

Poor ovarian response and the possible role of natural and modified natural cycles

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Abstract: About 20% of women undergoing *in vitro* fertilization struggle with poor ovarian response, indicating a poor prognosis related to low response following ovarian stimulation. Indeed, poor ovarian response, that is associated with both high cancelation rates and low live birth rates, still represents one of the most important therapeutic challenges in *in vitro* fertilization. In this context, natural cycle/modified natural cycle-*in vitro* fertilization, as a ‘milder’ approach, could be a reasonable alternative to high-dose/conventional ovarian stimulation in poor ovarian responders, with the aim to retrieve a single oocyte with better characteristics that may result in a single top-quality embryo, transferred to a more receptive endometrium. Moreover, modified natural cycle-*in vitro* fertilization may be cost-effective because of the reduced gonadotropin consumption. Several studies have been published during the last 20 years reporting conflicting results regarding the use of natural cycle/modified natural cycle-*in vitro* fertilization in women with poor ovarian response; however, while most of the studies concluded that mild stimulation regimens, including natural cycle/modified natural cycle-*in vitro* fertilization, have low, but acceptable success rates in this difficult group of patients, others did not replicate these findings. The aim of this narrative review is to appraise the current evidence regarding the use of natural cycle/modified natural cycle-*in vitro* fertilization in poor ovarian responders.

Keywords: IVF, modified natural cycle, ovarian stimulation, poor ovarian responders

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Introduction

Poor ovarian response accounts for up to 20% of women undergoing *in vitro* fertilization (IVF); this indicates that one of five patients struggles with poor prognosis related to low response following ovarian stimulation.^{1,2} Poor ovarian response, which is associated with both high cancelation rates³ and low live birth rates (LBRs),⁴ represents one of the most important therapeutic challenges in IVF.

Several stimulation protocols and adjuvant strategies have been developed in the last decade to improve the reproductive outcomes of these patients.⁵ Although the main strategy traditionally consisted of ovarian stimulation protocols with elevated doses of gonadotropins (up to 600 IU/

day), a milder approach, with lower gonadotropin doses, has appeared to be equally effective.^{6,7} In this regard, natural cycle and modified natural cycle (MNC-IVF) with minimal stimulation have emerged as a valuable therapeutic strategy to treat poor ovarian responders (PORs).^{8–10} Indeed, the aim of the ‘mild’ approach is to retrieve a single oocyte with better characteristics, which may result in a single top-quality embryo transferred to a more receptive endometrium.¹¹ Furthermore, avoidance of high doses of gonadotropins for ovarian stimulation in MNC-IVF cycles may also reduce the incidence of premature progesterone rise, which has a negative impact on pregnancy rates.¹² Finally, MNC-IVF may be cost-effective because of the reduced gonadotropin consumption; in addition, the use of low gonadotropin

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doses has also less impact in older age women, among which cancer of hormone-sensitive tissues is more common (e.g. breast cancer).

The aim of this article is to appraise the current evidence regarding the use of Natural Cycle/MNC-IVF in PORs.

Material and methods

MEDLINE, Embase, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, and Cochrane Library were used to search for all the relevant articles related to MNC-IVF and poor ovarian response from the inception of the database up to January 2021. A combination of the following text words was used to identify relevant studies: 'Modified Natural Cycle (MNC)', 'Natural Cycle', 'In Vitro Fertilization (IVF)', 'Poor Ovarian Response', 'Poor Ovarian Responders (PORs)'. The selection criteria of this narrative review included randomized clinical trials, nonrandomized controlled studies (observational prospective, retrospective cohort studies, case-control studies, and case series), and review articles of natural cycle/MNC-IVF in infertile women with poor ovarian response. A revision of articles also included the abstracts of all references retrieved from the search. Articles not written in English, conference papers and reviews, and studies with information overlapping another publication were excluded. In the event of overlapping studies, the most recent, comprehensive study, or both were selected.

Results

Retrospective studies

To date, several retrospective studies have investigated the role of natural cycle/MNC-IVF in PORs (Table 1). Elizur *et al.*¹³ evaluated the efficacy of gonadotropin-releasing hormone (GnRH) antagonist administration in natural cycles. A total of 540 IVF cycles were divided into three groups according to the stimulation protocol (modified natural, antagonist, and long agonist groups); according to their data, the implantation rates (IRs) and pregnancy rates (PRs) did not differ between the groups (10% and 14.3% *versus* 6.75% and 10.2% *versus* 7.4% and 10.6%, respectively; $p=NS$). The MNC-IVF with GnRH antagonist (GnRH-a) administration was therefore considered a feasible option for poor ovarian response. Similarly, Ata *et al.*¹⁴

retrospectively analyzed the embryo IR in cycles ending with single embryo transfer in 304 women who had poorly responded to ovarian stimulation in previous IVF cycles. The embryo IR was compared between the different stimulation protocols adopted with the results showing no statistically significant difference [natural cycle, 20% (6/30); gonadotropin only, 5.6% (3/54); long GnRH agonist, 3.8% (2/52); co-flare protocol, 1.9% (1/52); micro dose flare-up, 15.4% (4/26); GnRH antagonists, 14.4% (13/90)] but a trend for better outcomes in the natural cycle group. Partially in accordance with the aforementioned results, our own group evaluated the difference in ongoing pregnancy rate (OPR) between MNC-IVF and conventional high-dose ovarian stimulation (HDOS) in advanced-age poor responders according to the Bologna criteria (BC).¹⁵ 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. The OPR per patient was significantly higher in the HDOS group (29/287, 10.1%) compared with the MNC-IVF group (5/189, 2.6%) ($p=0.002$). However, the multivariate logistic regression analysis, allowing adjustment for relevant confounders (number of oocytes and presence of at least one top-quality embryo), revealed that the type of treatment strategy (HDOS *versus* MNC-IVF) was not significantly associated with OPR [odds ratio (OR) = 2.56, 95% confidence interval (CI) = 0.9–7.6]. In the same vein, Polyzos *et al.* conducted a retrospective cohort trial, including 164 consecutive patients, undergoing 469 natural cycle IVFs. Patients were divided to poor and normal responders according to the BC: 136 (390 cycles) were poor responders and 28 women (79 treatment cycles) who did not fulfill the criteria were considered normal responders. Poor ovarian responders had a significantly lower LBR compared with the control group of women (LBR per cycle: 2.6% *versus* 8.9%, $p=0.006$; LBR per treated patient: 7.4% *versus* 25%, $p=0.005$). However, although the LBRs were consistently lower in the PORs group, no statistical difference was reported among the age subgroups (≤ 35 , 36–39, and ≥ 40 years) ranging from 6.8% to 7.9%. The authors concluded that natural cycle IVF may have very limited potential when applied in women with poor ovarian response, irrespective of the patient's age.¹⁶ Interestingly, Lainas *et al.* showed a higher probability of live birth in favor of the MNC group when compared with high-dose FSH ovarian stimulation protocols. The authors performed a retrospective single-center study including 106 women in the MNC group and 164 receiving high-dose

Table 1. Retrospective studies investigating the role of natural cycle/MNC-IVF in PORs.

Author	Year	Study design	Inclusion criteria	Total n of patients included	Investigation group	Comparison group(s)	Results
Elizur <i>et al.</i>	2005	Retrospective	Poor responders defined as ≤ 4 oocytes obtained at OPU or an E2 level < 1000 pg/ml on the day of hCG administration	433 patients (540 cycles)	52 MNC-IVF cycles with antagonist	200 cycles of conventional ovarian stimulation with antagonist 288 long GnRH agonist cycles	IR and PR did not statically differ between the groups
Ata <i>et al.</i>	2008	Retrospective	Women who underwent a previous unsuccessful cycle in which < 5 oocytes had been collected at OPU Only cycles in which there was a single embryo available for transfer	304 patients	30 women undergoing natural cycles	54 women undergoing protocol with gonadotropin only 52 women undergoing Long GnRH agonist protocol 52 women undergoing co-flare protocol 26 women undergoing microdose flare protocol 90 women undergoing Antagonist protocol	PR did not statically differ between the groups
Polyzos <i>et al.</i>	2012	Retrospective	Women undergoing natural cycle IVF without any ovarian stimulation or use of GnRH antagonist	164 patients (469 cycles)	390 cycles with women fulfilling the BC undergoing natural cycle IVF	79 cycles with women, classified as normal responders, undergoing natural cycle IVF	LBR was significantly lower in PORs group
Kedem <i>et al.</i>	2014	Retrospective	Patients with poor ovarian response defined according to the BC, who underwent a subsequent MNC-IVF within 3 months of the previous failed conventional IVF/ICSI cycle	111 patients	111 women fulfilling the BC undergoing MNCs	Failed conventional IVF/ICSI cycle in the same patients	LBR and PR was significantly lower in MNC-IVF group
Lainas <i>et al.</i>	2015	Retrospective	Women fulfilling the BC for the definition of poor ovarian response	242 patients (325 cycles)	106 women treated with MNC-IVF	164 women treated with high-dose FSH antagonist protocol	LBR was significantly higher in MNC-IVF group
Drakopoulos <i>et al.</i>	2019	Retrospective	Advanced-age poor responders women fulfilling the BC	476 patients	189 women treated with MNC-IVF	287 women treated with high-dose gonadotropins antagonist protocol	OPR per patient was significantly higher in women treated with high-dose gonadotropins
Liu <i>et al.</i>	2021	Retrospective	Women fulfilling the BC for the definition of poor ovarian response	699 patients (1058 cycles)	374 patients (733 cycles) treated with minimal ovarian stimulation including natural cycles	325 women treated with GnRH antagonist cycles (325 cycles)	CLBR did not statically differ between the two groups

BC, Bologna criteria; CLBR, cumulative live birth rate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IR, implantation rate; IVF, *in vitro* fertilization; LBR, live birth rate; MNC-IVF, modified natural cycle-*in vitro* fertilization; n, number; OPR, ongoing pregnancy rate; OPU, oocytes pick up; PORs, poor ovarian responders; PR, pregnancy rate.

FSH (HDFSH) in a GnRH antagonist protocol. The patients included had to fulfill the BC for the definition of poor ovarian response. The results showed that the probability of live birth was significantly higher in the MNC group when compared with the HDFSH group (OR = 4.01, 95% CI = 1.14–14.09), after adjusting for basal FSH, female age, and cause of infertility.¹⁷ However, the study was criticized for several methodological issues, including the very low number of live births reported in the whole cohort.¹⁸ Recently, Liu *et al.* retrospectively compared the overall cumulative live birth rate (CLBR) among PORs undergoing IVF cycles with minimal ovarian stimulation and conventional GnRH-a cycles. A total of 699 patients (1058 cycles) fulfilling the BC were included and divided into 325 women who underwent GnRH-a cycles (325 cycles) and 374 patients (733 cycles) who were treated with minimal ovarian stimulation, including natural cycles. Results showed that CLBR was comparable between the two groups (12.92 *versus* 7.92%, adjusted OR = 1.702; 95% CI = 0.971–2.982, $p=0.063$).¹⁹

Conversely, the results by Kedem *et al.*²⁰ are in contrast with the aforementioned rather favorable results of MNC-IVF. These authors investigated the reproductive outcomes (LBR and PR) in 111 patients with poor ovarian response, defined according to the BC, undergoing MNC-IVF with GnRH-a supplementation. The LBR in PORs was <1%. Moreover, the subgroup of patients with poor ovarian response who had undergone a previous conventional IVF/intracytoplasmic sperm injection (ICSI) cycle with only one oocyte retrieved did not achieve any pregnancy.

Randomized controlled trials

To date, a very limited number of randomized controlled trials (RCTs) about the role of natural cycle/MNC-IVF in PORs have been published (Table 2). Morgia *et al.*²¹ compared the efficacy of natural cycle IVF with controlled ovarian hyperstimulation in PORs. In total, 114 natural IVF cycle and 101 IVF cycles under controlled ovarian hyperstimulation with micro dose GnRH analog flare were included in the study. The statistical analysis revealed that PORs treated with natural cycle IVF and those treated with micro-GnRH analog flare had similar PR per cycle and per transfer. However, the patients treated with natural cycle IVF had an IR significantly higher compared with controls (14.9% *versus* 5.5%). When

subdivided into three groups according to age (≤ 35 , 36–39, ≥ 40 years), younger patients had a better PR. Similarly, the prospective RCT performed by Kim *et al.*²² demonstrated that minimal stimulation in natural cycles results in equivalent PR compared with the GnRH-a multiple-dose protocol, with lower consumption of gonadotropins and less days of recombinant FSH (rFSH) administration.

Discussion

Given the fact that the overall oocyte yield is expected to be low in poor ovarian response, the alternative of using a mild stimulation approach has been recently recommended by the American Society for Reproductive Medicine (ASRM)²³ due the similar rates of clinical pregnancy achieved following conventional IVF gonadotropin protocols and mild ovarian stimulation protocols with low-dose gonadotropins (<150 IU/day).

Mild ovarian stimulation is a more patient-friendly and cost-effective approach when compared with conventional ovarian stimulation, reducing the duration of stimulation and gonadotropins total dosage.²⁴ In this context, there is strong evidence supporting that natural cycle/MNC-IVF are associated with acceptably low medications costs.^{25,26} Indeed, the analysis of simulated scenarios showed that a therapeutic strategy of three to six MNC-IVF cycles with minimized medication represents a cost-effective option compared with one cycle of controlled ovarian hyperstimulation with single embryo transfer.²⁷ With regard to psychological aspects, the performance of natural cycle/MNC-IVF almost does not require injections with no or minimal side effects; this fact is known to contribute with a low impact on psychological distress.²⁸ In the same vein, Haemmerli Keller *et al.*²⁹ showed that patients undergoing natural cycle/MNC-IVF had significantly lower level of depression and a higher satisfaction with the treatment compared with those undergoing conventional IVF.

However, although the option of MNC-IVF represents a reasonable alternative in PORs,¹⁵ LBR remains low.¹⁶ Several studies have been published during the last 20 years reporting conflicting results regarding the use of natural cycle/MNC-IVF in women with poor ovarian response, partially due to the heterogeneity of definitions of poor ovarian response used in the design of these

Table 2. Randomized controlled studies investigating the role of natural cycle/MNC-IVF in PORs.

Author	Year	Study design	Inclusion criteria	Total n of patients included	Investigation group	Comparison group(s)	Results
Morgia <i>et al.</i>	2004	RCT	Women \leq 43 years who underwent a previous IVF cycle with poor response considered as three or fewer follicles recruited, or cycle canceled because of no follicle activation.	129 patients	59 women undergoing 114 attempts with natural cycle IVF	70 women undergoing 101 attempts of IVF with ovarian stimulation with the microdose GnRH analog flare protocol	PR was similar between the groups both per cycle and per transfer, IR was significantly higher in the natural cycle IVF group
Kim <i>et al.</i>	2009	RCT	Women who underwent a previous IVF/ICSI cycle and failed to produce three or fewer follicles	90 patients	45 women undergoing IVF/ICSI with minimal stimulation	45 women undergoing IVF/ICSI with GnRH antagonist multiple-dose protocol	PR did not statically differ between the groups

GnRH, gonadotropin-releasing hormone; IR, implantation rate; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; MNC-IVF, modified natural cycle-*in vitro* fertilization; n, number; PORs, poor ovarian responders; PR, pregnancy rate; RCT, randomized controlled trial.

studies.^{13,20} However, while most of the studies concluded that mild stimulation regimens, including natural cycle/MNC-IVF, have low, but acceptable success rates in women with poor ovarian response,¹³⁻¹⁶ others did not replicate the same findings.^{19,20} In addition, similar reproductive outcomes (in most of the cases) have been reported by RCTs comparing the use of natural cycle/MNC-IVF *versus* conventional ovarian stimulation in PORs.^{21,22}

With regard to the similar reproductive outcomes (IR, PR, and OPR) reported comparing MNC-IVF with conventional ovarian stimulation protocols in PORs,¹³⁻¹⁶ the possibility that endometrial receptivity may play a role seems plausible. Scientific background has shown that, on the day of human chorionic gonadotropin (hCG) triggering, the expression levels of estradiol and progesterone receptors are similar to those occurring during the first days of the luteal phase in natural cycles.³⁰ Thus, it is reasonable to assume that an endometrial advancement may occur in stimulated cycles. Indeed, the significantly higher estradiol levels registered on the day of HCG administration in cycles stimulated with high-dose gonadotropins may have a detrimental effect on the endometrium with decreased receptivity.³¹⁻³³ Moreover, the embryo aneuploidy rates, which are increased in advanced-age women and cannot be mitigated by a higher oocyte yield, may

justify why the milder approach of the MNC-IVF could result in comparable reproductive outcomes. In addition, recent evidence suggests that aneuploidy rates, embryo quality, the number of metaphase II (MII) oocytes needed to obtain one euploid blastocyst, and embryo quality are similar between MNC-IVF and conventional ovarian stimulation.³⁴ Besides, given that the number of expected embryos per initiated cycle is low, the embryo banking strategy over a cohort of several mild stimulation cycles with the aim of collecting the top-quality embryos could represent a reasonable option.³⁵

Finally, it has to be mentioned that the last two decades have underlined the urgent necessity for physicians involved in assisted reproductive technology (ART) to speak 'the same language' with regard to poor ovarian response. One of the main limitations of the studies done in poor ovarian response relies on the fact that the population included was heterogeneous. The BC represented a step forward, although they did not remain without criticism.³⁶ A subsequent evolution of these criteria has been recently elaborated to overcome limitations of the BC, including the ambiguity in defining risk factors, the substantial heterogeneity, the lack of accounting for oocyte quality, and other factors that can be associated with a low ovarian reserve.³⁷⁻⁴⁰ In this regard, a revised definition of 'impaired ovarian response' has been proposed by

the Poseidon Group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number).⁴¹ This current classification has been developed to better differentiate the ‘low prognosis patient’ and accounts four subgroups considering (1) numerical and qualitative parameters such as the patient’s age and the aneuploidy rate expected; (2) markers of ovarian reserve [antral follicle count (AFC) and/or anti-Mullerian hormone [AMH]); and (3) ovarian response to previous stimulation cycle. Moreover, the Poseidon Group has presented a new marker to measure the potential success of ART, named the number of oocytes needed for a specific patient to obtain at least one euploid embryo for transfer.^{42,43} In this context, future studies are needed to evaluate the effectiveness of natural cycle/MNC-IVF among specific subgroups of low prognosis patients, stratified according to the Poseidon Group criteria. Last, the fact that MNC-IVF protocols may include various treatment modalities (use of clomiphene citrate, low-dose gonadotropins with or without GnRH antagonists, etc.), may represent a source of bias.¹⁵ In this regard, a clear definition of MNC-IVF is warranted.

In conclusion, natural cycle/MNC-IVF may have a role in PORs, offering a milder and patient-friendly approach that represent a valuable alternative to conventional/high-dose ovarian stimulation in this group of patients, especially after failure of stimulated cycles⁴⁴ and/or if they do not wish to undergo egg donation.

Nonetheless outcomes are disappointingly poor. Given the lack of robust evidence, prospective RCT comparing natural cycle/MNC-IVF with the high-dose ovarian stimulation strategy in this patient population are warranted to confirm the current evidence.

Author contributions

F.D.G. and P.D. contributed to the design and data collection. F.D.G wrote the first draft of manuscript. C.B., M.D.V., M.P., N.C. and H.T. participated to the revision process improving the quality of the paper. All authors discussed the results and contributed to the final manuscript with the specific support of P.D.

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