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GONADOTROPIN DOSE LIMIT IN ART

An upper limit of gonadotropin dose in patients undergoing ART should be advocated

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Abstract

Aim: As no upper limit of the daily dose of gonadotropins (DD GN) used for controlled ovarian hyperstimulation (COH) in patients undergoing assisted reproductive technology (ART) has been established, we aimed to evaluate the efficacy of using different DD GN in terms of live-birth achievement.

Methods: Data of patients treated at a single university medical center during the same period was analyzed retrospectively. Four groups were analyzed according to the DD GN administered: group I (“high dose”): >225 – ≤ 375 IU; Group II (“Very high dose”): 376–450 IU; group III (“extremely high dose”): 451–600 IU. Normo-responders treated with DD GN ≤ 250 IU served as control (C). Variables included were DD GN, total GN dose/cycle, age, FSH, BMI, gravidity, parity, cycle number, IVF/ICSI, infertility diagnosis treatment protocol and outcome parameters.

Results: The analysis of 1394 treatment cycles of 943 patients indicated that DD and total dose of GN correlated negatively with the number of oocytes, implantation, clinical pregnancy and live-birth rate (25.9%, 14.6%, 11.4% and 4.7% in groups C, I, II and III, respectively). The logistic regression analysis indicated that the adjusted odds ratios for LBR correlated inversely with the DD administered – independently from age, baseline FSH, BMI and previous failed cycles.

Conclusions: Increasing the daily dose of GN to doses higher than 450 IU or a total dose of 3000 IU/cycle is at least questionable if not harmful.

Keywords

COH, gonadotropin dose, IVF, live-birth rate, poor ovarian responder

History

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Introduction

The decision upon the optimal daily dose of GN (DD GN) in each individual patient undergoing assisted reproductive technology (ART) is a challenging task for the practicing physician [1].

In patients expected to be normo-responders, increasing the DD GN above 200–250 IU, failed to improve the pregnancy rates [2–4].

In patients suspected having diminished ovarian reserve increasing the DD GN above 450 IU (up to 600 IU) did not improve IVF outcome [4–6]. However, many of the reports included small-sized study group, lacked control groups or did not use live-birth rates (LBR) as a primary outcome parameter [see reviews 7,8]. No study established an upper limit for the GN dose used for controlled ovarian hyperstimulation (COH) for patients with poor response and the maximal DD GN recommended is determined on an empirical basis.

Even in the published Bologna criteria stating that two episodes of poor ovarian response after “maximal stimulation” are sufficient to define a patient as poor responder; the exact definition of “maximal stimulation” is not included [9].

Use of high DD GN poses considerable economic and physiologic strain on the patient and presently its cost efficacy is questionable.

Our study aimed to assess the effectiveness of using different high DD GN in patients undergoing COH for IVF, including LBR as an outcome parameter.

Methods

This study has a prospective cohort design comparing parameters of IVF-ET outcome in patients treated at our IVF unit during the period of January 2006 to December 2012. The data was collected retrospectively from the patients’ files. Patients expected to be normo-responders (aged <35 years, FSH <10 IU, BMI <30 , no severe endometriosis) were treated by a maximal DD GN of 150–225 IU. This patient group served as control, (group C).

Patients expected to be low responders (aged ≥ 35 years and/or FSH ≥ 10 and/or BMI ≥ 30 and/or severe endometriosis and/or AFC of <6) were treated by a DD GN dose of >225 to ≤ 375 IU, defined as “High dose group” (group I).

Patients proven to have a low response (retrieval of ≤ 5 oocytes) – were given in the next cycle a DD GN of >375 –450 IU. These were defined as – “Very high dose group” (group II).

If their ovarian response remained poor (with ≤ 3 oocytes retrieved) their DD GN was raised to >450 –600 IU, and they comprised the group defined as – “Extremely high dose group” (group III).

The COH protocols used were long agonist or the daily dose antagonist. The gonadotropins administered were pure rec-FSH or combined rec-FSH/LH/hCG. For final ovulation induction, we used rec-hCG 250 mcg (Ovitrelle, Merck-Serono, Geneva, Switzerland). The mean age, baseline (day 3) FSH levels, BMI, gravidity, parity and treatment cycle number (expressing previous

failed cycles) were calculated for each group. Also the main indication for IVF was tabulated for each group. Most transfers were done on day 3 if at least one good quality embryo was available. If not, the embryos were cultured till day 5. If no good quality blastocyst was available embryo transfer was canceled.

Parameters of ovarian response and the clinical outcome variables were tabulated and analyzed according to the various study groups. Clinical pregnancy was diagnosed when an intrauterine pregnancy sac containing positive fetal cardiac activity was demonstrated by the United State.

Approval for this study was granted by the Barzilai University Medical Center Research and Ethics Committee.

Statistical methods

In order to test the association between two categorical variables, the Chi-square and the Fisher's exact tests were used. The two-sample *t*-test was applied for comparing a quantitative variable between two independent groups. The comparison of a quantitative variable between three or more independent groups was carried out using the one-way ANOVA test with the Dunnett *Post-Hoc* procedure for multiple pairwise comparisons. The paired *t*-test was used for assessing a change in a quantitative variable, and the McNemar test for assessing a change in a dichotomous variable.

The stepwise logistic regression model was used for assessing the simultaneous effect of several variables on a dichotomous outcome variable. The analysis was done to compare the LBR between the different study groups. Variables included were daily dose of GN (DD GN), age, baseline FSH, BMI, gravidity, parity, cycle number, IVF/ICSI, infertility diagnosis and treatment protocol.

All tests applied were two-tailed, and *p* values of 5% or less were considered statistically significant.

Results

Overall 1394 treatment cycles of 943 patients were included in the study. Group I, the "High dose group" included 410 cycles of 301 patients; Group II, the "Very high dose group" included 343 cycles of 228 patients; Group III, the "Extremely high dose group" included 297 cycles of 169 patients; Group C, the "control", included 344 cycles in 245 patients. The prevalence of using antagonist protocol for COH was 82.4%, 54.7%, 54.1% and 59.3% in groups C, I, II and III respectively, the rest were treated using agonist protocol.

The patients' characteristics in the different study and control groups are presented in Table 1. Patients mean age and baseline FSH increased significantly between each group studied C versus I versus II versus III, ($p < 0.05$). The mean BMI, gravidity and parity although comparable between the study groups (I, II, III) was significantly higher compared to the control group (C). Treatment cycle number was comparable between group II and III but significantly higher compared to group I and C. The most prevalent indication for ART was male factor in all groups. (Table 1).

The mean DD GN administered (IU), the length of GN administration (days) and the total dose of GN used in each cycle (IU) as well as various parameters of ovarian response according to the DD GN groups are presented in Table 2. The length of treatment with GN and the total GN units used per cycle increased in positive correlation with the increase of the mean DD GN among the groups ($p < 0.001$) and resulted in a significant increase in the total dose of GN administered per cycle ($p < 0.001$) (Table 2).

The E2 levels and the number of leading follicles (≥ 15 mm) on the day of hCG administration and the total number of oocytes retrieved decreased significantly as the DD GN increased ($p < 0.001$) (Table 2). The mean progesterone (P) level on the day of hCG administration was lower in the control group when comparing with each of the study groups ($p < 0.001$). Endometrial thickness was significantly lower in groups II, III compared to I and the control (C) (Table 2).

Parameters of the treatment cycle's laboratory and clinical outcome according to the DD GN groups are presented in Table 3. The fertilization rate (FR) among the various DD GN groups was comparable. A comparable number of embryos were transferred between the control (C) and group III. The number of embryos transferred was significantly higher in group I and II compared to control (C) but not to group III. Implantation rate (IR) was significantly lower in group III compared with C, I, II ($p < 0.001$) while the differences between C, I and II were not statistically significant (Table 3).

The rate of clinical pregnancy (CPR) and live-birth (LBR) decreased as the DD GN increased ($p < 0.001$) (Table 3). The calculated total GN dose to achieve one live-birth increased 2.85-, 5.11-, 17.55-folds between the control (C) and the study groups (I, II and III, respectively).

The prevalence of cycles ending with no embryo transfer increased according to the DD GN group (10.6%, 15.3%, 35.5% for groups I, II, III, respectively). The reasons for this outcome were variable, in group III, mainly due to failure to retrieve

Table 1. Patients characteristics according to the DD GN groups.

	Control (group C)	High dose (group I)	Very high dose (group II)	Extremely high dose (group III)	<i>p</i>
Age (years) (mean \pm S.D)	31.1 \pm 4.8	33.9 \pm 5.5	36 \pm 5.2	39 \pm 4.4	$p < 0.05^*$
FSH (IU) (mean \pm S.D)	6.3 \pm 2.1	6.9 \pm 4	7.8 \pm 3.3	8.8 \pm 4.8	$p < 0.05^*$
BMI (mean \pm S.D)	24.4 \pm 4.7	26.6 \pm 5.7	25.9 \pm 6	26.3 \pm 5.1	$p < 0.05^\ddagger$
Gravidity (mean \pm S.D)	1.1 \pm 1.2	1.4 \pm 1.6	1.5 \pm 1.6	1.6 \pm 1.7	$p < 0.05^\ddagger$
Parity (mean \pm S.D)	0.5 \pm 0.7	0.7 \pm 0.9	0.8 \pm 1.0	0.8 \pm 1.0	$p < 0.05^\ddagger$
Treatment cycle number (mean \pm S.D)	2.2 \pm 1.4	2.6 \pm 1.6	3.2 \pm 1.7	3.4 \pm 1.7	$p < 0.05^\ddagger$
Infertility diagnosis					
Male factor	52.7%	53.1%	52.9%	50.0%	
PCO/dysovulation	19.0%	11.2%	7.2%	2.2%	
Unexplained	9.5%	10.7%	13.1%	8.8%	
Mechanical	9.8%	13.8%	15.4%	20.8%	
Endometriosis	0.6%	1.5%	1.3%	5.3%	
Combined	8.3%	9.7%	10.1%	12.8%	

* = C versus I versus II versus III, $p < 0.05$; ‡ = C versus I, II, III, $p < 0.05$; ‡ = C versus II, III; I versus II, III, $p < 0.05$.

Table 2. Parameters of ovarian response according to the DD GN groups (mean \pm SD).

	Control (group C)	High dose (group I)	Very high dose (group II)	Extremely high dose (group III)	<i>p</i>
Maximal daily dose GT (IU))	186 \pm 36	301 \pm 7	420 \pm 37	594 \pm 20	<i>p</i> < 0.001*
Length of treatment from GT till triggering (days)	10.2 \pm 2.6	10.6 \pm 2.7	10.8 \pm 2.6	11.9 \pm 3.7	<i>p</i> < 0.001*
Total GT unit in cycle (IU))	1687 \pm 562	2827 \pm 780	4042 \pm 1087	6705 \pm 2160	<i>p</i> < 0.001*
E2 on day of hCG administration (pg/ml)	1536 \pm 886	1509 \pm 887	1273 \pm 782	961 \pm 681	<i>p</i> < 0.001*
P on day of hCG administration (ng/ml)	0.5 \pm 0.4	0.7 \pm 0.5	0.7 \pm 0.4	0.7 \pm 0.5	<i>p</i> < 0.001†
Follicles number (> = 15) at triggering	7.2 \pm 3.9	6.7 \pm 3.9	5.4 \pm 3.4	3.7 \pm 2.4	<i>p</i> < 0.01*
Number of oocytes retrieved	9.3 \pm 5.8	7.6 \pm 5.4	6.0 \pm 4.9	3.3 \pm 3.3	<i>p</i> < 0.001*
Endometrial thickness at triggering	10.9 \pm 2.4	11.0 \pm 2.5	10.4 \pm 2.3	10.1 \pm 2.12.4	<i>p</i> < 0.001‡

* = C versus I versus II versus III, *p* < 0.05; † = C versus I, II, III, *p* < 0.05; ‡ = C versus II, III; I versus II, III, *p* < 0.05.

Table 3. Parameters of the treatment cycle's laboratory and clinical outcome according to the DD GN groups.

	Control (group C)	High dose (group I)	Very high dose (group II)	Extremely high dose (group III)	<i>p</i>
FR (mean \pm S.D)	78 \pm 21	74 \pm 23	76 \pm 25	76 \pm 27	<i>p</i> = 0.54
Number of embryos transferred (mean \pm S.D)	1.9 \pm 0.7	2.1 \pm 0.7	2.1 \pm 0.8	1.9 \pm 0.9	<i>p</i> < 0.001*
Implantation rate (%)	23 \pm 36	17 \pm 33	16 \pm 33	7 \pm 21	<i>p</i> < 0.001†
Clinical pregnancy rate (%)	30.5	23.2	17.5	7.7	<i>p</i> < 0.001‡
Live birth rate (%)	25.9	14.6	11.4	4.7	<i>p</i> < 0.001‡
Total GN dose to achieve one live-birth	719	2051	3678	12619	

* = I, II versus C *p* < 0.05; C versus III *p* > 0.05; † = III versus C, I, II *p* < 0.05; C versus I, II *p* > 0.05.

‡ = C versus I, II, III, *p* < 0.05. I versus II, *p* > 0.05.

oocytes at OPU or failure of fertilization (*p* < 0.001) but also OPU cancellation, no oocytes retrieved, no mature oocytes, and embryos with low morphology – all occurring more frequently as the DD GN increased (*p* < 0.001).

Figure 1 presents the relationship between the mean total GN dose used per cycle and LBR according to the DD GN groups. It shows that the use of extremely high doses of GN failed to increase LBR. In fact, using a total dose of GN above 3000 IU per cycle was associated with a decrease of LBR.

The major finding of our study was that the decrease in LBR as the DD GN increased occurred independently from other parameters that may affect LBR. Specifically, the logistic regression analysis indicated that the adjusted odds ratios for LBR decreased as the DD GN increased – independently from age, baseline FSH, BMI, number of previous failed cycles – in each study group compared to the control: 0.61 (CI95%, 0.38–0.98, *p* = 0.04), 0.57 (CI95%, 0.33–0.99, *p* = 0.05), 0.23 (CI95%, 0.1–0.52, *p* < 0.001).

Discussion

Although increase in the DD GN was advocated as an effective mean to increase ovarian response [10,11] the efficacy of this strategy is controversial and no upper limit was established. Systematic reviews [7,12,8] concluded that the few prospective randomized studies on use of high dose GN for patients with poor ovarian reserve (POR) have shown either minimal or no benefit at all. Due to the weaknesses in the various reports found including lack of control, or use of previous failed cycles as control limited the size of the study groups; no recommendation for clinical practice may be suggested. In fact, compared to the routine DD GN, using 300 IU had comparable outcome [13,14], using up to 450 IU had comparable [15,6] or lower [4] outcome, using up to 600 IU had comparable [16,17] or lower [18] outcome. A retrospective study (806 ART cycles) [19] reported that higher gonadotropin use lowered cycle cancellations but was associated

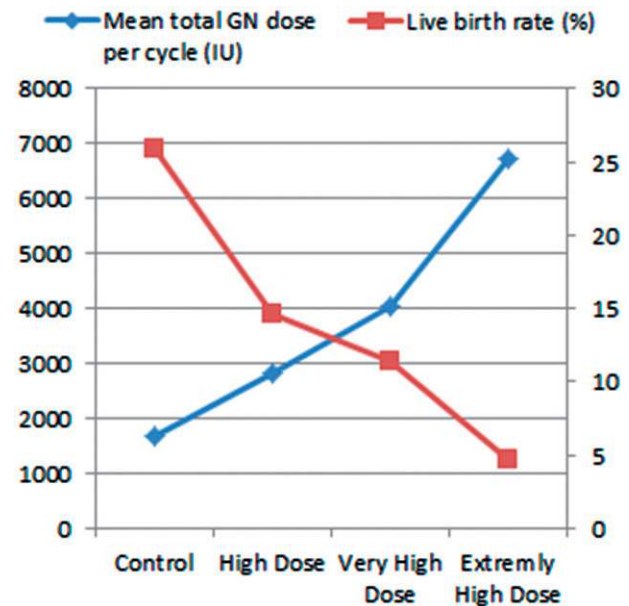


Figure 1. Mean total gonadotropin dose per cycle and LBR according to the DD GN groups.

with a significantly reduced CPR and LBR and a trend toward a higher likelihood for spontaneous miscarriage after IVF. A prospective multicenter study (265 patients with varying ovarian reserve based on AMH) [20] found that although increasing FSH doses results in a linear increase in number of oocytes retrieved in an AMH-dependent manner, FR and blastocyst/oocyte ratio decreased significantly with increasing FSH doses in both AMH

strata. None of the studies presented evidence for an upper limit of GN dosage to be used.

Therefore, we decided to examine the laboratory and clinical outcome of ART cycles in our population of patients with low ovarian response, according to the DD GN administered.

In our study groups II and III, patients who were low responders in their previous cycle were given very high and extremely high DD GN dose. Their ovarian response remained low compared to the control or the high dose group I.

Although FR and number of transferred embryos were comparable between the groups, the parameters of clinical outcome, including IR, CPR and LBR were inversely correlated with the increase in DD GN administered. In group III, in spite of the increased GN dose given the failure to achieve embryo transfer was the highest. In fact, administration of extremely high DD GN was associated with a significant deterioration of the clinical outcomes, including LBR. The significantly worse outcome could be due to negative selection but also it may insinuate a potential harmful effect of the excessive GN dose. Our stepwise logistic regression analysis revealed that higher doses of GN were inversely related to LBR – independently from the background parameters – including maternal age, baseline FSH, BMI, gravidity, parity, cycle number, infertility diagnosis and treatment protocol.

It is plausible that exposure to very high doses of GN is detrimental as *in vitro* exposure of oocytes to higher concentrations of FSH had higher prevalence of aneuploidy [21]. Use of lower doses of FSH correlated with lower incidence of aneuploidy [22–24]. Recently, a large retrospective study analyzing 650 000 cycles reported by SART found that LBR decreased with increasing total FSH dose, regardless of the number of oocytes retrieved and patient age, except for women aged ≥ 35 years with 1–5 oocytes retrieved [25]. Our study comprised women aged 39 ± 4.4 years and having 3.3 ± 3.3 oocytes retrieved, did find the correlation between use of extremely high DD GN and low LBR.

The main limitation of our study is its retrospective design with potential patients' selection bias. We compared DD GN administered and patients may have had different ovarian reserve. Current estimates of ovarian reserve such as antral follicles count (AFC) or anti-Müllerian hormone (AMH) were not recorded or measured consistently in our unit's database, so they were not included in our analysis. We analyzed the dose of GN administered in each cycle and did not examine the additional hCG/LH activity, if contained, in the specific medications used. We examined the correlations between the GN dose administered and outcome parameters but this study design cannot establish a causative effect.

The strength of our study is in the analysis based on all the treatments performed in a single center, including those using very high and extremely high DD of GN, prospective cohort design, the relatively big study groups, and including LBR as the main outcome parameter.

Our results emphasize the high cost versus the low efficacy in the higher GN groups. In the extremely high DD GN group, in order to achieve one live-birth, more than 20 COH cycles are needed using 17 times more gonadotropins compared to 4 cycles in the control. To conclude, even if extremely high DD GN lacks detrimental effect, this policy does not compensate for the diminished ovarian reserve, does not justify the increased costs and is ineffective regarding LBR. Therefore, a clinical decision of an upper limit of a total dose of 3000 IU GN/cycle or DD GN of 450 IU should be considered in patients with expected poor ovarian response.

Declaration of interest

The authors declare that they have no conflict of interest.

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