

# EMPIRICAL USE OF GH IN IVF IS USELESS

THE LARGEST RANDOMISED CONTROLLED TRIAL

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# Introduction

Based on the available evidence, there is an uncertainty regarding the benefice of use of GH therapy in IVF. The literature lacks a well-designed high quality RCT with an adequate sample size to answer the question in the general IVF population. The present study was undertaken to determine the efficacy and safety of adjuvant GH therapy in expected normal responders. It is, to our best knowledge, the largest RCT to address this topic of interest.

### Objective

To determine the efficacy and safety of adjuvant growth hormone (GH) therapy in GnRH antagonist cycles on reproductive outcomes in the general In-Vitro fertilization (IVF) population.

### Materials and Methods

This is a phase III open label randomised controlled trial involving a total of 288 patients who underwent an antagonist IVF cycle at OVO fertility center in Montreal, Canada, between June 2014 and January 2020. The study protocol was registered with Health Canada and approved by VERITAS IRB. The intervention group consisted of patients who received daily 2.5 mg subcutaneous injections of GH starting day 1 of ovarian stimulation until the day of oocyte retrieval, while the control group received standard ovarian stimulation without any adjuvant therapy. All embryo transfers (ET), fresh and/or frozen, resulting from this single IVF cycle were included in an intention-to-treat (ITT) and per-protocol (PP) analyses. The primary outcome was clinical pregnancy rate, while the number of retrieved oocytes and good quality embryos, maturation, fertilization, implantation and miscarriage rates and safety endpoints were recorded as secondary outcomes.

	GH group (n=144)	Control group (n=144)	Overall (n=288)	
Age (years)	38.2 (2.6)	37.8 (2.6)	38.0 (2.6)	
BMI (Kg/m2)	24.67 (3.91)	25.56 (4.09)	25.11 (4.02)	
AMH (ng/ml)	2.48 (2.65)	2.53 (2.54)	2.51 (2.59)	
FSH (IU/L)	6.58 (2.43)	6.68 (2.22)	6.63 (2.33)	
AFC	15.36 (10.69)	15.03 (9.69)	15.19 (10.18)	
Type of infertility, n (%)				
Primary infertility	73 (50.7%)	64 (44.4%)	137 (47.6%)	
Secondary infertility	71 (49.3%)	80 (55.6%)	151 (52.4%)	
Duration of infertility (years)	3.5 (2.8)	3.2 (2.1)	3.3 (2.4)	
Cause of infertility, n (%)				
Female factor	60 (41.7%)	46 (31.9%)	106 (36.8%)	
Male factor	39 (27.1%)	45 (31.3%)	84 (29.2%)	
Mixed factor	14 (9.7%)	14 (9.7%)	28 (9.7%)	
Unexplained infertility	22 (15.3%)	34 (23.6%)	56 (19.4%)	
Single women/same-sex couple	9 (6.3%)	5 (3.5%)	14 (4.9%)	
Prior IVF cycle, n (%)				
No	80 (55.6%)	71 (49.3%)	151 (52.4%)	
Yes	64 (44.4%)	73 (50.7%)	137 (47.6%)	
Number of prior IVF cycles	0.7 (1.1)	1.0 (1.6)	0.9 (1.4)	
Number of prior embryos transferred	0.7 (1.2)	0.8 (1.4)	0.8 (1.3)	

Table 1. Baseline characteristics of patients according to the intervention and control groups

Note: The group characteristics are expressed as mean (SD). BMI: Body Mass Index. AMH: Anti-Mullerian hormone. FSH: Follicular Stimulation Hormone. AFC: Antral Follicular Count

#### Inclusion Criteria **Exclusion Criteria**

- age between 30 and 42
- GnRH antagonist protocol
- 3. Primary or secondary infertility
- 4. No previous IVF cycle using the same proposed protocol with Saizen
- the last 24 months prior to randomization
- Contradiction to GH therapy
- $BMI \ge 35 \text{ kg/m}2$
- 3. Simultaneous participation in another clinical
- 4. AMH < 0.5pg/ml
- Anti-Mullerian Hormone (AMH) measured within 5. Known risk for gestational diabetes or diagnosed with diabetes

	GH group (n=144)	Control group (n=144)	P value
Total Dose of Gonadotropins (IU)	4602.9 (1504.9)	4657.1 (1357.3)	0.752
Number of Stimulation Days	11.4 (2.1)	11.7 (1.9)	0.118
Endometrial thickness (mm)	10.63 (2.82)	10.94 (2.85)	0.372
IGF-1 – Baseline (ng/nL)	139.6 (42.4)	132.0 (37.3)	0.110
IGF-1 - EoT (ng/nL)	229.6 (72.7)	125.1 (34.6)	<.0001
IGF-1 - Ratio (EoT/Baseline)	1.71 (0.55)	0.98 (0.24)	<.0001
(IGF–1 – EoT (ng/nL)) / (Utilizable Embryos)	122.5 (87.9)	61.7 (41.1)	<.0001
Cycle cancellation, n (%)	6 (4.2%)	3 (2.2%)	0.501
Insemination type, n (%)			
Standard IVF	19 (24.4%)	28 (31.1%)	
ICSI	55 (70.5%)	59 (65.6%)	0.718
Mixed	2 (2.6%)	1 (1.1%)	
PICSI	2 (2.6%)	2 (2.2%)	
Number of embryos transferred (fresh)	0.8 (0.8)	0.9 (0.7)	0.317
Number of embryos transferred (frozen)	1.7 (2.5)	1.7 (2.7)	1.000
Embryo age at transfer (fresh), n (%)			
Day 3 embryo	45 (57.7%)	51 (56.7%)	1000
Day 5-6 embryo	33 (42.3%)	39 (43.3%)	1.000
Embryo age at transfer (frozen), n (%)			
Day 3 embryo	21 (36.8%)	11 (25.6%)	
Day 5-6 embryo	36 (63.2%)	32 (74.4%)	0.282

# Table 2. IVF procedural outcomes by ITT analysis.

Note: The group characteristics are expressed as mean (SD). E2: serum estradiol level at the day of trigger. Progesterone: serum progesterone level at the day of trigger. IGF-1-EoT: Insulin-like growth factor 1 serum level at the end of treatment. ICSI: intra-cytoplasmic sperm injection. PICSI: physiological intra-cytoplasmic sperm injection

### Results

A total of 288 patients were recruited and randomly assigned at a 1:1 ratio to the GH or the control group. After removing the cycle cancellations and patients who did not undergo an ET, 105 patients remained in each group. The demographic characteristics in both groups were similar. The overall mean age was 38.0±2.6 years, the mean body mass index was 25.11±4.02 kg/m2 and the mean AMH was 2.51±2.59 ng/ml. The cycle characteristics were also similar between both groups. No differences were noted in terms of total dose of gonadotropin (4602.9 vs 4657.1 IU for the GH and control groups respectively, p=0.750), days of stimulation (11.4 vs 11.7 days, p=0.117) and endometrial thickness (10.63 vs 10.94 mm, p=0.372). The ITT and PP analyses detected similar results in terms of both IVF stimulation outcomes and reproductive outcomes. In the ITT analysis, no difference was noted in the number of follicles  $\geq$ 15 mm (7.8 vs 7.1, p=0.212), oocytes retrieved (11.7 vs 11.2, p=0.613), mature oocytes (8.5 vs 8.6, p=0.851), maturation rate (73.8 vs 78.4%, p=0.06), fertilization rate (64.3 vs 67.2%, p=0.388), good quality embryos (2.5 vs 2.6, p=0.767), implantation rate (42.7 vs 50.8%, p=0.234), miscarriage rate (26.9 vs 29.5%, p=0.761) and clinical pregnancy rate (48.6 vs 58.1%, p=0.167). The number of embryos needed to achieve a clinical pregnancy was 2.9 vs 2.5 in the GH and control groups respectively, with no significant difference (p=0.322). Finally, no or only mild side effects related to GH injection were noted.

ITT analysis					
	GH group (n=144)	Control group (n=144)	P value		
E2 (pmol/L)	7692.0 (5571.6)	8193.5 (5815.5)	0.472		
Progesterone (nmol/L)	2.66 (1.37)	2.77 (1.30)	0.466		
Number of Follicles ≥15 mm	7.8 (5.2)	7.1 (4.2)	0.212		
Number of Follicles <15 mm	7.3 (6.4)	7.8 (6.7)	0.556		
Number of Oocytes Retrieved	11.7 (8.5)	11.2 (7.9)	0.613		
Number of Mature Oocytes	8.5 (6.2)	8.6 (6.3)	0.851		
Maturation Rate, %	73.8% (21.6)	78.4% (17.6)	0.060		
Fertilization Rate - All Types Included, %	64.3% (29.1)	67.2% (25.7)	0.388		
Number of Embryos Available for Transfer	2.5 (2.4)	2.6 (2.6)	0.767		

Table 3. Ovarian stimulation outcomes by ITT analysis

Note: The group characteristics are expressed as mean (SD)

ITT analysis					
Implantation Rate, % (SD)	42.7% (48.8)	50.8% (49.5)	0.234		
Clinical pregnancy Rate, n (%)	51 (48.6%)	61 (58.1%)	0.167		
Miscarriage rate, n (%)	14 (26.9%)	18 (29.5%)	0.761		
Overall Average Number of Embryos Transferred per First Clinical Pregnancy [Total Transferred/Total Clinical Pregnancies]	2.9 [166/57]	2.5 [162/64]	0.322		

Table 4. Reproductive outcomes by ITT analysis in fresh and/or frozen embryo transfers

# Conclusions

GH adjuvant therapy in GnRH antagonist cycles is a safe procedure; however, it does not improve the results of IVF stimulation, nor the reproductive outcomes, namely implantation, miscarriage, and clinical pregnancy rates.

## Impact Statement

There is no benefit from adding GH therapy to ovarian stimulation in GnRH antagonist cycles for the general IVF population