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Full length article

The addition of growth hormone adjuvant therapy to the long down regulation protocol in poor responders undergoing in vitro fertilization: Randomized control trial

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ABSTRACT

Objective: to detect the impact of growth hormone (GH) co-treatment to the long down regulation protocol, on the outcomes of IVF/ICSI cycles in poor responders.
Study Design: this parallel open label randomized control trial was conducted in a university hospital. It included 240 females satisfying the bologna criteria for poor responders. The enrolled females were randomized into 2 groups: A (long/GH) receiving GH adjuvant therapy to the long protocol and group B (control) receiving the long protocol alone. The main outcome measure was the live birth rate (fresh, frozen and cumulative).
Results: GH supplementation improved the number of collected oocytes (5.4 ± 1.7 vs. 4.3 ± 2.1), MII oocytes (4.1 ± 2.1 vs. 2.1 ± 1.4), fertilized oocytes (4.0 ± 2.2 vs. 2.0 ± 1.2), transferred embryos (2.4 ± 0.9 vs. 1.6 ± 1.1) and cryopreserved (0.5 ± 0.7 vs. 0.2 ± 0.5). There was no significant difference in the live birth rate whether fresh (17.5% vs. 14.1%) or cumulative (18.3% vs. 14.7%).
Conclusions: Further studies are needed to know the true impact of adding GH to the induction protocols in poor responders, as there was no difference in the live birth rates between the study groups, indicating a lack of trend toward benefit from GH supplementation in poor responders.
Clinical Trial Registration: NCT02338206.

Introduction

The term 'poor responder', in assisted reproduction, refers to a subpopulation of patients, with diminished ovarian reserve, and major problems in conceiving using assisted reproductive techniques. Although, there is no standard definition of a 'poor responder' [1], the Bologna criteria suggested that classification of a poor responder requires two of the following features: (i) old age (≥40 years) or other factor for poor ovarian response, (ii) previous poor ovarian response (≤3 oocytes on ovulation induction), and (iii) low ovarian reserve test (antral follicle count <5–7 or anti-Müllerian hormone <0.5–1.1 ng/ml) [1].

However, several published studies suggested a variety of alternative criteria to define poor responders. Therefore the criteria, which define poor responders and their management options, are still debatable [2–5].

Many different ovarian hyperstimulation protocols have been tried to optimize the outcome for poor responders including increasing the gonadotrophins dose, short agonist protocol, microflare, antagonist protocol, minidose long protocol [6,7]. But the ideal protocol is not yet recognized.

Comparing the long protocol versus the short agonist protocol. Studies have shown that the long protocol gives better results when compared with the short protocol. On the other hand, the long protocol has a major adverse effect which is the long ovarian suppression, which is, in poor responders especially, will require the use of higher gonadotrophin doses and subsequently a modest ovarian response. Different modalities have been proposed to improve the outcome as the use of mini- dose long protocol as well as the addition of adjuvant treatment such as growth hormone (GH) [8].

Growth hormone, have long been studied as a co-treatment to the various ovarian stimulation protocols. GH can act directly or indirectly by releasing insulin-like growth factor 1 (IGF-1), as well as regulating oocyte maturation by increasing the ovarian sensitivity to gonadotrophins and enhancing early follicular

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development [9]. However, its effect on IVF cycle outcomes' is still controversial as some studies demonstrated its positive impact on GH oocyte, endometrium and embryo related outcomes, and others failed to reach the same result [10–13].

The aim of this study was to detect the impact of adding GH, to the long down regulation protocol, as adjuvant therapy on the outcomes of IVF/ICSI cycles in poor responders.

Material and methods

This open label randomized control trial was carried out in Cairo University hospital, Kasr Al-Aini, Egypt, from April 2015 to November 2017. Before commencing the trial, it was approved by the university ethical committee "institutional review board".

The study included poor responder females who satisfied the bologna criteria [1]. Females above 45 years, or having FSH > 20 IU/L, and those with other causes of infertility as tubal occlusion or severe male factor as severe azospermia or teratospermia, as well as couples who refused to participate were excluded from the trial.

Prior to starting the study, detailed explanation of the protocol and intervention to all the enrolled couples was done and a signed consent was obtained.

The participating females underwent full history taking, medical and gynecological examination. Transvaginal sonographic (TVS) evaluation by Voluson 730 Pro ultrasound machine (GE, Fairfield, CT) was done.

The participants were then randomized into two groups; group A: (Long/GH) undergoing ovarian stimulation the long down regulation protocol with the addition of GH, and group B (Control group): ovarian stimulation was done by the long protocol only.

Randomization was performed using specific computer programs and the results were placed in opaque sealed envelopes with the patients' number written outside (and after opening the envelope, it would reveal which group the patient belonged to (A or B).There was no blinding to either the participants or study conductors.

The treatment protocol was as following:

Group A and B: received down-regulation with triptorelin (Decapeptyl; Ferring, Switzerland) 0.1 mg/day from day 21 of the previous cycle. Reducing it to 0.05 mg/day from the start of the following cycle and continued till HCG administration.

Gonadotropins therapy started at day 2-3 of the menses by a dose of 300 IU of recombinant human FSH (Gonal-F, Serono, Switzerland) after confirming that proper down regulation was achieved. The gonadotropin dose was adjusted from day 6 of stimulation according to the ovarian response monitored by serial TVS until the day of HCG administration. 10000 IU of HCG (Choriomon, IBSA) were given IM, when at least two follicles had reached a diameter of 18 mm or more.

Group A patients (long/GH) received adjuvant Growth hormone co-treatment 2.5 mg subcutaneous injection of GH (equivalent to 7.5 IU) (Norditropin pen, Novo Nordisk, Denmark) from day 21 of the previous cycle along with GnRHa, until the day of HCG. Analysis of the serum progesterone, LH and E2 was performed on the day of HCG administration.

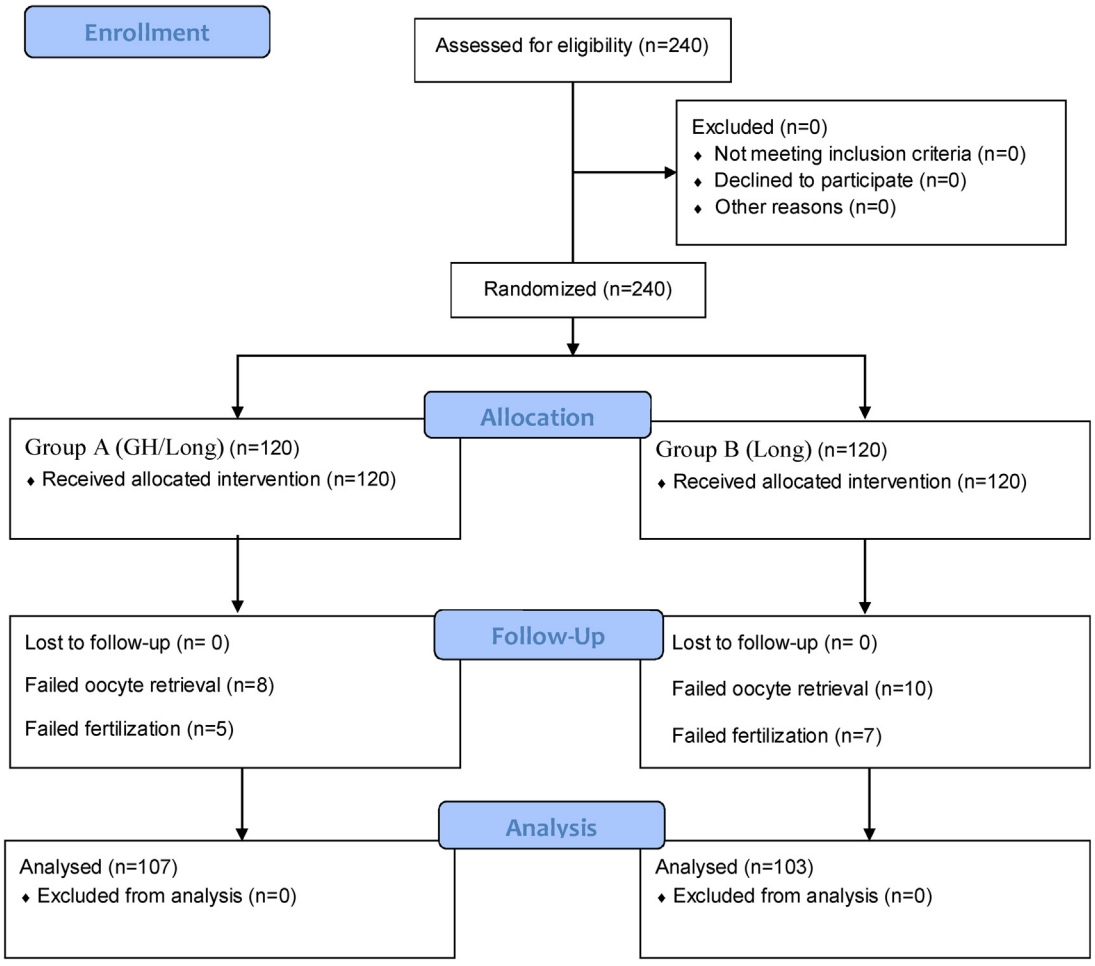

Fig. 1. CONSORT 2010 Flow Diagram.