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Does the dose or type of gonadotropins affect the reproductive outcomes of poor responders undergoing modified natural cycle IVF (MNC-IVF)?

Running title: MNC-IVF protocol modalities and reproductive outcomes in poor responders

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Introduction

Poor ovarian response (POR) is defined as the failure to respond adequately to standard ovarian stimulation protocols. Due to the limited oocyte yield, high cycle cancellation rates (Polyzos et al., 2015) and low live birth rates (LBR) (Zhang et al., 2020), POR remains a core challenge in IVF clinical practice. It has been estimated that the prevalence of POR ranges from 6% to 35% (Oudendijk et al., 2012; Patrizio et al., 2015). Although predicted POR has usually been treated with high doses of gonadotropins (Papathanasiou et al., 2016), milder stimulation approaches have recently gained interest. This interest had been fueled by studies showing no benefit from high doses of gonadotropins in predicted poor responders (Youssef et al., 2017,Youssef et al., 2018).

In this context, IVF in a modified natural cycle (MNC-IVF) with mild gonadotropin stimulation has emerged as a therapeutic option for women with POR (Kadoch et al., 2011, Nargund et al., 2017, Moffat et al., 2020). This "mild" approach could offer several advantages such as yielding of better quality oocytes (Weghofer et al., 2004) and embryos, that could be further transferred to a more physiological endometrial milieu (Reyftmann et al., 2007). In mild stimulation MNC-IVF protocols, GnRH antagonists are used to block the spontaneous LH surge and gonadotropins are administered as an add-back therapy to counterbalance the suppressed endogenous FSH levels. However, there is currently no evidence base for a specific protocol or gonadotropin type for MNC-IVF. In addition, although the POSEIDON classification seems a step in the right direction for the classification of POR, validation, and conduction of new studies in different subgroups are warranted. The aim of the present study is to investigate whether the daily dose or the type of gonadotropin may affect the reproductive outcomes of predicted poor responders undergoing MNC-IVF.

Material and methods

Study design

This was a retrospective, single-centre cohort study including consecutive subfertile patients

undergoing MNC-IVF with mild ovarian stimulation using gonadotropins at our centre. The study was approved by the institutional Review Board of Universitair Ziekenhuis Brussel (approval B.U.N. 143201938863). A cycle was considered cancelled when the patient failed to respond to gonadotropins with no possibility to perform the oocyte retrieval.

Study population

Data were retrieved from all predicted poor responders (Group 3 and 4) according to POSEIDON criteria (AMH <1.1 ng/ml) (Alviggi et al., 2016) undergoing at least one MNC-IVF cycle between 1st January 2017 and 1st March 2020. MNC-IVF cycles with administration of clomiphene citrate were excluded from the study.

Treatment protocol

Ovarian stimulation was started as a follicle with a mean diameter of 12-14 mm was observed on ultrasound scan, followed by GnRH antagonists (0.25mg/day) from the next day onwards. Gonadotropins used in doses <75 IU/d or 75 to <100 IU/d or ≥ 100 IU/d were recombinant FSH (rFSH) Gonal-F®, Merck Pharmaceuticals, Darmstadt, Germany; Ovaleap®, Theramex, Ireland Limited; Puregon®, MerckSharp&Dohme, Whitehouse Station, NJ, USA; urinary FSH (uFSH) Fostimon®, IBSA, Switzerland or highly purified HMG (hpHMG) Menopur®, Ferring Pharmaceuticals, St. Prex, Switzerland. Cycle monitoring was performed through serum E2, P, FSH and LH assessments, and serial transvaginal ultrasound examinations (Popovic-Todorovic et al., 2018). Ovulation triggering was performed with the administration of hCG when a single follicle of 17 mm diameter was observed (Humaidan et al., 2013), followed by oocyte retrieval 34-36 hours later. Collected mature oocytes were inseminated via intracytoplasmic sperm injection (ICSI). Embryos were cultured up to day cleavage stage or blastocyst stage following oocyte retrieval and the embryo transfer (ET) was performed under ultrasound guidance. Luteal phase support consisted

of vaginal progesterone tablets of 200 mg three times daily, administered from the day after oocyte retrieval onwards until 7 weeks of pregnancy (Kyrou et al., 2011, Liu et al., 2012).

Main outcome measures

The primary outcome parameter was live birth rate (LBR) per started cycle. Secondary outcomes were clinical pregnancy rate (CPR), ~~positive biochemical (hCG) rate,~~ and cycle cancellation rate (no response at day 10-11 of the cycle).

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) and categorical data were described as numbers and percentages. Continuous variables were analyzed using the independent t-test or Mann–Whitney U-test depending on the normality of the distribution. Normality was examined by the use of the Shapiro–Wilk test. Categorical variables were analyzed by Pearson's chi-squared test or Fisher's exact test, as appropriate. To account for the non-independent nature of the data (more than one cycle per patient), the association of the dose and type of gonadotropin with the reproductive outcomes (LBR, CPR ~~biochemical pregnancy rate~~), after adjusting for potential confounders, was examined by GEE multivariate regression analysis. All covariates (age, BMI, number of MII oocytes) were simultaneously entered into the GEE multivariate regression model. The assumptions for the final model were successfully tested. All statistical tests used a two-tailed α of 0.05. Analyses were performed using STATA 13.0. A p-value < 0.05 was considered as statistically significant.

Results

Cohort Baseline Characteristics

In total, 484 patients undergoing 1398 cycles were included. Mean (SD) age and serum AMH were 38.2 (3.7) years and 0.28 (0.26) ng/ml, respectively. The daily dose of gonadotropins was either <75 IU/d [11/1398 (0.8%)] or 75 to <100 IU/d [1303/1398 (93.2%)] or ≥ 100 IU/d [84/1398 (6%)]. Overall, rFSH was used for stimulation in 251/1398 (18%) cycles, uFSH in 45/1398 (3.2%) cycles and hp-hMG in 1102/1398 (78.8%) cycles (Table 1).

Reproductive outcomes

In total, ~~biochemical pregnancy rate and~~ CPR per started cycle was ~~were 142/1398 (10.1%) and~~ 119/1398 (8.5%). Live birth was achieved in 80/1398 (5.7%) of cycles.

LBR was similar across different types and doses of gonadotropins [10 (4%) vs 1 (2.2%) vs 69 (6.2%), p-value 0.3; 1 (9%) vs 76 (5.8%) vs 3 (3.6%), p-value 0.51, respectively] (Table II and III). Similarly, ~~positive hCG rates and~~ CPRs did not differ significantly between the different type and doses of gonadotropins [~~21 (8.4%) vs 3 (6.7%) vs 118 (10.7%) p-value 0.3;~~ 17 (6.8%) vs 2 (4.4%) vs 100 (9.1%), p-value 0.37; ~~2 (18.2%) vs 134 (10.3%) vs 6 (7.1%), p-value 0.3;~~ 1 (9%) vs 113 (8%) vs 5 (5%); p-value 0.6, respectively] (Table II and III). Moreover, the number of oocytes retrieved was comparable between the different groups (0.86 ± 0.75 vs 0.75 ± 0.48 vs 0.83 ± 0.64, p-value 0.84; 1.18 ± 0.75 vs 0.82 ± 0.65 vs 0.96 ± 0.82, p-value 0.13) (Table II and III). Cancellation rates were also similar [38 (15.4%) vs 8 (17.8%) vs 185 (16.8%), p-value 0.8; 0 (0%) vs 215 (16.5%) vs 6 (7.1%), p-value 0.3] (Table II and III).

Multivariable Regression Analysis

The GEE multivariate regression analysis adjusting for relevant confounders (age, BMI, number of MII oocytes) showed that the type of treatment strategy (rFSH/uFSH/hp-hMG) and the dose of

gonadotropins (<75 UI/d, 75 to <100 UI/d and ≥ 100 UI/d) were not significantly associated with LBR (p value 0.16 and 0.6, respectively) (Table IV)

Discussion

Our large retrospective study is the first to demonstrate that the type (rFSH/uFSH/hp-hMG) and the daily dose (<75 UI/d, 75 to <100 UI/d and ≥ 100 UI/d) of gonadotropins were not associated with LBR in predicted poor ovarian responders treated with MNC-IVF using GnRH-antagonists.

The term "mild (or minimal) stimulation" refers to the use of low doses of gonadotropins for a short period of time in a gonadotropin-releasing hormone (GnRH) antagonist co-treatment cycle (Nargund et al., 2017), either from the early or the mid-follicular phase onwards. The main benefit of mild stimulation regimens, including MNC-IVF, is that they are more cost-effective than conventional ovarian stimulation in some groups of patients, reducing gonadotropins consumption and thus the overall cost of treatment (Datta et al., 2020; Nargund et al., 2017)

So far, the scientific community had mainly focused on the efficiency of IVF in a (modified) natural cycle compared to IVF after conventional ovarian stimulation in women with predicted POR, without investigating whether the choice of type and dose of gonadotropin could have an impact on the clinical outcome of MNC-IVF cycles. In particular, two previous RCTs have shown similar pregnancy rates when comparing MNC-IVF to the microdose flare-up (Morgia et al., 2004) and the GnRH antagonist protocol (Kim et al., 2009). However, the findings of these studies were flawed by the absence of specific criteria for the selection of poor ovarian responders. In a retrospective study, Lainas *et al.* (2015) found significantly higher LBR after MNC– IVF in predicted POR women selected according to Bologna criteria (Ferraretti et al., 2011), when compared to women stimulated with high-dose gonadotropins (HDOS); albeit, several methodological issues about the statistical approach have been raised (Polyzos et al., 2016), questioning the robustness of the findings. On the

contrary, a retrospective study conducted by Kedem et al. (2014) on a cohort of one hundred eleven poor responders selected according to the Bologna Criteria, concluded that MNC-IVF is of no benefit for genuine poor ovarian responders due to the fact that LBR was <1%. Lastly, a recent retrospective study by Drakopoulos *et al.* (2019) showed similar ongoing pregnancy rate (OPR) in MNC-IVF and HDOS treated Bologna POR women of more than 40 years, suggesting that MNC-IVF may be an option in advanced age women.

Another group of patients in which mild stimulation has gained ground is oncofertility women who wish to preserve their fertility (Koch and Ledger, 2013). The aim of mild stimulation in that case is to reduce the duration of stimulation and gonadotropins total dosage consumption, decreasing thus the time of exposure to high estrogen concentrations (Meirow et al., 2014). In this regard, ultra-mild approaches have also been developed, including the administration of solely letrozole or tamoxifen for ovarian stimulation (Oktay et al., 2005).

Finally, it has to be mentioned that high doses of gonadotropins have been used over the decades in predicted poor responders (POSEIDON groups 3 and 4), increasing cost and treatment burden with low chance to alter their destiny (Klinkert et al., 2005). According to this, and in line with our results, increasing gonadotropins administration to higher doses does not show any improved ovarian response (Bastu et al., 2016; Berkkanoglu and Ozgur, 2010). Indeed, in this challenging category of women, the low number of recruitable follicles is independent from the gonadotropins' dosage administered that only support the cohort of follicles sensitive to stimulation, without generating follicles de novo.

A major strength of this study relies on its large sample size. Moreover, this is the first study evaluating MNC-IVF protocol outcomes in POSEIDON group 3 and 4 poor responders, who represent expected low prognosis women. The POSEIDON classification of poor responders is a relatively recent one and validation is mandatory (Esteves et al., 2019, 2016). Nonetheless, a number of limitations should be considered when interpreting the results. The retrospective nature of the

study is inherent to risk of bias. 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. Furthermore, the choice of the type and/or dose of gonadotropin used in the MNC-IVF cycles was not standardized and based on the physician's discretion.

In conclusion, in women with predicted POR according to the Poseidon classification treated with MNC-IVF, the type and dose of gonadotropin add-back stimulation does not influence live birth rates. Based on our data we considering the use of MNC-IVF with 75IU of gonadotropins daily as add-back therapy a feasible option in predicted poor responders.

Author's roles

P.D. was responsible for the concept and the statistical analysis. F.D.G was responsible for the draft of the article. L.B., S.M., M.D.V., G.V., H.T., C.B., contributed to the interpretation and editing of the article. C.B. contributed to the conception of the article. All authors critically reviewed the content and approved the final version of the work.

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Conflicts of Interest

The authors declare no conflict of interest.

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