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ARTICLE

Modified natural cycle IVF versus conventional stimulation in advanced-age Bologna poor responders

BIOGRAPHY

Panagiotis Drakopoulos is visiting Professor and senior fertility specialist, working at the Centre for Reproductive Medicine (UZ Brussel) in Belgium. His research focuses on poor ovarian responders and strategies to improve their outcome.

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KEY MESSAGE

Ongoing pregnancy rate was not associated with treatment type when comparing modified natural cycle IVF (MNC-IVF) with conventional high-dose ovarian stimulation by multivariate logistic regression analysis in advanced-age Bologna poor responders. MNC-IVF, which is a more patient-friendly approach, could be a reasonable treatment option for these difficult-to-treat women.

ABSTRACT

Research question: Do ongoing pregnancy rates (OPR) differ between modified natural cycle IVF (MNC-IVF) and conventional high-dose ovarian stimulation (HDOS) in advanced-age Bologna poor responders?

Design: This was a retrospective cohort study including patients with poor ovarian response (POR) attending a tertiary referral university hospital from 1 January 2011 to 1 March 2017. All women who fulfilled the Bologna criteria for POR and aged ≥40 years who underwent their first intracytoplasmic sperm injection (ICSI) cycle in the study centre were included.

Results: In total, 476 advanced-age Bologna poor responder patients were included in the study: 189 in the MNC-IVF group and 287 in the HDOS group. OPR per patient were significantly lower in the MNC-IVF group (5/189, 2.6%) compared with the HDOS group (29/287, 10.1%) ($P = 0.002$). However, after adjustment for relevant confounders (number of oocytes and presence of at least one top-quality embryo), the multivariate logistic regression analysis showed that the type of treatment strategy (HDOS versus MNC-IVF) was not significantly associated with OPR (odds ratio 2.56, 95% confidence interval 0.9–7.6).

Conclusions: In advanced-age Bologna poor responders, MNC-IVF, which is a more patient-friendly approach, could be a reasonable alternative in this difficult-to-treat group of women.

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KEYWORDS
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INTRODUCTION

Poor ovarian response (POR) remains one of the main therapeutic challenges in women undergoing ovarian stimulation for IVF (*Ubaldi et al., 2005*), associated with low live birth rates (LBR) (*Platteau et al., 2005*) and high cancellation rates (*Polyzos et al., 2015a*).

Various stimulation protocols have been developed to improve the reproductive outcome of these patients (*Papathanasiou et al., 2016*). Traditionally, the stimulation protocol for women with predicted POR includes high doses of gonadotrophins of up to 600 IU/day, although mild stimulation protocols with lower doses of gonadotrophins have recently been shown to be equally effective (*Youssef et al., 2016, 2018*).

In this regard, natural cycles or modified natural cycles (MNC-IVF) with minimal stimulation have been proposed as an alternative for conventional ovarian stimulation and have become increasingly popular in this challenging population with POR (*Kadoch et al., 2011*). The biological rationale for this mild approach is to obtain a single oocyte of better quality and thus to transfer a healthier embryo to a more receptive endometrial environment (*Reyftmann et al., 2007*). The lack of high doses of gonadotrophin stimulation in the follicular phase may prevent the premature rise in progesterone that is associated with conventional ovarian stimulation cycles and therefore avoid the associated endometrial–embryo asynchrony, which could negatively impact pregnancy outcomes (*Venetis et al., 2013*). Furthermore, MNC-IVF may reduce gonadotrophin consumption and could therefore be a cost-effective option.

However, although MNC-IVF has been shown to result in acceptable cumulative pregnancy rates in normal responders (*Nargund, 2001*), evidence is sparse in poor responders and, more specifically, in women of advanced age. Furthermore, previous studies evaluating MNC-IVF in poor responders included mainly young patients not fulfilling the Bologna criteria (*Morgia et al., 2004*), had relatively small sample sizes (*Kim et al., 2009; Morgia et al., 2004*) and no comparison group (*Kedem et al., 2014; Polyzos et al., 2012*).

Therefore, the objective of this study was to evaluate the clinical outcomes of MNC-IVF compared with high-dose ovarian stimulation (HDOS) in advanced-age Bologna poor responders.

MATERIALS AND METHODS

This was a retrospective, single-centre cohort study aiming to evaluate the difference in ongoing pregnancy rate (OPR) between MNC-IVF and HDOS in advanced-age poor responders according to the Bologna criteria. Demographic and clinical data were collected from intracytoplasmic sperm injection (ICSI) cycles performed at the Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Belgium, from 1 January 2011 to 1 March 2017.

This study was approved by the Ethics Committee of Brussels University Hospital (approval B.U.N. 143201837283) on 19 September 2018.

Patient selection and eligibility criteria

Poor ovarian responders were defined by the Bologna criteria (*Ferraretti et al., 2011*). It was decided to include exclusively women aged ≥40 years, with reduced ovarian reserve parameters. In order to avoid crossover between treatments, only the first cycle performed in the study centre within the aforementioned time interval was included in the analysis. Each patient was included only once in the study. Given the lack of evidence favouring a specific approach in this patient population, patients were allocated to the treatment protocol based on physician's preference.

Anti-Müllerian hormone (AMH) was measured in a previous cycle, irrespective of the cycle day, by means of the automated Elecsys Immunoanalyser (Roche Diagnostics, Mannheim, Germany) from September 2014 to March 2017. For the AMH assay used before this period, a conversion was performed using the formula described in the literature (*Kumar et al., 2010*). Antral follicle count was measured on Day 2–4 of a previous cycle.

Other inclusion criteria were: body mass index (BMI) of 17–35 kg/m^2, regular menstrual cycles, presence of both ovaries, absence of any untreated endocrine abnormality and priming in the cycle preceding the ovarian stimulation cycle.

Patients who underwent preimplantation genetic testing (PGT), IVF for fertility preservation or oocyte donation were excluded from the analysis.

Ovarian stimulation and IVF procedure

Basal serum hormone analysis (oestradiol, progesterone, FSH and LH levels) was performed on Day 2 or 3 of the menstrual cycle and from Day 7 or 8 of the cycle onwards. An ultrasound scan for the assessment of follicular growth was performed every second day from Day 7 or 8 of the cycle onwards.

In the MNC-IVF group, highly purified human menopausal gonadotrophin (hp-HMG) 75 IU (Menopur®; Ferring, Saint-Prex, Switzerland) and gonadotrophin-releasing hormone (GnRH) antagonist 0.25 mg/day (ganirelix, Orgalutran®; MSD, Oss, the Netherlands) were started concomitantly when a follicle with a mean diameter of 14 mm was present on ultrasound scan. Highly purified urinary or recombinant human chorionic gonadotrophin (HCG) 5000 IU (Pregnyl®; MSD or Ovitrelle®; Merck Serono Europe Ltd, London, UK) was administered as soon as the mean follicular diameter was ≥16 mm. Serum hormonal levels were evaluated to exclude a premature LH surge.

In the HDOS group, recombinant FSH (rFSH) (Puregon®, MSD) or hp-HMG (Menopur®; Ferring) was initiated on Day 2 or 3 of the cycle. The starting dose of rFSH or hp-HMG was 300 IU/day for all patients and continued daily thereafter until the day prior to HCG administration. Pituitary down-regulation was performed with daily administration of GnRH antagonist (ganirelix, Orgalutran®; MSD) starting from Day 6 of the stimulation onwards. Triggering of final oocyte maturation was performed using 5000 IU HCG (Pregnyl®, MSD) when at least two follicles reached a mean diameter of 17 mm. In cases of monofollicular development, patients were allowed to proceed to oocyte retrieval. In cases of no follicular development the cycle was cancelled.

Oocyte retrieval, laboratory procedures, embryo transfer and luteal phase support

In both groups, oocyte retrieval was performed 36 h after HCG administration. Oocyte insemination was

performed by ICSI (*Van Landuyt et al., 2005*).

The embryo quality was based on the Istanbul consensus workshop on embryo assessment (*Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology et al., 2011*): Day 3 embryos that reached the 6-cell stage with 20% fragmentation were classified as good-quality embryos, embryos that reached 7 cells with maximum 10% fragmentation were classified as top quality. Embryo transfer took place on Day 3.

The luteal phase was supplemented with vaginally administered tablets of natural micronized progesterone in three separate doses (Utrogestan®; Besins, Brussels, Belgium), 600 mg daily, starting on the day after the oocyte retrieval and continued until a negative pregnancy test or until the 7th gestational week in case of a positive pregnancy test.

Primary outcome

The primary outcome was the OPR, defined as the ultrasonographic visualization of an intrauterine sac with embryonic pole demonstrating cardiac activity at 10 weeks of gestation expressed per 100 initiated cycles (*Zegers-Hochschild et al., 2017*).

Secondary outcomes

The secondary outcomes were the positive HCG rate (defined as the detection of beta HCG in serum expressed per 100 initiated cycles), the clinical pregnancy rate (defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs expressed per 100 initiated cycles), the LBR (defined as delivery of a liveborn after 22 completed weeks of gestational age following the fresh ICSI cycle, expressed per 100 initiated cycles) (*Zegers-Hochschild et al., 2017*).

Statistical analysis

Continuous data are presented as median and interquartile range (IQR) or as mean ± SD. Categorical data are described by number of cases and percentages. Continuous variables were compared with the use of independent *t*-test or Mann–Whitney *U*-test, depending on the normality of the distribution, and categorical variables were compared with the chi-squared or Fisher's exact test, as appropriate. The level of significance was set at $P < 0.05$.

To identify characteristics that may be associated with the OPR, multivariate logistic regression analysis was performed with the OPR as the dependent variable and type of treatment as the main independent variable (MNC-IVF versus HDOS). OPR instead of LBR was chosen as main dependent variable in the regression model, given the low number of events (live births) expected in this poor prognosis population. It is well established that the reliability of the adjusted odds ratios (OR) derived from logistic regression models is strictly dependent on the number of events per variable included in the model and a common problem occurs when the outcome has few events; in such a case, parameter estimates may be biased.

Univariate regression analysis was performed to identify candidate factors that predict the OPR. The candidate variables were age, BMI, number of cumulus–oocyte–complexes (COC), and presence of at least one top-quality embryo. Variables showing a significant association with OPR ($P < 0.05$) in the univariate analysis were included in the multivariate model. Thus, COC ($P = 0.001$) and presence of at least one top-quality embryo ($P < 0.001$) were included as covariates in the final model. All independent variables were simultaneously entered into the logistic regression model. The likelihood of OPR after ICSI is presented as an OR with SE and 95% confidence interval (CI).

All statistical tests used a two-tailed α of 0.05. All analyses were performed using SPSS version 24.0 and STATA version 13.0.

RESULTS

Baseline characteristics

In total, 476 advanced-age (≥40 years) Bologna poor responders were included in the study: 189 in the MNC-IVF group and 287 in the HDOS group.

The baseline characteristics are shown in TABLE 1. No significant differences were found in the baseline characteristics regarding age and BMI. The basal FSH and AMH serum levels were significantly different between MNC-IVF and HDOS groups (12.6 IU/l versus 10.2 IU/l, $P < 0.001$ and 0.3 ng/ml versus 0.6 ng/ml, $P < 0.001$, respectively).

Ovarian response and characteristics of embryo development

The results are presented in TABLE 2. MNC-IVF were characterized by significantly fewer COC ($P < 0.001$) and metaphase II (MII) oocytes ($P < 0.001$), lower embryo transfer rates ($P < 0.001$) and top embryo quality rates ($P = 0.002$) compared with HDOS.

Reproductive outcome

Reproductive outcomes are shown in TABLE 2. Positive HCG (5.0% versus 19.0%; $P < 0.001$), clinical pregnancy (4.8% versus 17.4%; $P < 0.001$) and ongoing pregnancy rates (OPR) (2.6% versus 10.1%; $P = 0.002$) were significantly lower in the MNC-IVF group as compared with the HDOS group. OPR rates according to the number of oocytes retrieved and the type of treatment are shown in FIGURE 1. No significant differences were detected between groups for patients

TABLE 1 BASELINE CHARACTERISTICS IN THE TWO GROUPS

	MNC-IVF(n = 189)	HDOS(n = 287)	P-value
Age (years)	41 (40–42)	41 (40–42)	NS
BMI (kg/m^2)	24 (22–27)	24 (22–28)	NS
Basal FSH (IU/l)	12.6 (9.2–17.3)	10.2 (7.8–13)	<0.001
AMH (ng/ml)	0.3 (0.1–0.5)	0.6 (0.3–0.9)	<0.001
Number of previous IVF attempts	0 (0–2)	0 (0–2)	NS

Values are expressed as median (IQR).

AMH = anti-Müllerian hormone; BMI = body mass index; HDOS = high-dose ovarian stimulation; IQR = interquartile range; MNC = modified natural cycle; NS = not statistically significant.

TABLE 2 CHARACTERISTICS OF EMBRYO DEVELOPMENT AND REPRODUCTIVE OUTCOMES

	MNC-IVF(*n* = 189)	HDOS(*n* = 287)	*P*-value
COC:			
Mean (SD)	0.8 (0.6)	4.1 (3.2)	<0.001
Median (IQR)	1 (0–1)	3 (2–6)	
MII oocytes:			
Mean (SD)	0.7 (0.6)	3.4 (2.7)	<0.001
Median (IQR)	1 (0–1)	3 (1–5)	
Cancellation rate[a]	21 (11)	6 (2)	<0.001
Patients with embryo transfer	86 (45)	215 (75)	<0.001
Patients with at least one top-quality embryo	71 (83)	202 (94)	0.002
Number of embryos transferred/no. of patients			
1 embryo	80 (93)	79 (37)	<0.001
2 embryos	6 (7)	87 (40)	
3 embryos	0 (0)	49 (23)	
Implantation rate	10/86 (12)	55/215 (26)	0.008
Patients with embryos cryopreserved	8 (4)	42 (15)	<0.001
Pregnancy outcomes per patient			
Positive HCG	10 (5.0)	55 (19.0)	<0.001
Clinical pregnancy	9 (4.8)	50 (17.4)	<0.001
Ongoing pregnancy	5 (2.6)	29 (10.1)	0.002
LBR	3 (1.6)	23 (8.0)	0.003

Data are presented as *n* (%) unless otherwise stated.

[a] Refers to patients with no follicular development during ovarian stimulation.

COC = cumulus–oocyte–complex; HCG = human chorionic gonadotrophin; HDOS = high-dose ovarian stimulation; IQR = interquartile range; LBR = live birth rate; MII = metaphase II oocytes; MNC = modified natural cycle.

with either one or two or more oocytes (FIGURE 1). Live birth was achieved in three MNC-IVF and in 23 HDOS cycles (1.6% versus 8%; $P = 0.003$).

Variables associated with OPR

Multivariable logistic regression analysis showed that the type of treatment strategy (HDOS versus MNC-IVF) was not significantly associated with OPR (OR 2.56, 95% CI 0.9–7.6). The only variable significantly associated with OPR was the presence of at least one top-quality

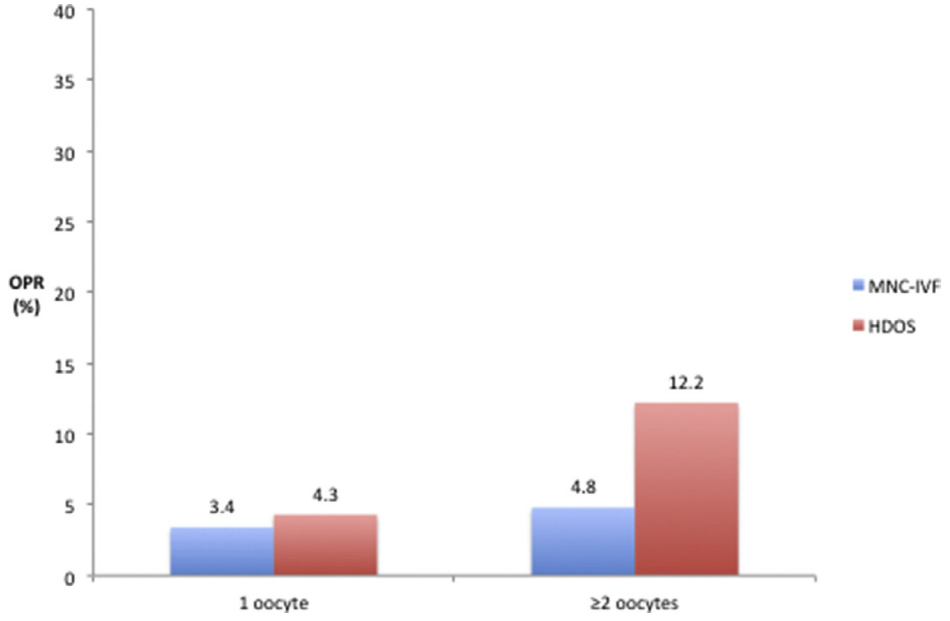

FIGURE 1 Ongoing pregnancy rate (OPR) according to the number of oocytes between modified natural cycle IVF (MNC-IVF) versus high-dose ovarian stimulation (HDOS). There was no significant difference between treatment groups.

TABLE 3 MULTIVARIATE LOGISTIC REGRESSION WITH OR FOR OPR

OPR	OR	95% CI	*P*-value	SE
COC	1.02	0.90–1.15	NS	0.07
At least one top-quality embryo				
No	1	–	–	–
Yes	5.25	2.03–13.6	0.001	2.55
Treatment type				
MNC-IVF	1	–	–	–
HDOS	2.56	0.9–7.6	NS	1.42

CI = confidence interval; COC = cumulus–oocyte–complex; HDOS = high-dose ovarian stimulation; MNC = modified natural cycle; NS = not statistically significant; OPR = ongoing pregnancy rate; OR = odds ratio.

embryo (OR 5.25, 95% CI 2.03–13.6). The results are presented in TABLE 3.

DISCUSSION

The current study provides evidence that in older Bologna poor ovarian responders, MNC-IVF and HDOS result in similar OPR after adjustment for relevant confounders. As far as is known, this is the first and largest study to evaluate the role of MNC-IVF in patients above 40 years of age, fulfilling the Bologna criteria.

Several retrospective studies have evaluated the role of natural cycle/MNC-IVF in poor responders, with conflicting results, probably due to the heterogeneity of definitions for poor ovarian response (POR) used in their clinical study design (*Ata et al., 2008; Elizur et al., 2005; Kedem et al., 2014*). While in most of them, mild stimulation regimens resulted in acceptable success rates (*Ata et al., 2008; Elizur et al., 2005*), others failed to replicate these findings, suggesting that MNC-IVF is of no benefit for genuine poor ovarian responders (*Kedem et al., 2014*).

To date, only two RCT have compared the use of natural cycle/MNC-IVF versus conventional ovarian stimulation in poor ovarian responders; the Bologna criteria were not used in these studies. Pregnancy rates were found to be similar when comparing MNC-IVF with either the microdose flare-up (*Morgia et al., 2004*) or the antagonist protocol (*Kim et al., 2009*). The only study using the definition of poor responders according to the European Society of Human Reproduction and Embryology (ESHRE) consensus (*Ferraretti et al., 2011*) was conducted by *Lainas et al. (2008)*. Based on the results of this retrospective study, LBR were significantly higher in the MNC group (OR 4.01, 95% CI 1.14–14.09) compared with HDOS; nonetheless, the study was criticized for its methodology, given the very low number of live births in the whole cohort (*Polyzos et al., 2015b*).

Based on the results of the current study, the origin of the similar probability of pregnancy in the MNC-IVF group as compared with the HDOS group after adjustment for confounders is unclear. Indeed, one would expect lower pregnancy rates after MNC-IVF due to the lower number of oocytes retrieved and fewer embryos transferred in the case of MNC-IVF. It would not be unreasonable to assume that differences in endometrial receptivity may play a role. In fact, it has been shown that the oestradiol and progesterone receptor expression levels in stimulated cycles on the day of HCG triggering is similar to the expression levels during the first days of the luteal phase in natural cycles (*Papanikolaou et al., 2005*), which may indicate endometrial advancement after ovarian stimulation. Indeed, high doses of gonadotrophins may result in significantly higher oestradiol levels on the day of HCG administration, which have been associated with decreased endometrial receptivity (*Devroey et al., 2004; Horcajadas et al., 2008*). Furthermore, the age-related increase in embryo aneuploidy rates, which cannot be mitigated by a higher oocyte yield in women of advanced age, may justify why the milder approach of the MNC-IVF could result in similar reproductive outcomes.

The rationale to include exclusively advanced-age Bologna poor responders in this study was that, at the study centre, these patients are more frequently counselled for a milder stimulation approach following several failed IVF attempts, compared with younger poor responders.

A major strength of this study lies in its large sample size, and the focus on advanced-age patients fulfilling the Bologna criteria. Nonetheless, the retrospective study design should be considered a limitation when interpreting results. Although a significant effort has been made to eliminate all known sources of systematic error through multivariable analysis, there might still exist non-apparent sources of bias confounding the comparison of pregnancy rates between the two strategies. Patients were allocated to the two stimulation protocols based on the physician's discretion and therefore patients counselled for MNC-IVF may have been of poor prognosis. Moreover, the primary outcome of the study was the OPR, and not the LBR; OPR was chosen due to the low number of events in terms of live births encountered in this population, not allowing the application of a valid methodological approach, having live birth as primary outcome.

In conclusion, in advanced-age Bologna poor responders, MNC-IVF may have a role. MNC-IVF is a more patient-friendly approach and could be a reasonable alternative in this difficult-to-treat group of women, who do not wish to undergo egg donation. However, a prospective RCT comparing MNC-IVF with the HDOS strategy in this patient population would be required to validate the role of MNC-IVF in advanced-age poor responders.

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