Research Article

Gynecology & Reproductive Health

Growth Hormone Improves Cycle Outcome and Pregnancy Rate in Patients with Poor Ovarian Response Undergoing *In Vitro* Fertilization

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Received: 14 April 2018; **Accepted:** 06 May 2018

Citation: Sabrina A Gerkowicz, Salatnay Henriquez, Michael Saad-Naguib, et al. Growth Hormone Improves Cycle Outcome and Pregnancy Rate in Patients with Poor Ovarian Response Undergoing In Vitro Fertilization. Gynecol Reprod Health. 2018; 2(3): 1-5.

ABSTRACT

Objective: *To examine the effect of growth hormone (GH) on in vitro fertilization (IVF) cycle outcome in patients with poor ovarian response (POR) as defined by the ESHRE Bologna criteria.*

Materials and Methods: *Ninety-nine patients with POR undergoing a total of 117 IVF cycles using gonadotropin-releasing hormone (GnRH) antagonist protocol from January 2012 through October 2016 in a single-institution were eligible and included in our study. Forty patients (50 cycles) received GH (5 IUI/day), and were compared to a control group of 59 patients (67 cycles) matched in age and FSH who did not receive GH. Primary outcomes were ongoing clinical pregnancy rate and pregnancy outcome. Statistical analysis was performed using chi-squared and student t-tests.*

Results: *There was no statistical difference between the two groups regarding the peak estradiol level, percentage of mature oocytes, fertilization rate, blastocyst formation rate, number of embryos transferred, or cancellation rate. There was a significantly shorter duration of stimulation and higher number of oocytes retrieved in the GH group compared to controls ($p<0.05$ and $p<0.03$; respectively) and a statistically significant difference in the percentage of pregnancy rate; 30% for GH group vs. 18% for the control ($p<0.05$).*

Conclusions: *GH could improve pregnancy rate in patients with POR.*

Keywords

In vitro fertilization, Growth hormone, Poor responder.

Introduction

Over the past decade, there has been a significant improvement in pregnancy rates in patients undergoing in vitro fertilization (IVF); however, similar gains have yet to be achieved for patients with poor ovarian response (POR). The incidence of POR is estimated to be between 9 to 24%, and it continues to pose a significant challenge in the field of assisted reproductive technologies [1]. In 2011, the European Society of Human Reproduction and Embryology (ESHRE) published the Bologna criteria that provided the first standardized definition of "poor response" to ovarian stimulation [2]. Subsequent research to best identify these patients and tailor stimulation protocols to improve their response has been pursued, leading to several revisions in protocols and the proposition of interventions to address this issue [1]. Despite this, the pregnancy rate still remains low for this patient population [3].

Several studies have examined the use of growth hormone (GH) in POR patients with controversial results. The idea of adjuvant GH stems from both animal and human studies demonstrating that growth hormone plays an important role in ovarian steroidogenesis and follicular development. Studies have found an improvement in fertilization rates compared to controls [4] and compared to prior cycles without GH treatment [5]. They have also shown an improvement in oocyte and embryo quality [5-8], as well as an improvement in cytoplasmic competence and maturation [6,7]. Subsequently improvements in implantation have been noted in prior studies with conflicting results.

Despite these findings, GH use still remains experimental and is not formally used due to cost of GH and the lack of uniformity of POR definition, stimulation, and GH protocols in studies previously published. Studies have also been small and lack statistical power, therefore the usefulness and application of GH has been limited. In our study, we sought to establish a homogenous population by applying the ESHRE Bologna criteria [2] for POR in patients undergoing IVF using the GnRH antagonist stimulation protocol and examining the effects of growth hormone on IVF cycle outcome and pregnancy rate.

Materials and Methods

In total, 99 patients with POR undergoing a total of 117 IVF cycles using GnRH antagonist protocol in a single-institution were eligible and included in our study. Forty patients undergoing a total of 50 stimulation cycles were identified as poor responders by meeting at least two of the three ESHRE Bologna criteria for poor ovarian response. Patients with missing data were excluded from the study. These patients were randomly matched by age and baseline follicle-stimulating hormone (FSH) to patients also identified as POR who did not receive GH with their stimulation cycle, forming a control group of 59 patients with a total of 67 cycles.

Patients in the GH group received a daily injection of 5 IU recombinant human growth hormone beginning three days prior to stimulation start through the day of oocyte retrieval. In both groups ovarian stimulation was started from the third day of the menstrual cycle with human menopausal gonadotropin (HMG) and recombinant FSH. Ovarian response monitoring included serial vaginal ultrasonography and serum estradiol (E2) levels. Measurements for dominant follicles, trigger, and retrieval were performed as per usual stimulation protocols. Conventional IVF or intra-cytoplasmic sperm injection (ICSI) was performed based on clinical indications. Embryos were transferred on day 3 or day 5 after oocyte retrieval. Luteal phase support with progesterone was administered beginning on the day after oocyte retrieval.

Outcome Definitions and Measures

Chemical pregnancy was defined as rising serum beta human chorionic gonadotropin (beta hCG) twelve days after embryo transfer. Clinical pregnancy was identified as observation of fetal heart activity by transvaginal ultrasound. Ongoing pregnancy was defined as pregnancy proceeding beyond the 12th gestational week. Abortion included all continuing subtypes (missed, spontaneous etc.) and was defined as pregnancy loss before 20th week of gestation. Cycle cancellation occurred when no oocyte(s) was obtained on the day of scheduled retrieval, and/or if no embryos were available for transfer secondary to failed fertilization and/or cleavage. Primary outcome measures were ongoing clinical pregnancy rate and pregnancy outcome. Secondary outcomes included total days of stimulation, number of oocytes retrieved, oocyte maturity, fertilization rate, blastocyst formation, and number of embryos transferred.

Statistical Analysis

Statistical analysis was performed using chi-squared and Student t-tests when applicable. $P<0.05$ was considered statistically significant.

Results

Patient Background

Demographic factors including age, body mass index (BMI), baseline FSH, anti-mullerian hormone (AMH), and number of previous IVF cycles were compared between the GH group and control group. No statistical difference was noted regarding age (mean age of 39.14 years vs. 39.98 years in GH group vs. control) and FSH (10.01 IU/mL ± 5.22 vs. 8.66 IU/mL ± 3.47; $p = 0.068$) (Table 1). Patients in the GH group had a significantly higher number of previously failed IVF cycles (2.36 ± 1.27 vs. 1.32 ± 0.72; $p<0.001$) and lower baseline AMH levels (0.69 ng/mL ± 0.54 vs. 1.05 ng/mL ± 0.84; $p<0.05$) compared to the control group. Primary etiology of infertility was diminished ovarian reserve; other etiologies of infertility of both patient groups were comparable.

Parameter	GH (+)	GH (-)	p value
Mean age ± SD (years)	39.14 ± 0.51	39.98 ± 2.03	0.07
Mean BMI ± SD	24.54 ± 5.80	25.59 ± 6.30	0.374
Mean baseline FSH ± SD (IU/mL)	10.01 ± 5.22	8.66 ± 3.47	0.068
Mean baseline AMH ± SD (pmol/L)	0.69 ± 0.54	1.05 ± 0.84	0.05
Max estradiol level ± SD (pg/mL)	1742.54 ± 1059.01	2409.21 ± 2955.73	0.054
No. previous IVF cycles	2.36 ± 1.27	1.32 ± 0.72	0.001

Table 1: Baseline Patient Characteristics.

Stimulation Cycle and Transfer

The peak serum estradiol level achieved at hCG trigger day was not statistically significant between the groups (1742.5 pg/mL ± 1059 vs. 2409.2 pg/mL ± 2955.7; $p=0.054$) (Table 1). There was significantly shorter duration of stimulation (10.94 ± 1.97 days vs. 11.58 ± 1.73 days) and higher number of oocytes retrieved (7.77 ± 4.87 oocytes vs. 6.11 ± 4.36 oocytes) in GH group compared to control ($p<0.05$ and $p<0.03$; respectively) (Table 2).

Parameter	GH (+)	GH (-)	p value
No. Cycles (total)	50	67	
Total days of stimulation	10.94 ± 1.97	11.58 ± 1.73	0.037
Total dose of gonadotropin (IU)	5775 ± 1372	5594 ± 1459	0.499
No. Oocytes retrieved	7.77 ± 4.87	6.11 ± 4.36	0.033
% Mature oocytes	0.84 ± 0.15	0.85 ± 0.24	0.40
% Normal fertilization	63.76 ± 33.11	65.99 ± 30.31	0.35
% Blastocyst formation from 2PN (day 5 transfer)	41.12 ± 24.42	52.26 ± 23.97	0.09

Table 2: Stimulation Cycle Results.

There was no statistically significant difference between the two groups regarding the percentage of mature oocytes, fertilization rate, blastocyst formation rate, or number of embryos transferred (Table 2). There were no serious or adverse reactions requiring termination of therapy in the GH group.

Cycle Outcomes

There was a statistically significant difference in the clinical pregnancy rate per embryo transfer between the two groups. The clinical pregnancy rate was 30% for the GH group vs. 18% for the control group (12 clinical pregnancies out of 40 ETs in GH group vs. 10 clinical pregnancies out of 57 ETs in the control group; $p<0.05$) (Figure 1). Of the clinical pregnancies, there were 10 live births and 2 spontaneous abortions in the GH group, compared to 6 live births and 4 spontaneous abortions in the control group ($p<0.01$). Abortion and ectopic rates were 7.5% vs. 7.1% and 0 vs. 3.4%, in the patients who received GH vs the control patients, respectively. There were a total of 20 cycle cancellations, 10 in both the GH and control groups. In both groups, there was one cancellation prior to oocyte retrieval, and nine patients failed to reach embryo transfer.

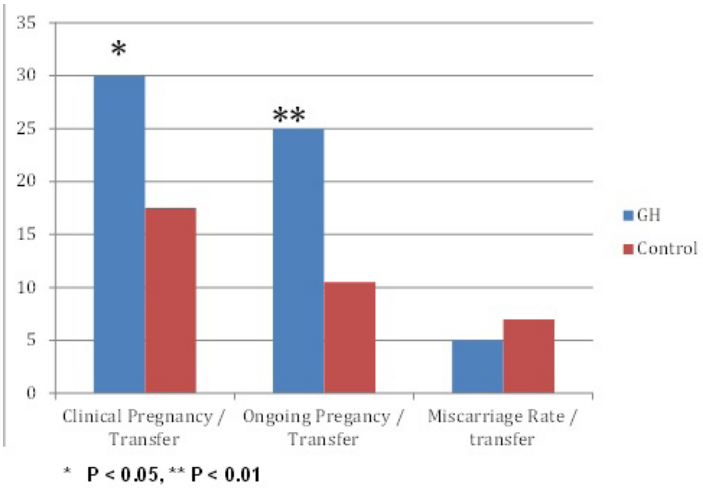

Figure 1: Clinical pregnancy and ongoing pregnancy.

Discussion

In our study we found a significant difference in ongoing clinical pregnancy rate of 30% vs. 18% in the GH group compared to the control group, respectively. In a systemic review and meta-analysis by Kyrou et al., pooling the results of the included studies revealed an additional 16% increase in pregnancy rate in patients who received GH vs. placebo [1]. Similarly, a systematic review and meta-analysis by Kolibianakis et al. found an increase in live birth rate of 17% in patients receiving GH vs. controls. Our study showed an increase in live birth rates by 12% for patients who received GH, which is still consistent with published data.

Our study also found a significant increase in number of oocytes retrieved in patients receiving GH vs. controls (7.77 +/- 4.87 vs. 6.11 +/- 4.36; $p = 0.033$), similar to [8,9]. There was no significant sifference; however, between the two groups regarding the percentage of mature oocytes, fertilization rate, and blastocyst formation rate as shown in Table 2. This is contrary to findings by [8,10], who report an increased number of metaphase II oocytes and 2-pronuclear stage embryos (2PNs) in patients treated with GH.

We found a decrease in total days of stimulation in the GH group compared to the control group, but did not find a significant difference in total dose of gonadotropins. Early studies by Homburg and Ostergaard demonstrated a 43% reduction in the dose of required stimulation gonadotropins and a significant reduction in the duration of treatment [11,12]. We did not, however, find a significant difference between peak serum estradiol levels on human chorionic gonadotropin (hCG) trigger day between the two groups. This is contrary to a study by [13,8] where they found increased peak serum estradiol levels in women co-stimulated with GH compared to controls [8,13]. However both studies used higher doses of GH and prolonged GH administration compared to our study [8].

Growth hormone supplementation has been shown to enhance the effect of gonadotropins on granulosa cells [1, 14, 15]. It also enhances oocyte, nuclear, and cytoplasmic maturation, as well as blastocyst development [6,7,16-19]. Furthermore, it was found that patients receiving adjuvant GH therapy had increased serum and follicular fluid levels of insulin-like growth factor I (IGF-I) [12], estrogens [14] and growth hormone [13] all of which have been associated with improved oocyte maturity, fertilization, and embryo quality, thus improved IVF outcomes [20,21]. These findings and hypotheses of GH action have guided subsequent study designs on the dose and timing of GH administration. Many of the published studies begin GH administration after the start of ovarian stimulation and continue until hCG trigger with doses ranging from 4 to 24 IUs of GH per injection.

In a study by Yovich and Stanger (2010) both pre- or peri-treatment cycle administration of GH were tested by administering 10 IU of GH given on day 7, 14, 21 of previous cycle, and day 2 of treatment cycle (pre-treatment) vs. day 21 of preceding cycle and day 2, 6, 8, 10, 12 of treatment cycle (peri-treatment). Both of these administration schedules were guided by the following theories on modes of GH action: either a synergistic effect of FSH stimulation on follicle recruitment and development, or a role in oocyte maturation [7,8,22,23]. Clinical pregnancy rate per embryo transfer in pre-treatment group was 40% compared to 8% in controls and 24% in the peri-treatment group compared to 8% in controls. They concluded that GH administration in the cycle preceding the IVF cycle led to better outcomes compared to GH administration during the treatment cycle.

In our study, we started GH administration three days prior to start of stimulation with a standard GnRH antagonist protocol and continued with daily GH injections through day of oocyte retrieval. We therefore aimed to maximize the GH benefit, spanning both of these important windows while specifically including the final stages of oocyte and follicular development and maturation that occur after hCG trigger. We chose to administer a dose of 5 IU GH daily as low doses of 4IU have been proven to be effective [8,9]. To our knowledge, we are the first to administer GH through day of oocyte retrieval.

Despite the promising findings related to adjuvant GH treatment in poor responder patients undergoing IVF, GH remains experimental

and far from the standard of care. Much of this can be attributed to the drawbacks of the current literature regarding GH and IVF in poor responders – which include the lack of uniformity of GH dose or timing of GH administration, the heterogeneity in definition of poor responder and patient populations included, and the differences in stimulation protocols in prior studies. In addition, small sample sizes of the prior studies and inconsistent/deficient reporting of adverse events further complicate the application of the results [1,22]. Cost has also been cited as a significant factor, which might further impede more widespread use of GH in IVF. Long-term outcome data is also lacking.

Conclusions

Our study of patients classified as POR using the ESHRE criteria undergoing IVF with GH co-treatment revealed a significant increase in pregnancy rate, number of oocytes retrieved, and a shorter duration of stimulation. Our study is unique in that we attempted to minimize previously mentioned confounding factors and reduce selection bias via implementation of the standardized POR definition criteria and GnRH antagonist stimulation protocol. Our paper is the first to implement the ESHRE classification as a means of selecting a patient population; therefore, our study results could yield more applicable and generalizable results to the targeted population. We also implement a low dose GH administration regimen given through oocyte retrieval in order to include the final stages of follicular and oocyte maturation. This study was limited, however, by its retrospective design and non-randomized nature, which inherently poses some limitations. Further studies are needed to determine the most effective dose of GH required, as well as an optimal administration regimen to achieve clinical benefit. We believe that GH could be a very promising adjuvant to IVF stimulation protocols for a well-defined patient population with POR.

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