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Efficacy of modified natural cycle vs. hormone replacement therapy in oocyte donation for recipients of advanced maternal age: a retrospective study

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Abstract

Purpose To compare the efficacy of modified natural cycle (mNC) preparation versus hormone replacement therapy (HRT) for endometrial preparation in recipients of donated oocytes, specifically focusing on pregnancy rates in women of advanced maternal age.

Methods Retrospective multicenter analysis conducted between 2021 and 2024. It includes 220 cycles of fresh single blastocyst transfers resulting from oocyte donation. The participants were divided into two groups based on their endometrial preparation method: modified natural cycle (nNC) ($n = 105$, 47.7%) and hormone replacement therapy (HRT) ($n = 115$, 52.3%). Ongoing pregnancy rate was the main outcome.

Results Both groups were similar in terms of donor (24.8 vs 25.1 years) and recipient age (42.3 vs 42.8 years), BMI, and the origin of the semen used. The ongoing pregnancy rate was comparable between the mNC group (44.8%) and the HRT group (40.0%), showing no significant difference ($p = 0.47$). The mNC group had significantly higher progesterone levels compared to the HRT group (26.45 vs. 16.63, respectively; $p < 0.001$). In the multivariate analysis, which accounted for factors such as donor and recipient age, BMI, semen origin, progesterone levels, and endometrial thickness, no significant differences were observed between the two groups for the main outcome of ongoing pregnancy rate.

Conclusions The use of a modified natural cycle for endometrial preparation in advanced-age recipients of fresh single blastocyst transfers from vitrified donor oocytes results in ongoing pregnancy rates equivalent to those achieved with hormone replacement therapy.

Keywords Oocyte donation · Embryo transfer · Natural cycle · Hormone replacement therapy · Pregnancy outcome

Introduction

Today, oocyte donation constitutes an increasingly significant proportion of all ART cycles across Europe [1]. The successful implantation of a fertilized oocyte relies on a complex sequence of events that synchronize embryonic and endometrial development. Early attempts to synchronize donor and recipient ovulation presented unique challenges for clinicians [2]. Later studies on estrogen and progesterone replacement cycles led to the first successful IVF with a donated oocyte transferred at the two-cell stage. Since then, hormonal replacement therapy (HRT) protocols have become the routine treatment for endometrial preparation in egg recipients. Although this approach offers flexible scheduling and ensures embryo implantation, it is associated with poor obstetric and perinatal outcomes [3].

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Recently, advancements in the efficiency of oocyte vitrification [4] in donor oocyte programs have led to a renewed interest in natural cycle endometrial preparation for ovulatory recipients. While the question of endometrial preparation using hormone replacement therapy (HRT) versus natural cycles has been extensively investigated through prospective randomized trials, these studies have predominantly focused on IVF cycles using the patient's own eggs. To the best of our knowledge, there is a notable lack of medical evidence comparing these two protocols in recipients of donated oocytes. Given that the mean age of recipients in donor oocyte programs is significantly higher than that of patients undergoing own-egg IVF cycles, and considering the inherently increased obstetric risks associated with advanced maternal age, any strategy that offers the advantage of reducing ART-related obstetric risks in this population warrants further exploration.

Our study aimed to explore the reproductive outcomes in recipients receiving a single fresh blastocyst stage embryo from vitrified oocytes, comparing modified natural cycle endometrial preparation with HRT protocols.

Materials and methods

Study design

This retrospective observational cohort study reports data from the Oocyte Donation Programme at Instituto Bernabeu Palma de Mallorca and Madrid between January 2021 and July 2024. The data included in this study was framed in the routine clinical activity and was validated by the Institutional Review Board in January 16, 2024 (reference number IBMR49).

Eligibility criteria and ovarian stimulation

All donors included in the study were voluntary, healthy women, 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, gynecological examination, and a rigorous screening for infectious diseases and genetic abnormalities. As routine, contraceptive pills were not necessarily prescribed in the previous cycle; nonetheless, 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.

Donors started stimulation with an initial dose of 100–300 UI/day of FSH (Fostipur®, Angelini Pharma, Spain; Bemfola®, Gedeon Richter, Spain) according to antral follicular count (AFC) and BMI. To prevent a premature LH peak, the study group received 200 mg natural micronized progesterone orally (Utrogestan®, Besins Healthcare, Dublin, Irlanda) once per day (in the evenings) concurrently with FSH administration. The gonadotropin 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 (OHSS). The initial dose could be adjusted at the clinician's discretion at any point during stimulation. Final oocyte maturation was induced with 0.2 mg of a GnRH agonist (GnRHa) (Decapeptyl 0.1 mg®, Ipsen Pharma, Spain) when at least three follicles larger than 17 mm were detected by ultrasound. Oocyte aspiration was performed 36 h after induction by transvaginal ultrasound-guided needle-aspiration.

Recipients and endometrial preparation

Recipients were women under 50 years old with a normal uterine cavity who attended the clinic to undergo their first cycle of donated oocyte reception. The majority of patients had ovulatory cycles. Among those who underwent HRT, some had irregular cycles or ovarian failure. Most participants in this cohort were predominantly Caucasian.

Hormone replacement therapy

In patients with regular ovarian function, a single dose of a GnRH analogue (Gonapeptyl 3.75 mg®, Ipsen-Pharma, Spain) was administered in the midluteal phase of the immediate previous cycle for pituitary desensitization. Subsequently, for endometrial preparation, they were subjected to standard substitutive hormonal therapy with transdermal estrogen (Evopad 50®, Janssen-Pharmaceutica, Belgium) or oral estradiol valerate (Progynova®, Delpharm, France) at increasing doses for at least 12 days. Endometrial thickness $\geq$ 7 mm and trilaminar appearance at ultrasound were confirmed prior to oocyte reception. Micronized progesterone supplementation started with intravaginal capsules 400 mg/12 h (Cyclogest®, Gedeon Richter Ibérica, Spain) as soon as normal fertilization was confirmed in the laboratory.

Circulating β-hCG levels were determined 13 days post-ICSI and in case of a positive test result, the presence of a gestational sac was confirmed by ultrasound after 5 weeks. Ongoing pregnancy was documented by ultrasound at 12 gestational weeks that showed the presence of fetal heartbeat. In pregnant patients, the hormonal treatment was sustained for 12 weeks.

Modified natural cycle

An initial baseline scan was conducted during the early follicular phase (days 1–3 of menstruation) to rule out any pathological conditions (e.g., ovarian cysts). Follow-up scans were scheduled around day 10 of menstruation, depending on the individual's menstrual pattern. hCG was administered to trigger ovulation when the endometrial thickness reached at least 7 mm with a trilaminar appearance and a dominant follicle measured 17–22 mm [5]. Embryo transfer was scheduled for 7 days post-trigger.

Progesterone supplementation (Cyclogest® 400 mg) was initiated 2 days after ovulation triggering and administered vaginally once daily in the evening. Circulating β-hCG levels were measured 13 days post-ICSI. If the test was positive, an ultrasound was performed 5 weeks later to confirm the presence of a gestational sac, at which point progesterone support was discontinued. Ongoing pregnancy was documented by ultrasound at 12 gestational weeks that showed the presence of fetal heartbeat.

Progesterone levels

In our protocol, progesterone levels were measured 3 days after ICSI in both groups. Subcutaneous progesterone supplementation (Prolutex® 25 mg; IBSA Pharma Limited, UK) was administered when progesterone levels were found to be below < 9.2 ng/ml [6].

Laboratory procedures

Retrieved oocytes were denuded and metaphase II (MII) oocytes were vitrified following the Cryotop protocol with Kitazato solutions for deferred donation.

In brief, oocytes were first equilibrated in a solution containing 7.5% (v/v) ethylene glycol (EG) and 7.5% (v/v) dimethylsulfoxide (DMSO) in M-199 medium. They were then transferred into vitrification solution (VS) containing 15% (v/v) EG, 15% (v/v) DMSO, 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 VS until the plunge in liquid nitrogen, is completed in 50–60 s.

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

Oocytes were fertilized with intracytoplasmic sperm microinjection (ICSI). After 16–18 h post-insemination, oocytes showing two pronuclei and two polar bodies were considered correctly fertilized and were disposed individually in 30 µl micro drops of pre-equilibrated continuous culture media (Global Total®, LifeGlobal) in 5% O2 6% CO2 at 37 °C and cultured to day 5–6 blastocyst stage. Blastocyst were graded according to Istanbul consensus scoring on embryo assessment [7]. Embryos of higher quality were selected to be transferred and supernumerary good quality blastocysts were cryopreserved.

Outcomes of the study and statistical analysis

The primary outcome of this study was the ongoing pregnancy rate per embryo transfer defined as a pregnancy documented by ultrasound at 10–12 gestational weeks that showed the presence of fetal heartbeat [8]. Secondary outcomes analyzed included biochemical pregnancy (a pregnancy diagnosed only by the detection of beta hCG in serum or urine at 13 days post-donation) and early pregnancy loss (spontaneous pregnancy demise before 10 weeks of gestational age) [9, 10]. Additionally, the following parameters were explored: sperm source (partner vs donor), endometrial thickness, and progesterone levels at transfer. Cycles requiring testicular samples were excluded.

Logistic regression for the primary variable, ongoing pregnancy rate (dependent variable), was performed, including potential confounders such as the recipient's age and BMI, donor's age sperm source (partner vs donor), and endometrial thickness and progesterone levels on the day of transfer.

Given the exploratory nature of the study, a formal sample size analysis was not performed. However, it is noteworthy that a similar number of patients have been included in previously published prospective randomized trials on the subject. [11]. A descriptive analysis of the variables studied was performed, presenting the results as frequency and range and percentages when appropriate. For statistical analysis, the chi-square test was used to compare frequencies between donor age groups. Multivariate logistic regression analysis was performed to determine the association between ongoing pregnancy rates by study group, adjusting for other relevant variables. Values of $p < 0.05$ were considered statistically significant.

Statistical analysis was done with the statistic software R, version 4.2.0 and the Statistical Product and Service Solutions software, version 23.0 (SPSS, Chicago, IL, USA).

Results

The participant flow in the study is shown in Fig. 1. Among the 220 recipients included in the study, 105 employed the modified natural cycle while 115 received HRT for endometrial preparation.

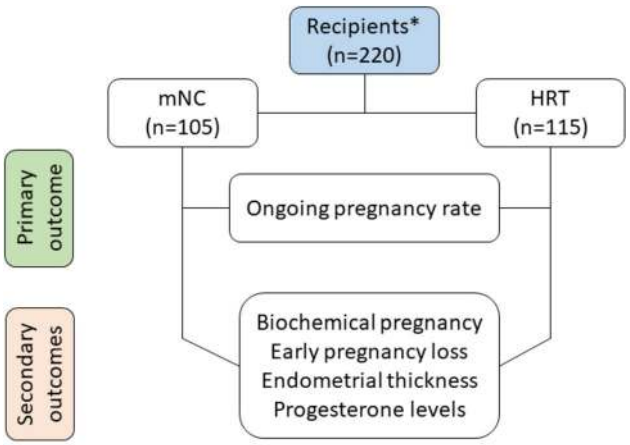

Fig. 1 Flowchart. Distribution of groups, number of cases, and outcomes

Overall, baseline characteristics were similar between mNC vs HRT cycles with regard to recipient's age (42.3 ± 2.8 vs 42.8 ± 4.6 years), BMI (23.17 ± 3.9 vs 24.04 ± 4.2 kg/m^2), and endometrial thickness (8.4 ± 1.5 vs 8.0 ± 1.2 mm), oocyte donor age (24.8 ± 4.0 vs 25.1 ± 3.8 years), and sperm source (81% vs 84%, partner and 19% vs 15%, donor) respectively (Table 1).

In recipients, the endometrial thickness was similar between groups. However, as expected, the progesterone values at transfer were higher in the mNC vs HRT (26.4 ± 9.2 vs 16.3 ± 8.8 ng/ml, respectively; $p < 0.001$). In recipients receiving a single fresh blastocyst stage embryo transfer after synchronized vitrified egg donation, there were no differences between groups in terms of biochemical pregnancy (62.9% and 58.3%), early pregnancy loss (16.7% and 10.4%), and ongoing pregnancy rate (44.8% vs 40.0%) per embryo transfer (Table 2). One ectopic pregnancy was reported in the HRT protocol group. Upon analyzing the blastocysts in both groups, we found no significant differences in either embryo quality or the day of transfer (day 5 or 6).

Table 1 Baseline characteristics of oocyte donation cycles by study group

	mNC $n = 105$	HRT $n = 115$	p
Recipients			
Age, years, $n \pm$ SD (range)	42.3 ± 2.8 (40.0, 44.0)	42.8 ± 4.6 (40.0, 46.0)	0.06
BMI (kg/m^2), mean ± SD (range)	23.17 ± 3.9 (20.7, 25.7)	24.04 ± 4.2 (21.4, 27.4)	0.07
Endometrial thickness, mm, mean ± SD (range)	8.44 ± 1.5 (7.53, 9.00)	8.06 ± 1.2 (7.00, 8.93)	0.1
*Progesterone levels (ng/ml), $n \pm$ SD (range)	26.45 ± 9.2 (21, 30)	16.63 ± 8.8 (12, 19)	< 0.001
Oocyte donors			
Age, years, mean ± SD (range)	24.89 ± 4.0 (22.0, 26.8)	25.16 ± 3.8 (22.0, 28.0)	0.4
Sperm source			0.5
Partner, n (%)	85 (81%)	97 (84%)	
Donor, n (%)	20 (19%)	18 (15%)	

BMI, body mass index; *mNC*, modified natural cycle; *HRT*, hormonal replacement therapy

*Progesterone levels were measured 3 days after ICSI

Table 2 Outcomes of recipients undergoing single fresh embryo transfer by study group

	mNC $n = 105$	HRT $n = 115$	p
Primary outcome			
Ongoing pregnancy rate,, n (%)	47/105 (44.8%)	46/115 (40.0%)	0.47
Secondary outcomes			
Biochemical pregnancy rate,, n (%)	66/105 (62.9%)	67/115 (58.3%)	0.1
Early pregnancy loss rate, n (%)	11/66 (16.7%)	7/67 (10.4%)	0.2

mNC, modified natural cycle; *HRT*, hormonal replacement therapy

Logistic regression analysis for the primary variable, ongoing pregnancy rate, included potential confounders such as the recipient's age and BMI, donor's age, sperm source (partner vs donor), and endometrial thickness and progesterone levels on the day of transfer. This analysis did not identify any significant influence from these potential confounders (Fig. 2).

Discussion

To the best of our knowledge, our study presents novel evidence comparing modified natural cycle and hormone replacement therapy protocols for endometrial preparation in recipients of donated oocytes. In this study, we evaluated the outcomes of women undergoing a single fresh blastocyst transfer from vitrified oocytes, using either modified natural cycle or hormone replacement therapy for endometrial preparation. We found no statistically significant differences between the two groups in terms of the primary outcome (ongoing pregnancy rate) or secondary outcomes (biochemical pregnancy and early pregnancy loss). The only significant difference noted was in the level of progesterone before embryo transfer, which was higher in the mNC group (26.45 vs. 16.63 ng/ml, $p < 0.001$). This difference in progesterone values was expected since the mNC incorporates activity from the corpus luteum, which is further boosted by the use of hCG triggering together with the additional vaginal progesterone employed in our protocol. This enhancement of the corpus luteal activity provided by the mNC might be particularly beneficial for recipients considering the advanced age of this population, which is at risk of reduced corpus luteum activity [12]. Our findings align with previous studies, including a Cochrane meta-analysis that compared different endometrial preparations and found no significant differences in live birth or miscarriage rates for either fresh or frozen embryo transfers [13].

There is growing evidence supporting the benefits of mNC preparation in terms of obstetric and neonatal outcomes. Studies have reported a lower prevalence of low birth weight, lower risk of early pregnancy loss, large-for-gestational-age fetus, macrosomia, small-for-gestational-age fetus, hypertensive disorders of pregnancy, pre-eclampsia, postpartum hemorrhage, and preterm delivery in pregnancies resulting from mNC preparation compared to HRT [3]. This difference is likely due to the presence of the corpus luteum in natural cycles, which produces relaxin and other vasoactive substances essential for maternal adaptation to pregnancy [14]. Additionally, mNC has been shown to have a more favorable effect on the endometrial transcriptome compared to HRT cycles [15]. In our study, the age range for recipients was 40–46 years. Therefore, these advantages of natural cycle endometrial preparation are particularly important in the context of oocyte recipients, where increased maternal age confers additional age-related risks compared to younger cohorts [16].

Initially, HRT endometrial preparation was developed for women with premature ovarian failure undergoing donation cycles [17]. However, HRT then became traditionally expanded and preferred for all oocyte donation cycles mainly due to logistic reasons. It allows for easy scheduling, which is advantageous for both the patient and the IVF personnel. Weekend work can be easily eliminated, and the workload on weekdays can be balanced effectively [18]. In contrast, natural cycles could be unpredictable. However, recent advancements suggest that the mNC may also offer more

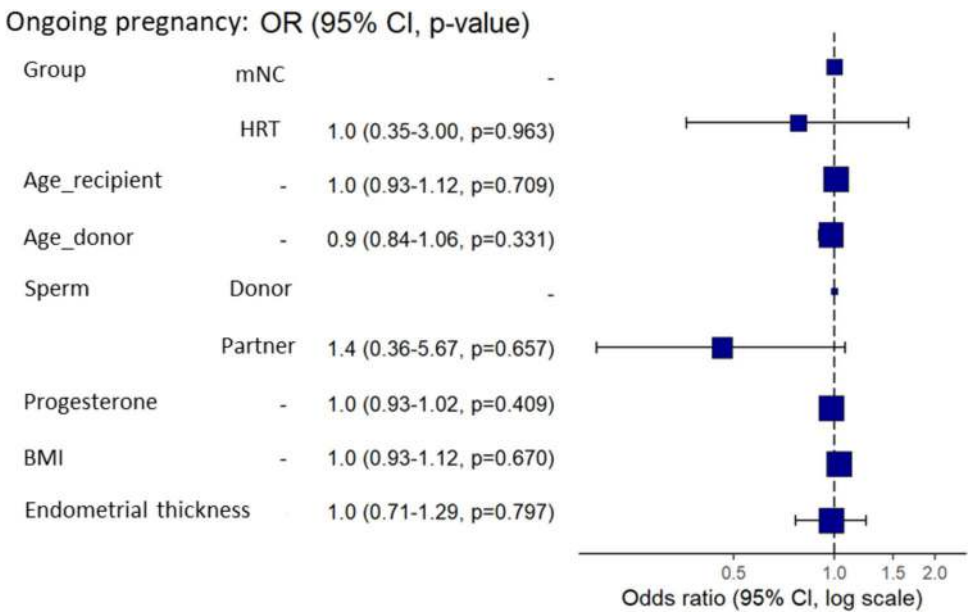

Fig. 2 Logistic regression for ongoing pregnancy rates. mNC, modified natural cycle; HRT, hormone replacement therapy

flexibility than previously thought. For example, triggering ovulation at different follicle sizes (between 13 and 22 mm) has been shown to result in similar ongoing pregnancy rates, allowing for a flexible 5 to 7-day window for fresh embryo transfer planning [19]. Furthermore, the natural proliferative phase protocol (NPP), where exogenous progesterone is started once a follicle of at least 14 mm is present without an hCG trigger, has shown promising preliminary results. Although this study did not systematically assess the presence of a corpus luteum, a corpus luteum was frequently observed during the early gestation scan in patients from this group. This observation suggests that the approach may preserve the benefits of a corpus luteum while providing some scheduling flexibility. [20]. The use of vitrified donor oocytes (or embryos) may add to this flexibility.

To the best of our knowledge, our study represents the first investigation into fresh single blastocyst transfer in mNC among egg recipients, comparing it with HRT protocols. While there exists a previous larger study similar to ours [21], it primarily focused on frozen single blastocyst transfer. In that trial, the live birth rate significantly favored the mNC group (47%) over the HRT group (38%), with a *p*-value of 0.046. However, this study was only published as an abstract, and thus, additional details regarding medication dosages and the protocol for endometrial preparation were unavailable. It is plausible that these factors, combined with the transfer of frozen embryos, could have contributed to the observed differences in outcomes. Of note, both our study and the aforementioned one included patients with a mean age of over 40 years, suggesting that mNC may be effective even in populations of advanced maternal age, provided menstrual regularity is present. This finding underscores the potential utility and efficacy of mNC across various patient demographics.

This study has several limitations inherent to its retrospective design, which we addressed by conducting a multivariate logistic regression analysis to account for relevant confounders. Additionally, a formal sample size analysis was not conducted, and the moderate sample size may restrict the generalizability of our findings. The statistical power is likely low, increasing the risk of false negatives. These limitations are key reasons why our study is presented as an observational initiative. However, our study also has notable strengths. It was conducted across multiple centers, enhancing the generalizability of our results. We included a homogeneous population by focusing on single fresh blastocyst embryo transfers, reducing variability in outcomes.

Conclusion

In donor programs, employing a modified natural cycle for endometrial preparation in normo-ovulatory recipients of fresh single blastocyst transfers from vitrified donor oocytes yields ongoing pregnancy rates comparable to those achieved with hormone replacement therapy. This method not only mirrors the biological processes of natural conception but also presents notable advantages in obstetric outcomes and patient convenience, which are especially important for the typically older recipient population. The enhanced corpus luteum activity associated with the modified natural cycle may contribute to improved pregnancy outcomes. However, further research and larger-scale studies are needed to comprehensively explore and confirm these benefits.

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Author contribution C.G. and J.C.: study conception and design; C.G., J.M., and C.Q.: collection of data; C.G., J.C., and J.O.: statistical analysis and interpretation of data; C.G.: wrote the first draft of the manuscript; J.C. wrote sections of the manuscript; C.G., J.C., J.O., J.M., C.Q., A.B., and R.B.: critical review of the article. All the authors have seen and approved the final version of this manuscript.

Data availability The data that support the findings of this study are available from the corresponding author, JC, upon reasonable request.

Declarations

Ethics approval The study conformed to the Declaration of Helsinki for Medical Research about human subjects. In addition, approval was obtained from the institutional review board at Instituto Bernabeu, reference number IBMR49 (January 16, 2024).

Conflict of interest The authors declare no competing interests.

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