfer. Two randomized controlled trials (RCTs) have demonstrated the effectiveness of PPOS in inhibiting LH surges compared with GnRH antagonists, with consistent numbers of collected oocytes and mature oocytes. Findings on pregnancy outcomes for recipients, however, are conflicting, with one study reporting lower outcomes and another showing similar results to the conventional GnRH antagonist protocol (Beguería *et al.*, 2019; Giles *et al.*, 2021). Notably, these trials used MPA as the progestin agent, and there is a gap in research exploring the use of natural micronized progesterone for LH prevention in oocyte donation cycles.

The aim of the present study was to investigate whether ovarian stimulation outcomes in oocyte donors, as well as laboratory and clinical outcomes in recipients whose oocyte donors received oral micronized progesterone for LH surge prevention, are comparable to those obtained using the GnRH antagonist ovarian stimulation protocol.

MATERIALS AND METHODS

Study design

A retrospective observational cohort study was conducted in the Oocyte Donation Programme at Instituto Bernabeu Alicante between January 2018 and December 2022 (FIGURE 1). The data included in this study were framed in the routine clinical activity and were approved by the Institutional Review Board on 19 October 2022 (reference number MR44).

Donor eligibility criteria and ovarian stimulation

All donors included in the study were voluntary, in good health, aged younger than 33 years, with a body mass index (BMI) ranging from 18 to 28 kg/m² and reported regular menstrual cycles, i.e. between 26 and 35 days. Recruitment adhered to the clinical and legal stipulations outlined in the Spanish Assisted Human Reproduction Act (RD 9/2014), which mandated a psychological assessment, gynaecological examination and thorough screening for infectious diseases and genetic abnormalities. Individuals using hormonal intrauterine devices were excluded from participating

in this cohort study owing to potential interference.

Donors initiated ovarian stimulation during the early follicular phase (day 1–3 of the menstrual cycle). To prevent a premature LH peak, the study group received 200 mg natural micronized progesterone orally (Utrogestan®) (Besins Healthcare, Dublin, Ireland) once a day (in the evenings) concurrently with FSH administration, whereas the control group began GnRH antagonist treatment (0.25 mg Cetrotide®) (Merck-Serono, Madrid, Spain) upon identification of a leading follicle measuring 14 mm or wider until the day of the triptorelin acetate administration (trigger day). Both groups used an initial dose of 100–300 IU/day of FSH (Fostipur®) (Angelini Pharma, Barcelona, Spain) or Bemfol® (Gedeon Richter, Barcelona, Spain) for ovarian stimulation. The gonadotrophin starting dose was determined by a fertility expert overseeing each patient, considering factors such as antral follicle count and previous stimulations, with the aim of minimizing the risk of ovarian hyperstimulation syndrome. The initial dose could be adjusted at the clinician's discretion at any point during stimulation.

The first transvaginal ultrasound control was conducted on day 5–6 of stimulation, followed by subsequent checks every 1–3 days. Oocyte maturation was triggered by administering 0.2 mg of a GnRH agonist (Decapeptyl 0.1 mg®) (Ipsen Pharma, Barcelona, Spain) when more than three follicles larger than 17 mm were observed. According to the protocol, donors were required to confirm appropriate trigger administration by notifying a fertility nurse, and oocyte aspiration was carried out 36 h later.

Recipients and endometrial preparation

Recipients were women under the age of 50 years who underwent a normal physical examination and attended the clinic to receive donated oocytes. In accordance with Spanish legislation, recipients were meticulously matched with donors, prioritizing shared phenotypes, blood groups and genetic compatibility for carrier screening tests, without resorting to randomization.

Before commencing any endometrial preparation, a transvaginal sonographic scan is carried out to screen for uterine anomalies that could interfere with implantation. Any abnormal uterine

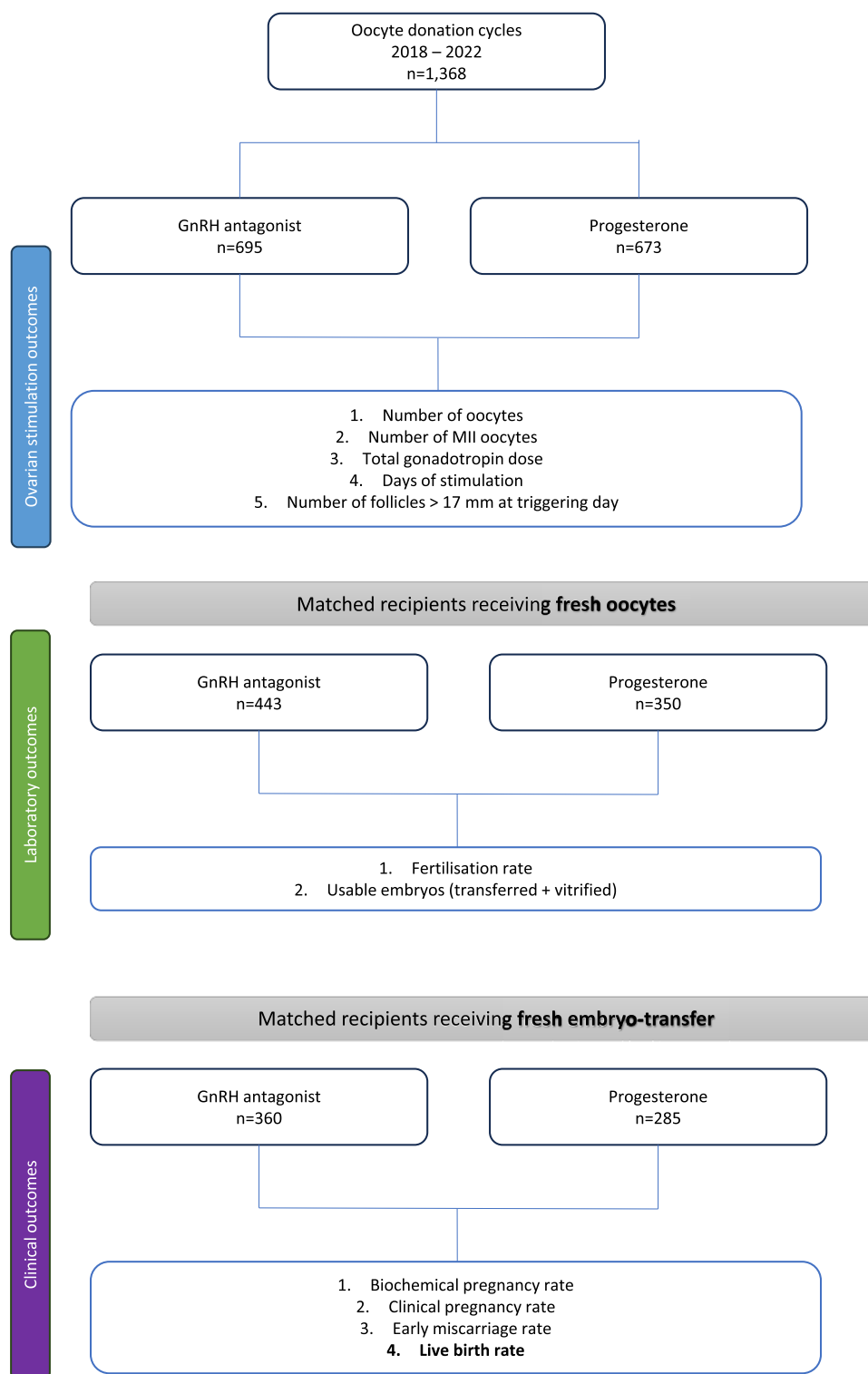


FIGURE 1 Oocyte donation cycles and oocyte recipients included in the study and the outcomes reported. GnRH, gonadotrophin releasing hormone.

findings detected during the ultrasound undergo further evaluation via three-dimensional scan, hysteroscopy, or both. 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 preceding cycle for pituitary desensitization. Hormone replacement therapy was initiated after the menstruation immediately after the GnRH analogue administration 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

more and trilaminar appearance at ultrasound were confirmed before oocyte reception. Luteal support was initiated with 400 mg twice daily of vaginal micronized progesterone (Utrogestan®) (Besins Healthcare, Dublin, Ireland) the day after intracytoplasmic sperm injection (ICSI).

To mitigate additional confounding factors associated with oocyte and embryo vitrification, laboratory outcomes beyond oocytes collected were restricted to recipients who received fresh oocytes, and only clinical outcomes per fresh embryo transfer were evaluated. All transfers were conducted at the blastocyst stage, and circulating beta-HCG levels were assessed 13 days after donation. In the event of a positive test, the presence of an intrauterine pregnancy was confirmed via ultrasound at the sixth week of gestation. Hormone replacement therapy was continued in pregnant women until the 12th week of pregnancy.

Laboratory procedures

For conventional IVF, oocytes were assigned to their matched recipients, with three cumulus–oocyte complexes (COC) placed in each well of a four-well culture dish containing Global Fert Medium® (LifeGlobal, Toronto, Ontario, Canada). The COC were inseminated with 150,000 motile spermatozoa per millilitre. After the incubation period of 16–18 h after insemination, all inseminated oocytes were denuded of cumulus cells and fertilization was evaluated, as well as the maturation stage of non-fertilized oocytes (fertilized oocytes and non-fertilized metaphase II oocytes [MII] were counted as mature oocytes). For ICSI, oocytes were denuded and MII oocytes were assigned to their matched recipients. Oocytes were fertilized using ICSI, and were evaluated after 16–18 h after insemination. Oocytes showing two pronuclei and two polar bodies were considered correctly fertilized, and were individually cultured in 30- μ l micro drops of pre-equilibrated continuous culture media (Global Total®) (LifeGlobal, Toronto, Ontario, Canada) in an environment of 5% O₂, 6% CO₂, at 37° C, and cultured until the blastocyst stage on day 5–6. Blastocysts were graded according to the Istanbul Consensus scoring system for embryo assessment (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Higher quality embryos were selected for transfer, and any supernumerary good-quality blastocysts were cryopreserved.

Study outcomes

The main outcome of the present study was the live birth rate. Secondary outcomes analysed included the total gonadotrophin dose, stimulation length and number of follicles measuring over 17 mm at triggering day. Regarding laboratory and clinical outcomes in matched recipients, the following parameters were explored: fertilization, usable blastocyst-stage embryos (defined as good or excellent quality, expanded, hatching or hatched blastocysts available: transferred plus cryopreserved) (Nguyen et al., 2021), 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), early miscarriage (intrauterine pregnancy loss before 10 weeks' gestational age as determined by ultrasound) and live birth (the delivery of at least one live born infant at 22 completed gestational weeks) (Kolte et al., 2015; Zegers-Hochschild et al., 2017).

Statistical analysis

For categorical variables, a descriptive analysis was conducted using frequency and percentage. For the univariate statistical analysis of comparison between study groups, the chi-squared test or Fisher's exact test was used. Additionally, a multivariable logistic regression analysis was conducted to control for potential confounding factors affecting laboratory and reproductive outcomes. The confounding variables introduced in the analysis are presented in the corresponding tables.

Numerical variables were presented as number of cases, mean and SD. For the evaluation of normal distributions, the Shapiro–Wilk test was conducted. If the variable had a normal distribution, Student's test or the Wilcoxon rank sum test were used. The multivariate analysis was carried out using linear regression, introducing the confounding variables detailed in the different tables. Where a donor has more than one recipient, a term was added to account for the internal variability of each oocyte donor (random effects), in addition to the covariates (fixed effects). For numerical variables, mixed-effects models (linear or multilevel models) were used. For binary categorical variables, a generalized linear mixed model (binomial option) was used. $P < 0.05$ was considered statistically significant.

R statistical software, version 4.3.1 (R Core Team, Vienna, Austria) and Statistical Product and Service Solutions software, version 23.0 (SPSS, Chicago, IL, USA) were used for statistical analysis.

RESULTS

A total cohort of 1368 oocyte donors was analysed. Among them, 695 (50.8%) used the traditional GnRH antagonist protocol, whereas the remaining 673 (49.2%) received oral micronized progesterone to prevent a premature LH surge. No significant differences were observed between the two groups in mean donor age (25.6 ± 4.2 years in the antagonist group versus 25.5 ± 4.3 years in the NMP group; $P = 0.665$) or BMI (22.4 ± 2.7 versus 22.7 ± 3.1 , respectively; $P = 0.244$). Among the 968 ovarian stimulation cycles with available data, however, a significantly higher percentage of donors in the NMP group received recombinant FSH (75.2% versus 89.8%; $P < 0.001$) (TABLE 1).

Regarding ovarian stimulation outcomes, both protocols showed comparable stimulation lengths (10.1 ± 1.8 days with GnRH antagonists versus 10.0 ± 1.5 days with NMP; $P = 0.170$), gonadotrophin consumption (2064.8 ± 643.7 versus 2122.9 ± 645.0 ; $P = 0.174$) and the number of follicles measuring over 17 mm at trigger (8.2 ± 4.6 versus 8.3 ± 4.9 ; $P = 0.6$). Even though the GnRH antagonist group yielded significantly fewer total retrieved oocytes (13.1 ± 7.9 versus 15.9 ± 8.5 ; $P < 0.001$) and MII oocytes (11.7 ± 7.3 versus 12.8 ± 7.3 ; $P = 0.003$) the oocyte maturation rate favoured the GnRH antagonist group ($89.49 \pm 14.48\%$ versus $80.89 \pm 16.78\%$; $P < 0.001$) (TABLE 1). The difference remained significant for the number of oocytes collected ($P < 0.001$) and the number of MII oocytes collected ($P = 0.019$) after adjusting for confounding factors (donor age, BMI, type of gonadotrophin used and repeated-effect variable) using multivariate analysis (Supplementary Table 1). Specifically, 508 donors donated to a single recipient, whereas 165 donors donated to two recipients. Additionally, 64 donors donated to three recipients, 32 to four, 12 to five, 13 to six, and three donors each donated to seven, eight and nine recipients, respectively. In most cases, ICSI was exclusively used as the insemination method (TABLE 2).

TABLE 1 DEMOGRAPHIC AND OVARIAN STIMULATION CYCLE CHARACTERISTICS OF OOCYTE DONORS

Characteristics	GnRH antagonist (n = 695)	Progesterone (n = 673)	P-value
Age, years	25.63 (4.21)	25.52 (4.33)	0.665 ^a
BMI, kg/m ²	22.47 (2.73)	22.69 (3.07)	0.244 ^a
Gonadotrophin, n (%)			<0.001 ^b
Highly purified human FSH	155 (24.8)	35 (10.2)	
Recombinant FSH	471 (75.2)	307 (89.8)	
Total dose of gonadotropin, IU	2064.82 (643.68)	2122.88 (645.04)	0.174 ^a
Duration of stimulation, days	10.14 (1.78)	9.97 (1.52)	0.170 ^a
Follicles >17 mm at trigger, n	8.23 (4.59)	8.25 (4.87)	0.677 ^a
Oocytes retrieved, n	13.13 (7.93)	15.85 (8.52)	<0.001 ^a
Mature oocytes (MII), n	11.70 (7.30)	12.83 (7.34)	0.003 ^a
Oocyte maturation rates, n (%)	89.49 (14.48)	80.89 (16.78)	<0.001 ^a

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

^a Wilcoxon rank sum test.

^b Pearson's chi-squared test.

BMI, body mass index; GnRH, gonadotrophin releasing hormone; MII, metaphase II.

Among the 793 recipients using fresh oocytes, 443 received oocytes from donors after the GnRH-antagonist protocol, whereas 350 received those using oral NMP. The mean age of recipients was slightly higher in the progesterone group (42.01 [4.11] years) compared with the GnRH antagonist group (41.28 [4.26] years), with the difference reaching statistical significance ($P = 0.0162$). A greater proportion of recipients in the antagonist group used fresh spermatozoa from their partners compared with the NMP group (73.8% versus 63.4%, respectively). Additionally, recipients in the antagonist group were allocated a higher mean number of mature oocytes (9.8 ± 1.8) compared with recipients in the NMP group (9.2 ± 1.2) ($P < 0.001$). The fertilization rate (74.3% versus 81.3%; $P < 0.001$) and the number of usable embryos (4.1 ± 2.0 versus 4.6 ± 2.0 ; $P < 0.001$), however, were both lower in the GnRH antagonist group compared with the NMP group (TABLE 2). These differences persisted after adjusting for confounding factors, including sperm source, insemination technique (conventional IVF or ICSI), number of MII oocytes and repeated-effect variable, using multivariate analysis. The fertilization rate and number of usable embryos remained significantly different between groups ($P < 0.001$ for both) (Supplementary Table 2).

Among the 645 recipients undergoing a fresh embryo transfer, 360 received

oocytes from donors after the GnRH-antagonist protocol, whereas 285 received those using oral NMP. The mean number of transferred embryos was similar between groups, most undergoing single blastocyst embryo transfer (320 out of 360 patients in the antagonist group [88.9%] and 263 out of 285 patients in the progesterone group [92.3%]). The between-group comparisons showed comparable biochemical pregnancy (62.8% and 63.2%, $P = 0.921$), clinical pregnancy (54.2% and 54.0%, $P = 0.973$) and live birth rate (47.2% versus 44.6%, $P = 0.501$) per fresh embryo-transfer (TABLE 2). After accounting for confounding factors, including recipient's age, insemination technique (conventional IVF, ICSI), number of embryos transferred and repeated-effect variable) in our adjusted analysis, pregnancy outcomes were consistent between the two groups. No statistically significant differences were observed, with odds ratios and 95% confidence intervals as follows: OR 0.84 (95% CI 0.59 to 1.20; $P = 0.351$) for biochemical pregnancy; OR 0.87 (95% CI 0.62 to 1.22; $P = 0.430$) for clinical pregnancy and OR 0.81 (95% CI 0.55 to 1.14; $P = 0.225$) for live birth (Supplementary Table 3).

DISCUSSION

Our large observational study reveals that the likelihood of live birth in fresh embryo transfers for recipients of oocytes from

donors using the NMP stimulation protocol was comparable to that of recipients from conventional ovarian stimulation protocols. Oocyte donors who received oral micronized progesterone for LH peak prevention achieved a higher oocyte yield and a higher number of mature oocytes while exhibiting a lower oocyte maturation rate. These donors had higher fertilization rates and produced a greater number of usable blastocyst-stage embryos compared with those treated with a GnRH antagonist. To the best of our knowledge, this is the first study to investigate the use of oral micronized progesterone for LH suppression in oocyte donation cycles.

The positive trends in stimulation and laboratory outcomes observed in the present study align with existing research but require cautious interpretation. Our findings of improved oocyte yield align with those of *Ghasemzadeh et al. (2019)*, who used micronized progesterone in infertile patients. They contrast, however, with studies by *Beguería et al. (2019)* and *Giles et al. (2021)*, which reported no difference in oocyte yield between medroxyprogesterone acetate and GnRH antagonist groups in donors. This discrepancy could stem from the milder pituitary suppression seen in PPOS protocols, potentially allowing additional endogenous FSH/LH release. Supporting this, previously published studies have reported higher oestradiol and LH levels on the day of trigger in medroxyprogesterone acetate protocols (*Beguería et al., 2019; Giles et al., 2021*) and a similar trend with micronized progesterone in infertile women (*Ghasemzadeh et al., 2019*). Further research is needed to investigate hormonal dynamics in oocyte donors undergoing NMP protocols to better understand their effect on ovarian stimulation and outcomes. This includes studies that track hormonal levels throughout the donor stimulation cycle. As blood sampling is not routinely carried out on oocyte donors at our centre (*Castillo et al., 2012*), however, systematic hormonal testing to explore this hypothesis is currently unavailable. An ongoing RCT (NCT05954962, registered at ClinicalTrials.gov) monitoring hormonal levels during the donor stimulation process will provide valuable insights into this area.

To further analyse the performance of oocytes derived from micronized progesterone protocols, we included data from a subset of recipients who received fresh oocytes. Our results indicate a higher

TABLE 2 CHARACTERISTICS OF RECIPIENTS, AND LABORATORY AND CLINICAL OUTCOMES AFTER DONATION OF FRESH OOCYTES

	GnRH antagonist (n = 443)	Progesterone (n = 350)	P-value
Recipient age, years	41.28 (4.26)	42.01 (4.11)	0.016 ^a
Sperm source, n (%)			<0.001 ^b
Partner fresh spermatozoa	327 (73.8)	222 (63.4)	
Partner frozen spermatozoa	83 (18.7)	85 (24.3)	
Surgical sperm retrieval	12 (2.7)	3 (0.9)	
Donated spermatozoa	21 (4.7)	40 (11.4)	
Donor			
Donated MII	9.88 (1.88)	9.24 (1.23)	<0.001 ^a
2PN	7.32 (2.13)	7.51 (1.70)	0.058 ^a
Fertilization rate (%) mean (SD)	74.38 (17.63)	81.39 (15.51)	<0.001 ^a
Insemination method, n (%)			<0.001 ^b
IVF	28 (6.3)	2 (0.6)	
ICSI	399 (90.1)	346 (98.9)	
Both	16 (3.6)	2 (0.6)	
Usable embryos (transferred + vitrified)	4.06 (2.04)	4.59 (2.01)	<0.001 ^a
Patients undergoing fresh embryo transfer, n	360	285	
Embryos transferred, n	1.11 (0.31)	1.08 (0.27)	0.147 ^a
Biochemical pregnancy rate, n (%)	226 (62.8)	180 (63.2)	0.921 ^b
Clinical pregnancy rate, n (%)	195 (54.2)	154 (54.0)	0.973 ^b
Early miscarriage rate, n (%)	24 (12.3)	26 (16.9)	0.226 ^b
Gestational sacs	1.08 (0.29)	1.05 (0.21)	0.301 ^a
Live birth rate, n (%)	170 (47.2)	127 (44.6)	0.501 ^b

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

One fetal miscarriage (≥ 10 weeks' gestational size) occurred in each group.

^a Wilcoxon rank sum test.

^b Pearson's Chi-squared test.

GnRH, gonadotrophin releasing hormone; ICSI, intracytoplasmic sperm injection; MII, metaphase II; 2PN, two pronuclei.

fertilization rate in the NMP group (74.3% versus 81.3%; $P < 0.001$), a distinction that remained significant even after adjusting for confounding factors through adjusted analysis (Supplementary Table 2). This notable finding contrasts with previous RCTs that used MPA in oocyte donors showing similar fertilization rates compared with GnRH antagonist protocol. Unfortunately, we cannot compare our results with the RCT focused on infertile women using oral NMP as fertilization rates were not reported (Ghasemzadeh et al., 2019). Most likely because of the higher fertilization rate, the number of usable, good-quality blastocyst-stage embryos was higher in the NMP protocol group (4.1 ± 2.0 versus 4.6 ± 2.0 ; $P < 0.001$). This difference remained statistically significant after adjusted analysis, suggesting a potential improvement in cumulative pregnancy rates favouring the NMP protocol. Although these promising

laboratory results are encouraging, they should be interpreted with caution, as they may be influenced by chance owing to the observational nature of our study and the unclear biological mechanisms underlying the outcome, particularly the fertilization rate. Nevertheless, the age of the recipients was comparable between the groups, and even though the number of MII oocytes provided to recipients from donors in the GnRH antagonist group was higher, the fertilization rate was greater in the NMP protocol group. Our findings suggest that the progesterone protocol may enhance oocyte competence, although this requires confirmation in larger prospective studies designed to control for potential confounding factors.

In a similar vein, to mitigate additional confounding factors associated with embryo vitrification, we restricted clinical

outcomes to recipients undergoing fresh embryo transfers. We observed no significant differences between the NMP and GnRH antagonist groups in reproductive outcomes, including clinical pregnancy rate, ongoing pregnancy rate and live birth rate in recipients. Once again, caution is warranted when comparing reproductive outcomes with previous studies, as both RCTs published on this subject using MPA (Beguería et al., 2019; Giles et al., 2021) did not have pregnancy outcomes as their primary objective, and recipients were not randomized, which presents a further limitation. Additionally, variations in the number of eggs provided to recipients and the timing of embryo transfer warrant caution when interpreting the data, as these factors may explain the divergent results. Nevertheless, while acknowledging some variations in the stimulation

protocols across trials, our data provide additional support for the viability of oocytes obtained from natural NMP protocols, as previously described for progestins in oocyte donors (Giles *et al.*, 2021) and in the IVF/ICSI population using utrogestan (Zhu *et al.*, 2017). After adjusting for confounding factors, the odds of pregnancy outcomes in fresh cycles were not significantly different, suggesting that NMP protocols had no discernible effect on embryo competence. Moreover, a higher number of usable embryos indicates a greater potential for improved cumulative pregnancy rates in NMP cycles. Taken altogether, and even acknowledging the inherent limitations associated with a retrospective data analysis, our findings provide reassurance of a comparable reproductive outcome, specifically biochemical pregnancy, clinical pregnancy and live birth rates, of oocytes derived from natural NMP protocols compared with GnRH-antagonist protocols, and support the notion that the cohort of follicles recruited after the exposure of 200 mg of oral NMP during ovarian stimulation demonstrate optimal competence. Prospective studies, however, are necessary to consolidate this promising retrospective data, and our group is currently conducting a RCT on the subject (NCT05954962, registered at ClinicalTrials.gov). Additionally, long-term studies should be conducted in the future to assess peri- and post-natal outcomes to confirm the safety of NMP protocols.

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. Second, the interventions in the study were not explored in parallel but rather sequentially across participant groups. The potential effect of time-related effects was not formally assessed. Nevertheless, treatment protocols at the study centre remained consistent throughout the study time frame. Moreover, certain variables, such as the anti-Müllerian hormone levels of donors, were unavailable for our analysis and merit investigation in prospective trials. Additionally, to mitigate confounding factors associated with oocyte and embryo vitrification, laboratory outcomes beyond oocytes collected were restricted to recipients who received fresh oocytes, and only clinical outcomes for one fresh

embryo transfer per recipient were evaluated. Although this approach ensures a comparable group of patients for a fair comparison, it also excludes the evaluation of the entire cohort of oocytes generated from the study group. Consequently, cycles using cryopreserved oocytes or patients proceeding with freeze-all embryos for later frozen embryo transfer were excluded from the analysis of the primary outcome and several secondary outcomes.

Although not the core focus of the present study, the additional benefits of using NMP protocols deserve discussion. Some studies have shown that simpler protocols are associated with reduced treatment burden and psychological distress, optimizing the patient's experience towards ovarian stimulation protocols (Devroey *et al.*, 2009). An advantage of natural NMP is its oral administration, diverging from injections and further reducing the treatment burden on the patient. It is also worth noting that oral administration of progesterone gives rise to metabolites, such as allopregnanolone (3 α ,5 α -tetrahydroP4) and 3 α ,5 α -tetrahydrodeoxycorticosterone, after metabolism in the gut and liver. These metabolic byproducts serve as natural positive modulators of the neuronal GABAA receptor, which provides an explanation for the drug's mild anxiolytic properties (Piette, 2020). In our protocol, we harness this advantageous effect for patients undergoing ovarian stimulation by scheduling the intake of NMP before bedtime. Finally, while not analysed in this study, the cost (euros) of using oral progesterone seems intuitively lower than that of protocols involving GnRH-antagonist injections.

In conclusion, this large observational study found no significant differences in clinical outcomes between natural micronized progesterone-primed protocols and GnRH antagonist protocols in oocyte donation treatments. Our data suggest that progesterone priming may positively influence oocyte donation cycles while potentially offering a more patient-friendly and cost-effective option for donors.

kindly used their time to make this study possible.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.rbmo.2025.104864](https://doi.org/10.1016/j.rbmo.2025.104864).

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REFERENCES

- Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Hum Reprod* 26, 1270–1283. <https://doi.org/10.1093/humrep/der037>.
- Beguería, R., García, D., Vassena, R., Rodríguez, A., 2019. Medroxyprogesterone acetate versus ganirelix in oocyte donation: a randomized controlled trial. *Hum Reprod* 34, 872–880. <https://doi.org/10.1093/humrep/dez034>.
- Bodri, D., Guillén, J.J., Trullenque, M., Schwenn, K., Esteve, C., Coll, O., 2010. Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study. *Fertil Steril* 93, 2418–2420. <https://doi.org/10.1016/j.fertnstert.2009.08.036>.
- Castillo, J., Dolz, M., Moreno, J., Gijón, L., Ferrer, R., Ferrero, E., Bonilla-Musoles, F., 2012. Triggering with GnRH agonist in oocyte-donation cycles: oestradiol monitoring is not necessary during ovarian stimulation. *Reproductive biomedicine online* 24, 247–250. <https://doi.org/10.1016/j.rbmo.2011.11.006>.
- Chen, Q., Wang, Y., Sun, L., Zhang, S., Chai, W., Hong, Q., Long, H., Wang, L., Lyu, Q., Kuang, Y., 2017. Controlled ovulation of the dominant follicle using progestin in minimal stimulation in poor responders. *Reprod Biol Endocrinol* 15, 71. <https://doi.org/10.1186/s12958-017-0291-0>.
- Devroey, P., Aboulghar, M., Garcia-Velasco, J., Griesinger, G., Humaidan, P., Kolibianakis, E., Ledger, W., Tomás, C., Fauser, B.C.J.M., 2009. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. *Hum Reprod* 24, 764–774. <https://doi.org/10.1093/humrep/den468>.
- Ghasemzadeh, A., Dopour Faliz, M., Farzadi, L., Navali, N., Bahramzadeh, B., Fadavi, A., Hakimi, P., Tehrani-Ghadim, S., Abdollahi Fard, S., Hamdi, K., 2019. Effect of oral Utrogestan in comparison with Cetrotide on preventing luteinizing hormone surge in IVF cycles: A randomized controlled trial. *Int J Reprod Biomed* 18, 41–46. <https://doi.org/10.18502/ijrm.v18i1.6197>.
- Giles, J., Alama, P., Gamiz, P., Vidal, C., Badia, P., Pellicer, A., Bosch, E., 2021. Medroxyprogesterone acetate is a useful alternative to a gonadotropin-releasing hormone antagonist in oocyte donation: a randomized, controlled trial. *Fertil Steril* 116, 404–412. <https://doi.org/10.1016/j.fertnstert.2021.02.036>.
- Guo, H., Gao, H., Li, J., Cong, Y., Chen, Q., Wang, Y., Zhu, Q., Lyu, Q., Wu, L., Chai, W., Kuang, Y., 2020. Impacts of medroxyprogesterone acetate on oocytes and embryos: matched case-control study in women with stage III-IV ovarian endometriosis undergoing controlled ovarian hyperstimulation for in vitro fertilization. *Ann Transl Med* 8, 377. <https://doi.org/10.21037/atm.2020.02.15>.
- Kolte, A.M., Bernardi, L.A., Christiansen, O.B., Quenby, S., Farquharson, R.G., Goddijn, M., Stephenson, M.D., ESHRE Special Interest Group, Early Pregnancy, 2015. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. *Hum Reprod* 30, 495–498. <https://doi.org/10.1093/humrep/deu299>.
- Kuang, Y., Chen, Q., Fu, Y., Wang, Y., Hong, Q., Lyu, Q., Ai, A., Shoham, Z., 2015. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. *Fertil Steril* 104, 62–70.e3. <https://doi.org/10.1016/j.fertnstert.2015.03.022>.
- Nguyen, E.B., Jacobs, E.A., Summers, K.M., Sparks, A.E., Van Voorhis, B.J., Klenov, V.E., Duran, E.H., 2021. Embryo blastulation and quality between days 5 and 6 of extended embryo culture. *J Assist Reprod Genet* 38, 2193–2198. <https://doi.org/10.1007/s10815-021-02156-7>.
- Perone, N., 1993. *The History of Steroidal Contraceptive Development: The Progestins. Perspectives in Biology and Medicine* 36, 347–362.
- Piette, P.C.M., 2020. The pharmacodynamics and safety of progesterone. *Best Pract Res Clin Obstet Gynaecol* 69, 13–29. <https://doi.org/10.1016/j.bpobgyn.2020.06.002>.
- Simon, J.A., Robinson, D.E., Andrews, M.C., Hildebrand, J.R., Rocci, M.L., Blake, R.E., Hodgen, G.D., 1993. The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone. *Fertil Steril* 60, 26–33.
- Van Uem, J.F., Garcia, J.E., Liu, H.C., Rosenwaks, Z., 1986. Clinical aspects with regard to the occurrence of an endogenous luteinizing hormone surge in gonadotropin-induced normal menstrual cycles. *J In Vitro Fert Embryo Transf* 3, 345–349. <https://doi.org/10.1007/BF01133245>.
- Wang, Y., Chen, Q., Wang, N., Chen, H., Lyu, Q., Kuang, Y., 2016. Controlled Ovarian Stimulation Using Medroxyprogesterone Acetate and hMG in Patients With Polycystic Ovary Syndrome Treated for IVF: A Double-Blind Randomized Crossover Clinical Trial. *Medicine (Baltimore)* 95, e2939. <https://doi.org/10.1097/MD.0000000000002939>.
- Zegers-Hochschild, F., Adamson, G.D., Dyer, S., Racowsky, C., de Mouzon, J., Sokol, R., Rienzi, L., Sunde, A., Schmidt, L., Cooke, I.D., Simpson, J.L., van der Poel, S., 2017. The International Glossary on Infertility and Fertility Care, 2017. *Fertil. Steril.* 108, 393–406. <https://doi.org/10.1016/j.fertnstert.2017.06.005>.
- Zhu, X., Ye, H., Fu, Y., 2017. Use of Utrogestan during controlled ovarian hyperstimulation in normally ovulating women undergoing in vitro fertilization or intracytoplasmic sperm injection treatments in combination with a “freeze all” strategy: a randomized controlled dose-finding study of 100 mg versus 200 mg. *Fertil Steril* 107, 379–386.e4. <https://doi.org/10.1016/j.fertnstert.2016.10.030>.

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