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Original Article

Growth hormone supplementation may improve the pregnancy rate and endometrial receptivity among women aged more than 40 years undergoing in vitro fertilization

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ABSTRACT

Background: Growth hormone (GH) supplements have been shown to improve pregnancy and live-birth rates, suggesting that GH has a beneficial effect on oocyte quality. However, the effects of GH on implantation and receptivity remain unknown. This study evaluated the efficacy of GH in women aged more than 40 years participating in assisted reproductive technology (ART) programs.

Methods: Cycles of in vitro fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) in women aged more than 40 years (range, 40–43 years) between January 2009 and March 2014 at a university-based reproductive center were reviewed. Women were divided into two groups, those with and without GH co-stimulation. ART outcomes were evaluated.

Results: Supplement of GH significantly lowered cycle cancellation rate by increasing the per cycle rates of harvesting at least one oocyte and transferring at least one embryo (80.2% vs. 69.4%). GH increased the per cycle clinical pregnancy (15.9% vs. 6.8%) and favorable ultrasonic endometrial pattern (60.9% vs. 39.3%) rates. GH also increased the per transfer clinical pregnancy (19.9% vs. 9.9%) and implantation (11.2% vs. 5.2%) rates and the rate of a favorable ultrasonic endometrial pattern (65.1% vs. 45.0%).

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Conclusion: GH supplementation reduces the cycle cancellation rate in women aged more than 40 years, and increases the favorable ultrasonic endometrial pattern, pregnancy, and implantation rates by its beneficial actions on embryo quality and endometrial receptivity.

At a glance of commentary

Scientific background on the subject

Growth hormone (GH) supplements to control ovarian hyperstimulation (COH) have been shown to improve pregnancy and live-birth rates, suggesting that GH has a beneficial effect on oocyte quality. To date, the relationship between GH and implantation has not been thoroughly assessed.

What this study adds to the field

Growth hormone supplementation reduced the cycle cancellation rate in women aged more than 40 years poor responders, while increasing the rates of favorable ultrasonic endometrial pattern, implantation and pregnancy by having beneficial actions on embryo quality and endometrial receptivity.

Adjuvant therapies to control ovarian hyperstimulation (COH), including treatments with growth hormone (GH), pyridostigmine, glucocorticosteroids, and transdermal testosterone, have been reported to improve pregnancy rates in poor ovarian responders (PORs) [1–4]. Although studies have shown that the addition of GH may improve the probability of pregnancy in PORs [5–8], two trials found that GH cotreatment during antagonist protocols of patients with a history of poor response during previous in vitro fertilization-embryo transfer (IVF-ET) cycles did not increase pregnancy rates [9,10]. The finding, that GH supplementation did not increase controlled ovarian hyperstimulation response or the number of oocytes but improved pregnancy and live-birth rates, suggested that GH may enhance oocyte quality [7]. At present, however, there is insufficient evidence to recommend that poor responders be treated with GH, because studies of these methods have used different definitions of POR, making it difficult to interpret their relative effects.

The Bologna criteria, first proposed in 2011, sought to standardize the terminology and define POR [11]. However, recent research has indicated that women classified as PORs by these criteria are still highly heterogeneous [12]. Thus, current criteria for POR include heterogeneous populations and, importantly, do not offer any recommendations for clinical handling. Recently, the POSEIDON group (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**D** **O**ocyte **N**umber) proposed a new stratification of assisted reproductive technology (ART) [13] in patients with reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotropins [14].

Indeed, the prevalence of PORs is greater than 50% in women aged more than 40 years [11]. Maternal age has been found to predict the outcomes of ARTs, as pregnancy rates decline with age, especially after age 40 years [11,15–17]. Interestingly, impaired meiotic spindle assembly has been reported in oocytes of women aged 40–45 years [18].

Pregnancy and live birth do not depend solely on oocyte quality, but also on implantation and endometrial effects. To date, the relationship between GH and implantation has not been thoroughly assessed. The present study analyzed women aged 40–43 years undergoing ART treatment at our institution.

Materials and methods

Subjects

This study included women aged more than 40 years (range, 40–43 years) with previous experience of POR or poor ovarian reserve (POSEIDON group 4) undergoing their first ART treatment in our institution between January 2009 and March 2014. All women were informed about the off-label use of GH and all provided written informed consent. These patients were given the option of using GH, but may or may not have elected to utilize GH during the cycle when initially offered (due to costs or other concerns). This cohort study evaluated 182 cycles with and 160 without GH supplementation. Women were excluded if they had a history of intrauterine synechiae due to traumatic uterine surgery, congenital mullerian duct anomaly, endometrial fluid from hydrosalpinx, submucosal myoma, or endometrial lesions incidentally found during the course of COH. Patients were unselected for sperm parameters.

Ethics statement

This study was approved by the Ethics Committee of Chang Gung Memorial Hospital (CGMH). Approval from the institutional review board was obtained for the analysis of this series (CGMH: 103-0379B and 102-5596A3).

Controlled ovarian hyperstimulation protocol

The ovarian stimulation protocols included gonadotropin-releasing hormone (GnRH) agonist (Lupron, Abbott, IL, USA), with all stimulation protocols following standard clinical practices [19,20]. Each patient was administered an initial dose of 150–300 IU human menopausal gonadotropin (hMG) or recombinant follicle-stimulating hormone (FSH; Gonal-F, Merck Serono, Aubonne, Germany). Women undergoing the GnRH antagonist protocol who had at least one

leading follicle ≥14 mm in diameter received an additional 0.25 mg/day GnRH (Cetrotide, Merck Serono, Aubonne, Germany) until the day of human chorionic gonadotropin (hCG) injection. Doses were adjusted during each cycle based on individual responses to gonadotropin, as assessed by measuring serum estradiol (E2) concentration and sonographic monitoring of follicular growth. Following the maturation of two additional follicles, each ≥17 mm in diameter, a 6500 IU dose of hCG (Ovidrel, Merck Serono, Modugno, Italy) was administered, and oocytes were retrieved 36 h later by transvaginal aspiration under ultrasound guidance. Patients receiving GH were administered 8 IU/day GH (Saizen®, Merck Serono, Modugno, Italy), starting on the day the first leading follicle was ≥14 mm in diameter until the day of hCG administration. Standard IVF and ICSI procedures were used for oocyte grading, assessment of fertilization, embryo culture, zygote and embryo grading and embryo transfer with the luteal phase supported [20,21].

Hormone measurements

FSH and luteal hormone (LH) were measured on day 3 of the menstrual cycle before gonadotropin administration. Serum progesterone and E2 concentrations were measured on the day of hCG administration during each IVF cycle using standard immunoassay systems (ADVIA Centaur ® XP, Siemens, Tarrytown, NY, USA). The intra-assay and inter-assay coefficients of variation were 5.2% and 3.5%, respectively, for progesterone and 5.0% and 4.1%, respectively, for E2.

Assessment of endometrial patterns and receptivity

Endometrial patterns were determined by transvaginal ultrasonography [22,23]. Endometrial thickness was divided into two categories, < 10 mm and >10 mm. Endometrial pattern, which was categorized as triple line or non-triple line, was assessed in the central longitudinal axis from the echogenic interphase of the endometrium junction. The triple-line pattern was defined as the appearances of triple hyperechoic lines in the center of the uterine body, with other patterns defined as non-triple line. An endometrial triple line pattern with a thickness >10 mm was defined as a favorable endometrial ultrasonographic pattern.

Statistical analysis

All statistical analyses were performed with SPSS 20.0 software (Statistical Package for Social Sciences, Inc., Chicago, IL, USA). Continuous data were summarized as the mean ± standard deviation. Multiple regression analysis using the stepwise forward procedure (multivariate analysis) was performed to identify independent factors and to test for interactions between covariates. Normally distributed variables were analyzed by two independent t-tests. Categorical variables, reported as proportions, were compared using the chi-square or Fisher's exact test, as appropriate. All p values were two-sided, with $p < 0.05$ considered statistically significant.

Results

A review of the medical records of our institution identified patients aged 40–43 years who underwent their first ART treatment in our institution between January 2009 and March 2014. Fifteen women, nine with and six without GH supplementation, were excluded, four due to a history of intrauterine synechiae, six due to mullerian duct anomalies, three due to endometrial lesions, and two due to endometrial fluid. This study therefore included 342 cycles, 182 with and 160 without GH supplementation. The addition of GH resulted in statistically significant advantages, including higher percentages of cycles during which at least one oocyte was retrieved and at least one embryo was transferred [Table 1]. The occurrence of a favorable endometrial ultrasonographic pattern on the day of hCG administration, the clinical pregnancy rate (per cycle and per transfer) and the implantation rate per transfer were significantly higher in the GH than in the non-GH group [Table 1]. Comparisons between the 146 embryo transfer cycles with and the 111 without GH showed no significant differences in age, body mass index (BMI), days of gonadotropin stimulation, gonadotropin doses, number of oocytes collected, normal fertilization rate and concentrations of most hormones (except for progesterone) on hCG days [Table 2]. Binary logistic regression analysis showed that patient age, transfer embryo score, and the addition of GH were significantly associated with pregnancy rates per cycle and per transfer [Table 3].

Table 1 Demographic and clinical characteristics of patients who underwent IVF regimens with (n = 182) and without (n = 160) cycles of GH stimulation.

Variable	Cycles with GH (n = 182)	Cycles without GH (n = 160)	*p* value
Age (years), mean ± SD (range)	41.3 ± 1.2 (40–43)	41.1 ± 1.2 (40–43)	NS
Favorable good EM pattern (COH cycles)	60.9% (111/182)	39.3% (63/160)	<0.001
No. of cycles with no oocytes retrieved or no embryos available	36 (19.8%)	49 (30.6%)	0.021
Clinical pregnancy rate per cycle	15.9% (29/182)	6.8% (11/160)	0.009
No. of embryo transfer cycles	146	111	
Favorable good EM pattern (Transfer cycles)	65.1% (95/146)	45.0% (50/111)	0.001
Clinical pregnancy rate per transfer	19.9% (29/146)	9.9% (11/111)	0.029
Implantation rate per transfer	11.2% (35/313)	5.2% (13/248)	0.012

All values reported as percentages, unless indicated otherwise.
Abbreviation: NS: not significant.
Good EM pattern: favorable endometrial ultrasonographic pattern, multilayered triple-line pattern and thickness >1.0 cm.

Table 2 Demographic and clinical characteristics of patients who underwent transfer cycles of IVF/ICSI regimens with (n = 146) and without (n = 111) GH stimulation.

Variable	Transfer cycles with GH (n = 146)	Transfer cycles without GH (n = 111)	p *value*
Age (years)	41.3 ± 1.2	41.0 ± 1.1	*NS*
BMI, kg/m^2	22.2 ± 2.7	22.6 ± 3.1	*NS*
Ampoules of 75 IU FSH	33.9 ± 12.3	37.7 ± 14.4	*NS*
Injection days	8.3 ± 1.8	9.3 ± 2.2	*NS*
Follicles ≥10 mm in diameter on hCG day	6.5 ± 3.7	7.5 ± 4.8	*NS*
Follicles ≥16 mm in diameter on hCG day	3.5 ± 2.0	3.3 ± 2.2	*NS*
LH on hCG day (mIU/mL)	3.6 ± 5.7	3.6 ± 3.6	*NS*
Mean no of oocytes collected	4.2 ± 2.3	4.6 ± 3.9	*NS*
Normal fertilization rate	78.8%	77.6%	*NS*
Progesterone on hCG day (ng/mL)	0.8 ± 0.8	1.1 ± 0.8	0.04
Estradiol on hCG day (pg/mL)	1403.2 ± 1067.6	1608.5 ± 1342.5	*NS*
No of embryos transferred	2.2 ± 1.0	2.3 ± 0.9	*NS*
Score of embryos transferred	5.8 ± 3.9	5.7 ± 4.0	*NS*

Note: Results are expressed as mean ± SD.
Abbreviation: NS: not significant.

Table 3 Binary logistic regression analysis of variables associated with pregnancy.

Variable	B	SEM	Wals	*p* value	Exp(B)	95% CI
Clinical pregnancy rate per *cycle*						
Age of female partner	−1.443	0.373	14.955	< 0.001	0.236	0.114, 0.491
Score of embryo transferred	−0.219	0.066	11.099	0.001	1.245	1.095, 1.417
Add GH or not	−1.862	0.577	10.034	0.002	0.161	0.052,0.498
Clinical pregnancy rate per *transfer*						
Age of female partner	−0.863	0.234	13.561	< 0.001	0.422	0.266, 0.668
Add GH or not	−0.962	0.450	4.568	< 0.001	0.382	0.158, 0.923

Discussion

This study assessed the effects of GH in women aged more than 40 years undergoing IVF/ICSI cycles. We found that ovarian co-stimulation with GH was significantly associated with a favorable endometrial ultrasonographic pattern and IVF outcome. Moreover, we found that GH may improve endometrial receptivity.

Several physiological and pathophysiological considerations suggest that GH supplementation may benefit women undergoing ART [1,7,9,24–26]. Data from both human and animal studies suggest that GH plays a critical role in the processes of ovarian steroidogenesis and the development of follicles. GH is also thought to play an important role in ovarian function, stimulating follicular development, estrogen production, and oocyte maturation [27–29].

Insulin-like growth factor (IGF)-1 has been shown to improve the response to gonadotropin stimulation [28]. During folliculogenesis and oogenesis, oocytes are surrounded by granulosa cells. During follicular maturation, the oocyte and surrounding granulosa cells communicate with each other. In several animal models, exogenous administration of GH increased follicular IGF-1, as well as oocyte competence [7,30]. In addition, GH may increase the DNA repair capacity in oocytes [31].

Several studies have assessed the ability of adjuvant GH to improve the results of IVF/ICSI cycles in PORs. These studies have reported that GH increased the numbers of retrieved oocytes [1,9,25] and of MII oocytes [25], resulting in higher fertilization rates and more embryos available for transfer. A systematic review [7] showed statistically significant GH-associated increases in both the clinical pregnancy and live birth rates, encouraging the use of adjuvant GH during IVF protocols in PORs without increasing adverse events. GH seems to be underutilized as adjuvant therapy in PORs. Our results suggest that combining supplementary GH with a proven POR protocol is clinically sound, although the specific subgroups of patients who would benefit most from such treatment could not be identified.

The present study, however, showed that use of GH reduced the cycle cancellation rate by increasing the likelihood of retrieving at least one oocyte per cycle [Table 1], a finding consistent with that of a recent meta-analysis [26].

To our knowledge, this study is the first to assess the effects of cotreatment with GH on the endometrium of women classified as POSEIDON group 4 undergoing GnRH analog IVF/ICSI cycles. A previous study of women aged more than 40 years found that the addition of GH to the ICSI program significantly increased live birth rates [24]. Although this effect was likely due to an improvement in oocyte development potential, GH may also have an effect on the uterus. That study, however, provided no information about the effects of GH on the endometrium.

The supplement of GH showed a significant association with a favorable endometrial pattern. Endometrial receptivity is defined as the ability of the endometrium to successfully attach the blastocyst and to nourish it and keep it alive [32]. This can only be achieved after the endometrium undergoes a number of histological changes while also increasing in thickness. Although histological changes can only be assessed by biopsy and assessments of molecular endometrial receptivity have the

limitations of in vitro molecular assays, transvaginal ultrasound is a non-invasive, easy and reliable method to measure parameters like endometrial thickness and pattern [22,23,33,34]. It may therefore be appropriate to use a simple and accurate measuring tool like grey-scale ultrasound to evaluate endometrial thickness, pattern or volume as a surrogate marker of endometrial receptivity. Many studies have used ultrasound to examine the endometrium; these studies have yielded varying results, with each having individual limitations. Nevertheless, our findings suggest that ultrasound examination of the endometrium cannot predict successful implantation [Table 3]. In practice, however, ultrasound may provide at least some information about endometrial receptivity during ART. Endometrial pattern has been found to correlate with IVF success rates, with an endometrium of adequate thickness (>10 mm) and a trilaminar pattern having more favorable results than an endometrium with a homogeneous luteal pattern on the day of hCG treatment [34,35].

We found that increasing the dose of GH could increase the expression of mRNAs encoding LIF, CSF-1, IL-1RtI and integrin B3. The expression profiles of endometrial receptivity markers [32,36,37] were assessed in human endometrial T-HESCs cells by quantitative real-time RT-PCR (Supplemental figure). We also found that GH stimulation of T-HESCs significantly increased the percentage of blastocyst spheroids that attach to underlying endometrial cells (Supplemental figure).

Our finding was supported by a recent report, showing that GH can improve pregnancy outcomes in patients with thin endometrium who undergo frozen embryo transfer. GH was found to act on human endometrial cells, promoting proliferation and vascularization and up-regulating receptivity-related molecular expression [38].

Another case report found that GH may play a role not only in inducing ovulation, but in enhancing endometrial thickness in women with hypopituitarism [39]. GH may also improve uterine receptivity of RIF patients, further confirming our results [40].

We also found that progesterone concentrations during transfer cycles were significantly lower in the GH group. A premature increase in serum progesterone concentration has been associated with lower pregnancy rates in various ART cycles [21]. Although the mechanisms by which elevated P4 has a detrimental effect on IVF outcomes remain unclear, premature P4 elevation is thought to cause an asynchronous endometrium, resulting in a negative impact on implantation and pregnancy [21]. It is therefore worthwhile to further study the direct or indirect interactions between GH and progesterone.

The effects of GH on the endometrium in GnRH antagonist cycles are unclear, as are the effects of GnRH antagonists used in IVF protocols on endometrial tissue remodeling, embryo implantation and the programming of early pregnancy. GnRH antagonists may have detrimental effects on endometrial receptivity and embryo implantation, which may explain the lower pregnancy rate during GnRH antagonist cycles [41,42]. However, the present evaluation of the effects of GH addition on women undergoing IVF found no significant differences between GnRH agonist and antagonist protocols.

In conclusion, GH supplementation reduced the cycle cancellation rate in women aged more than 40 years poor responders, while increasing the rates of favorable ultrasonic endometrial pattern, implantation and pregnancy by having beneficial actions on embryo quality and endometrial receptivity. These findings indicate that GH supplementation can improve outcomes in IVF patients with POR.

Conflicts of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2019.05.003.

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