

GnRH agonist versus GnRH antagonist in ovarian stimulation: the influence of body mass index on in vitro fertilization outcome

In an attempt to examine whether body mass index (BMI) may influence IVF outcome in patients undergoing COH with either GnRH-agonist (agonist group) or GnRH-antagonist (antagonist group), we studied 799 IVF cycles: 481 in the agonist group and 318 in the antagonist group. In patients with BMI >25 kg/m², COH with either GnRH-agonist or GnRH-antagonist achieved a comparable outcome; whereas in patients with BMI <25 kg/m², the use of GnRH-agonist suppressive protocol revealed significantly higher pregnancy rates. (Fertil Steril® 2007; ■: ■-■. ©2007 by American Society for Reproductive Medicine.)

Controlled ovarian hyperstimulation (COH) appears to be a key factor in the success of in vitro fertilization–embryo transfer (IVF-ET). The ability of GnRH-analogue cotreatment to prevent a premature increase in luteinizing hormone during COH has made it the standard of care worldwide. Studies comparing GnRH-agonist long protocols with GnRH-antagonist protocols have yielded conflicting results (1–4), leading to an ongoing debate in the medical community. The observed lower pregnancy rate during the GnRH-antagonist cycles was related to their use in cycles with an unfavorable prognosis a priori, or “centers’ clinical inexperience” (5–7).

Obesity has recently become a major health problem. The magnitude of its associated health detriments increases with increasing body mass index (BMI). Although being overweight (BMI >25 kg/m²) or obese may reduce a woman’s fertility and increase risks associated with pregnancy, the data regarding the impact of obesity on IVF cycles outcome are controversial. Several reports have shown no effect of increasing BMI on IVF success rates, except for higher cancellation rates (8–10). Other reports have demonstrated a lower cumulative live birth rate in overweight patients (11–14). In all the aforementioned studies, patients underwent COH using a GnRH-agonist.

Prompted by these findings, we examined whether BMI affects IVF cycle outcome in patients undergoing COH protocols using GnRH-agonists versus GnRH-antagonists. These findings may help to clarify the proper approach to GnRH analogues in COH and to aid fertility specialists and their patients in the decision-making process.

We reviewed the computerized files for all women admitted to our IVF unit during a 3-year period, who reached the

ovum pickup (OPU) stage. Exclusion criteria included use of donor oocytes or transfer of frozen-thawed embryos, and use of other than a midluteal long GnRH-agonist suppressive protocol (agonist group) or the flexible multidose GnRH-antagonist protocol (antagonist group). Which type of analogue used was the decision of the treating physician and was largely dependent on the fashion at that time.

Data on the patients’ age, BMI, and infertility-treatment-related variables were collected from the files. Ovarian stimulation characteristics, number of oocytes retrieved, and number of embryos transferred per cycle were recorded.

Results are presented as mean \pm standard deviation. Differences in variables were statistically analyzed with the nonparametric Wilcoxon’s signed rank test, Student’s *t* test, and chi-square test, as appropriate. A *P* value of less than .05 was considered statistically significant.

Seven hundred and ninety-nine IVF cycles were evaluated: 481 in the agonist group and 318 in the antagonist group. Pregnancy was achieved in 138 patients in the agonist group (pregnancy rate, 28.7% per cycle) and 62 patients in the antagonist group (pregnancy rate, 19.5% per cycle); this difference was statistically significant ($P<.01$) despite the older age of the patients in the agonist group (33.1 ± 5.8 vs. 31.6 ± 5.9 years, respectively; $P<.001$). As expected (1, 2), the agonist group used significantly more gonadotropin ampoules (42.7 ± 23.0 vs. 36.4 ± 21.0 , respectively; $P<.001$), required longer stimulation (10.5 ± 2.3 vs. 9.8 ± 2.2 days, respectively; $P<.001$), and had higher estradiol levels on the day of hCG administration ($2,153 \pm 1,698$ vs. $1,651 \pm 899$ pg/mL, respectively; $P<.001$). There were no differences between the groups in peak progesterone levels, number of oocytes retrieved, or embryos transferred.

Patients were further divided into two subgroups according to their BMI (A <25 kg/m²; B ≥ 25 kg/m²). In the agonist group, patients in subgroup A (<25 kg/m²) used significantly less gonadotropin ampoules (40.8 ± 22.0 vs.

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45.7 ± 23.9, respectively; $P < .03$) and had higher estradiol (2,287 ± 1,594 vs. 1,942 ± 1,835 pg/mL, respectively; $P < .04$) and progesterone levels (0.9 ± 1.1 vs. 0.7 ± 0.5 ng/mL, respectively; $P < .01$) on the day of hCG administration, as compared with subgroup B (≥ 25 kg/m²). Furthermore, there were no differences between the subgroups in the length of stimulation, number of oocytes retrieved, number of embryos transferred, and clinical pregnancy rate (29.9% vs. 26.7%, respectively). In the antagonist group, no differences were observed between subgroups A (< 25 kg/m²) and B (≥ 25 kg/m²) in the aforementioned stimulation variables, including clinical pregnancy rate (17.5% vs. 22%, respectively).

We further analyzed patients according to their different BMIs. Of all patients in subgroup A (BMI < 25 kg/m²), those in the agonist group were significantly older ($P < .01$), used significantly more gonadotropin ampoules ($P < .01$), required longer stimulation ($P < .001$), had higher estradiol levels on the day of hCG administration ($P < .001$), and achieved a higher clinical pregnancy rate ($P < .002$) compared with the antagonist group (Table 1). There were no in-between group differences in peak progesterone levels, number of oocytes retrieved, or number of embryos transferred.

Moreover, of those patients in subgroup B (BMI ≥ 25 kg/m²), the agonist group used significantly more gonadotropin ampoules ($P < .002$) and required longer stimulation ($P < .001$) compared with the antagonist group, with no differences between the groups in patient age, estradiol, and progesterone levels on the day of hCG administration, number of oocytes retrieved, number of embryos transferred, or clinical pregnancy rate (Table 1).

In the present study, we observed a significantly higher clinical pregnancy rate in patients undergoing the midluteal long GnRH-agonist suppressive protocol than in patients undergoing the flexible multidose GnRH-antagonist protocol. Although these results are in accordance with other reports (2, 3), other studies (4, 15, 16) failed to confirm this difference in outcome between the treatment options.

We further demonstrated in the agonist group that patients with BMI < 25 kg/m² used significantly less gonadotropin ampoules and had higher estradiol and progesterone levels on the day of hCG administration compared with patients with BMI ≥ 25 kg/m², with no differences between the subgroups in length of stimulation, number of oocytes retrieved, number of embryos transferred, or clinical pregnancy rate. These observations agree with Dokras et al. (9), who recently demonstrated in patients undergoing IVF cycles using GnRH agonist that patients with higher BMI required more days of stimulation, used more gonadotropin ampoules, and achieved lower peak estradiol levels. Conversely, while Ku et al. (14) also showed that higher BMI is associated with an increase in the gonadotropin requirement and with no differences in the number of

TABLE 1

Comparison between IVF cycles in the GnRH agonist and GnRH antagonist groups according to the different BMI subgroups.

	BMI < 25 kg/m ²			BMI ≥ 25 kg/m ²		
	Agonist	Antagonist	P value	Agonist	Antagonist	P value
Number of cycles	294	177		187	141	
Patient age (yrs)	32.6 ± 5.7	31.2 ± 5.8	$P < .01$	34.1 ± 6.0	32.9 ± 5.8	ns
Day 3 FSH levels (IU/L)	7.0 ± 2.5	6.6 ± 2.5	ns	6.8 ± 2.9	6.0 ± 2.3	$P < .01$
Number of gonadotropin ampoules used	40.8 ± 22.0	35.0 ± 21.0	$P < .01$	45.7 ± 23.9	38.0 ± 20.1	$P < .01$
Length of stimulation (days)	10.6 ± 2.2	9.85 ± 2.1	$P < .001$	11.0 ± 2.4	9.8 ± 2.1	$P < .001$
Peak E2 levels on day of hCG administration (pg/mL)	2,287 ± 1,594	1,644 ± 967	$P < .001$	1,942 ± 1,835	1,660 ± 924	ns
Progesterone levels on day of hCG administration (ng/mL)	0.9 ± 1.1	0.8 ± 0.7	ns	0.7 ± 0.5	0.7 ± 0.7	ns
Number of oocytes retrieved	11.0 ± 6.9	10.8 ± 7.2	ns	10.3 ± 6.4	11.0 ± 6.7	ns
Number of embryos transferred	2.2 ± 0.7	2.1 ± 0.7	ns	2.4 ± 1.4	2.2 ± 0.7	ns
Pregnancy rate	29.9% (88/294)	17.5% (31/177)	$P < .002$	26.7% (50/187)	22.0% (31/141)	ns

Note: BMI = body mass index; ns = nonsignificant.

Robinson. BMI and IVF cycles outcome. Fertil Steril 2007.

retrieved oocytes or embryos transferred, they found higher BMI to be associated with decreased clinical pregnancy and implantation rates.

Moreover, we could not demonstrate any differences in the aforementioned variables within the antagonist group, despite a nonsignificant trend toward decreased pregnancy rate with lower BMI (17.5% vs. 22%). Anecdotally, it seems that whereas BMI has no significant effect on stimulation variables, lower BMI might have a detrimental effect on the IVF outcome of patients undergoing COH using GnRH-antagonists.

In the present study, we also observed a significantly higher pregnancy rate in the agonist groups compared with the antagonist groups, in patients with normal weight or who were underweight (BMI <25 kg/m²). This observation might be explained by the following: (a) GnRH antagonists have a known inhibitory effect on the cell cycle that decreases the synthesis of growth factors; therefore, if mitosis is essential for folliculogenesis, blastomere formation, and endometrium development, the interaction between the GnRH antagonist and the GnRH receptor may compromise the mitotic program of these cells (17); (b) because patients received a fixed dose of GnRH antagonist, its tissue concentration, as well as its effect in lean patients, are expected to be more pronounced with the consequent lower pregnancy rate.

This observation may partially address the controversy regarding the difference between GnRH-agonist and GnRH-antagonist: In patients with BMI >25 kg/m², COH with either GnRH-agonist or GnRH-antagonist would achieve comparable results, whereas in those with BMI <25 kg/m², the GnRH-agonist suppressive protocol should be the protocol of choice.

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