Flexible Gnrh Antagonist Protocol Versus Gnrh Agonist Long Protocol In Patients With Polycystic Ovary Syndrome Treated For IVF: A Prospective Randomised Controlled Trial (RCT)

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Citation

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Abstract

Background: Women with polycystic ovary syndrome (PCOS) are at risk of developing ovarian hyper stimulation syndrome (OHSS) during ovarian stimulation. Use of GnRH antagonist in the general sub-fertile population is associated with lower incidence of OHSS than agonists and similar probability of live birth but it is unclear if this is true for patients with PCOS. Our aim was to compare the flexible GnRH antagonist and GnRH agonist long protocols in patients with PCOS undergoing IVF (primary end-point: ongoing pregnancy rateper patient randomized).Methods: In this randomized controlled trial (RCT), 220 patients with PCOS were randomly allocated in two groups: long GnRH agonist down-regulation protocol (n = 110) and flexible GnRH antagonist protocol (n = 110).Results: No differences were observed in ongoing pregnancy rates [50.9 versus 47.3%, difference 3.6%, 95% confidence interval (CI): 29.6 to 16.8%] in the agonist and antagonist protocols, respectively. Incidence of OHSS Grade II was lower in the antagonist comparedwith agonist group (40.0 versus 60.0%, difference 20.0%, 95% CI: 27.1 to 32.9%, P : 0.01). Duration of stimulation (10 versus 12 days, difference 2 days, 95% CI: p1 to p2, P : 0.001) and total gonadotrophin required (1575 IU versus 1850 IU, difference 2275 IU, 95% CI: 225to 2400, P : 0.05) were also lower in the antagonist compared with agonist protocol.Conclusions: The current RCT suggests that the flexible GnRH antagonist protocol is associated with a similar ongoing pregnancy rate, lower incidence of OHSS grade II, lower gonadotrophin requirement and shorter duration of stimulation, compared with GnRHagonist. The GnRH antagonist might be the treatment choice for patients with PCOS undergoing IVF.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that affects 5–10% of women of reproductive age. Despite the development of universally accepted criteria for the diagnosis of the syndrome by the European Society for Human Reproduction (ESHRE) and the American Society of Reproductive Medicine (ASRM) (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004), the optimal infertility treatment for PCOS women is still a matter of controversy. Recently, a consensus was reached on treatment for PCOS patients, that includes the use of clomiphene citrate, exogenous gonadotrophins, laparoscopic ovarian surgery and IVF (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008).

PCOS patients undergoing IVF have a high risk of developing ovarian hyperstimulation syndrome (OHSS) (Delvigne et al., 1993), a serious iatrogenic complication of ovarian stimulation, triggered by exogenous and/or endogenous hCG. The introduction of GnRH antagonists in recent years, with a now established decrease in the incidence of OHSS as compared with GnRH agonists in the general population (Kolibianakis et al., 2006; Aboulghar et al., 2007), might offer a new safer treatment option for these patients.

However, in PCOS patients very few studies have been published comparing agonist and antagonist protocols (Hohmann et al., 2003; Hwang et al., 2004; Bahceci et al., 2005; Ragni et al., 2005; Lainas et al., 2007). As a result, available data so far cannot lead to reliable conclusions

(Griesinger et al., 2006).

The aim of the present RCT was to compare the flexible GnRH antagonist and the GnRH agonist long protocols in a large group of PCOS patients undergoing IVF treatment, with primary end-point being ongoing pregnancy rate per patient randomized.

MATERIALS AND METHODS

PATIENT POPULATION AND STUDY DESIGN

This is a single center RCT performed at the Eugonia-Iatriki Erevna IVF unit from November 2004 to February 2008. Random allocation was performed by a study nurse at consultation, using a computer generated randomization list, in a 1:1 ratio. Patients were treated either by a long GnRH agonist down regulation protocol (n = 110, agonist group) or by a flexible GnRH antagonist protocol (n = 110, antagonist group). Neither patients nor doctors were blinded to the treatment assigned. The study was approved by our institutional ethics review board. An informed consent was obtained from all patients included in this study.

Patients could enter the study only once after being diagnosed as PCOS [presence of oligo-ovulation/anovulation (Ehrmann et al., 2006) and polycystic ovaries]. Additional inclusion criteria were: age 18–39 years, no endometriotic cyst present, as assessed by transvaginal ultrasound examination, and basal hormonal levels of FSH in the early follicular phase of 10 IU/ml. Patients with known previous poor ovarian response (Kolibianakis et al., 2004) were excluded.

OVARIAN STIMULATION

All patients received oral contraceptive pill (OCP) starting on Day 2 of spontaneous menses of the cycle prior to the treatment cycle, after blood test confirmed the presence of a baseline hormone profile. The OCP contained 0.03 mg ethinyl estradiol (E2) and 0.075 mg gestodene (Minulet, Wyeth, Greece). OCPs were taken daily for 21 days.

Patients in the agonist group were administered s.c. GnRH agonist 0.1 mg triptorelin (Arvekap, Ipsen, France) daily. The agonist was started 3 days before discontinuation of the OCP. All patients had blood loss after discontinuation of the OCP. When desensitization was achieved (10–15 days after the initiation of GnRH agonists), as evidenced by plasma E2 levels of 50 pg/ml, the absence of ovarian follicles and endometrial thickness 6 mm on transvaginal ultrasound examination (Barash et al., 1998), daily s.c. injection of recombinant FSH (rFSH, Puregon, Organon, The Netherlands) was commenced. The dose of GnRH agonist was decreased on that day to 0.05 mg/day and continued until and including the day of triggering of final oocyte maturation.

In the flexible GnRH antagonist protocol (antagonist group) daily s.c administration of ganirelix 0.25 mg (Orgalutran, Organon, The Netherlands) was initiated when at least one of the following criteria were fulfilled: (i) the presence of at least one follicle measuring: 14 mm; (ii) serum E2 levels :600 pg/ml; and (iii) serum LH levels:10 IU/l (Lainas et al., 2005).

In the antagonist protocol patients started daily rFSH treatment with s.c injections of follitropin b (Puregon, Organon, The Netherlands), on Day 2 of cycle that followed the discontinuation of the OCP. Treatment with rFSH and GnRH antagonist continued daily thereafter, until and including the day of triggering of final oocyte maturation.

The starting dose of rFSH was 150 IU/day for all patients in both groups. This dose was adjusted after Day 5 of stimulation, depending on the ovarian response, as assessed by E2 levels and ultrasound. As soon as three follicles reached a mean diameter of 17 mm, 5000 IU of hCG (Kolibianakis et al., 2007b) (Pregnyl, Organon, The Netherlands) were administered IM.

OOCYTE RETRIEVAL, EMBRYO TRANSFER, LUTEAL SUPPORT

Oocyte retrieval was performed 35–36 h after the hCG injection by transvaginal ultrasound-guided double lumen needle aspiration. ICSI was performed only in cases with severe male factor or previous fertilization failure. Ultrasound guidance was used for all embryo transfers, which were performed 2 or 3 days post-oocyte retrieval, depending on the weekly clinical program (i.e. to avoid embryo transfer on Sundays). Day 2 and Day 3 embryo transfers were equally distributed in the two groups. Luteal phase support with 600 mg of micronized progesterone (Utrogestan Laboratoires Besins-International S.A., France) was initiated 2 days after oocyte retrieval.

Embryo transfer was cancelled and elective embryo cryopreservation was performed in cases of early OHSS, detected 3 days post-oocyte retrieval, that could possibly lead to life-threatening OHSS (Navot et al., 1992), or in cases fulfilling one or more of the criteria for hospitalization

(The Practice Committee of the American Society for Reproductive Medicine, 2004), described below in grade III OHSS.

CLASSIFICATION OF OHSS

A modified classification system based on combined criteria previously reported (Golan et al., 1989; Navot et al., 1992; Rizk and Aboulghar, 1999) was used in the current study.

Grade I included patients with no or mild manifestations of OHSS who did not need any treatment or monitoring as a result of ovarian hyper-stimulation.

Grade II included patients who were not hospitalized as a result of OHSS and required monitoring on an outpatient basis. These patients had either (a) moderate OHSS, with discomfort, abdominal pain, nausea, distension, ultrasonic evidence of ascites, haematocrit (Ht) : 45%, white blood cells (WBC) : 15 000 (Golan et al., 1989; Navot et al., 1992; Rizk and Aboulghar, 1999) and enlarged ovaries (maximum diameter ,10 cm), requiring frequent monitoring, or (b) severe OHSS requiring daily monitoring, with Ht : 45%, WBC : 15 000, nausea, abdominal pain, clinical evidence of ascites, marked distension of the abdomen, marked ascites (Golan et al., 1989; Navot et al., 1992; Rizk and Aboulghar, 1999) and ultrasound showing large ovaries (maximum diameter .10 cm).

Grade III OHSS included women who were hospitalized either because they developed critical OHSS (Navot et al., 1992) (i.e: Ht : 55, WBC :25 000 and creatinine :1.5), or because they fulfilled one or more of the criteria for hospitalization described by the Practice Committee of the ASRM (2004). These criteria include severe abdominal pain or peritoneal signs, intractable nausea and vomiting, severe oliguria or anuria, tense ascites, dyspnea or tachypnea, hypotension, dizziness or syncope, severe electrolyte imbalance, haemo concentration and abnormal liver functiontests (The Practice Committee of the American Society for Reproductive Medicine, 2004).

ULTRASOUND AND LABORATORY ASSAYS

All ultrasound measurements were performed using a 7.5 or 6 or 5 MHz vaginal probe (Sonoline Adara, Siemens). FSH, LH, E2 and progesterone levels were measured using an Immulite analyzer and commercially available kits (DPC, Los Angeles, CA, USA). Analytical sensitivity were 0.1 mIU/ml for FSH, 0.1 mIU/ml for LH, 15 pg/ml for E2 and 0.2 ng/ml for progesterone. Intra- and inter-assay precision at the concentrations of most relevance to the current study (expressed as coefficients of variation) were 2.6 and 5.8% for FSH, 5.9 and 8.1% for LH, 6.3 and 6.4% for E2 and 7.9 and 10% for progesterone, respectively.

OUTCOME MEASURES

The primary outcome measure was ongoing pregnancy rate per patient randomized. Ongoing pregnancy and clinical pregnancy were defined as the presence of gestational sac with fetal heart beat detection at 12 weeks and at 6–7 weeks of gestation, respectively.

Secondary outcome measures were incidence of OHSS, duration of rFSH stimulation, total dose of rFSH, E2 and progesterone concentration on the day of hCG administration, cycle cancellation rate, number of cumulus-oocyte complexes (COCs) retrieved, number of metaphase II oocytes and fertilization rates.

STATISTICAL ANALYSIS

Proportions were compared with the Fisher's exact test or the x2 test, where appropriate. Continuous variables (age, BMI), were compared with the Student's t-test for independent samples or the Mann–Whitney depending on the normality of their distribution. Statistical significance was accepted when P : 0.05.

POWER ANALYSIS

We selected to set the baseline ongoing pregnancy rate for PCOS patients at 35%, and the detectable difference between groups at 5%, assuming an alpha level of 0.05. It was calculated that a sample size of 1471 patients was required in each group to achieve a 0.80 power. In confirmation of the values used for power analysis, Griesinger et al. (2006) reported 41.6 and 37.1% clinical pregnancy rates in PCOS patients treated by agonist and antagonist protocols respectively. In addition, Heijnen et al. (2006) showed that PCOS and control IVF patients achieve similar clinical pregnancy rates of approximately 35%, a percentage that was also accepted by The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008).

Obtaining such a sample size (1471 patients per group) is not easy to achieve in a single center, and is also extremely difficult for multicenter studies, especially when it refers to a small proportion of the population, such as PCOS patients, even during a 4-year period. Even for a 20% baseline

pregnancy rate with 5% difference, more than 900 patients per group

would be required. In addition, detecting a difference of 10% in pregnancy rates, which is not supported by the data published so far, would still require a considerable number of patients in each group (n = 376).

Despite this, however, we decided to embark on this trial with the aim to produce, to the best of our knowledge, the largest comparative trial to date of GnRH analogues in PCOS patients that could be incorporated in a future meta-analysis.

RESULTS

Baseline characteristics and hormonal profile of the patients analyzed are shown in Table I, although Table II shows ovarian stimulation characteristics and hormonal data on the day of hCG administration.

No significant differences were observed between the agonist and the antagonist group regarding baseline characteristics and hormonal profile

Figure 1

Table I Baseline characteristics and hormonal profile of patients with PCOS in the GnRH agonist and GnRH antagonist

	Agonist group (n 5 110)	Antagonist group (n 5 110)
Baseline characteristics		
Age (years)	32(29–35)	31(28–35)
BMI (kg/m2)	23.2 (20.9–25.8)	24.6 (20.9–29.3)
Duration of infertility (years)	3(2-5)	3(2-5)
Subjects with previous IVF attempts, n (%)	69 (62.7, 53.7–71.7)	69 (62.7, 53.7–71.7)
Indication for IVF, n (%, 95% CI		
PCOS only	22 (20.0, 12.5–27.5)	28 (25.5, 17.3–33.6)
PCOS p male factor	53 (48.2, 38.9–57.5)	52 (47.3, 38.0–56.6)
PCOS p tubal factor	27 (24.5, 16.5–32.5)	18 (16.4, 9.5–23.3)
PCOS p other	8 (7.3, 2.4–12.2)	12 (10.9, 5.1–6.7)
Baseline hormonal profile		
FSH (IU/l)	6.0 (4.3–6.9)	6.2 (4.8–7.5)
LH (IU/l)	5.9 (3.4–7.6)	5.3 (4.0–7.5)
E2 (pg/ml)	30 (19–44)	30 (19–43)

Figure 2

Table II Ovarian stimulation characteristics and hormonal data on the day of hCG in the GnRH agonist and antagonist

	Agonist group (n 5 110)	Antagonist group (n 5 110)	P-value
Stimulation period (days)	12 (10–12)	10 (9–11)	0.001
Total FSH (IU)	1850 (1370–2480)	1575 (1306–2212)	0.019
Number of oMature oocytes (in ICSI patients)	18 (11–25)	21 (10–26)	0.604
Type of fertilization, n (%, 95% CI)			
IVF	58 (52.7, 43.4–62.0)	52 (47.3, 38.0–56.6)	0.578
ICSI	38 (34.5, 25.6–43.4)	39 (35.5, 26.6–44.4)	
IVF / ICSI	14 (12.7, 6.5–18.9)	19 (17.3, 10.2–24.4)	
Fertilization rate (%)	53.3 (40.6–68.5	55.0 (38.9–66.7)	0.795
Within IVF	62.2 (47.7–74.7	64.0 (50.0–71.1)	0.959
Within ICSI	45.5 (41.2–56.5)	46.9 (34.4–57.1)	0.962
Within ICSI / IVF	42.0 (32.1–56.6)	44.8 (38.4–60.5)	0.414
E2 concentration on hCG day (pg/ml)	2850 (1994–3585)	2144 (1533–2977)	0.004
PRG concentration on hCG day (ng/ml)	1.1 (0.7–1.4)	1.1 (0.9–1.4)	0.185
Number of embryos transferred	3 (2–4)	3 (2–3.5)	0.297
Embryo transfer day (Day 3/Day 2)	75/35	72/38	0.668
Cycle/embryo transfer cancellations	5 (4.5%)	4 (3.6%)	0.734

Statistical differences were calculated using the non-parametric Mann–Whitney test, except for type of fertilization where the x2 test was used. Values are expressed as medians (lower-upper quartiles) unless stated otherwise. P-values in bold indicate statistical significance: PRG, progesterone

Figure 3

Table III Achievement of pregnancy in the GnRH agonist and antagonist groups

	Agonist group (n 5 110)	Antagonist group (n 5 110)	Difference % (95% CI)	P (Fisher's exact test)
Biochemical pregnancy, % (n)	**68.2**	**62.7**	**5.5(27 to p17.9)**	**0.479**
Clinical pregnancy, % (n)	**61.8**	**52.7**	**9.1(23.9 to p22.0)**	**0.220**
Ongoing pregnancy, % (n)	**50.9**	**47.3**	**3.6(29.6 to p16.8)**	**0.686**

The antagonist group was characterized by a shorter stimulation period [10 versus 12 days, difference 2 days, 95% confidence interval (CI): 1 to 2, P , 0.001], a reduced amount of total gonadotrophin units required (1575 versus 1850 IU, difference 2275 IU, 95% CI: 225 to 2400, P , 0.05) and a lower E2 concentration on the day of hCG administration (2144 versus 2850 pg/ml; difference 2706 pg/ml, 95% CI: 2240 to 2841; P , 0.01).

No significant differences were observed in ongoing pregnancy rates [50.9% (56/110) versus 47.3% (52/110)], as well as in biochemical [68.2% (75/110) versus 62.7% (69/110)], and clinical pregnancy rates [61.8% (68/110) versus 52.7% (58/110)] between the agonist and the antagonist group, respectively (Table III). Logistic regression with the dependent variable ongoing pregnancy, and independent variables the baseline characteristics of

patients recruited and type of stimulation protocol, revealed a significant negative (adverse) effect of the number of previous attempts and BMI on the outcome (Table IV).

A significantly higher proportion of women (55.5 versus 34.5%, P :0.001) in the antagonist as compared with the agonist group developed Grade I OHSS (Table V). Conversely, a significantly greater proportion of women developed grade II OHSS in the agonist group (60.0 versus 40.0%, P , 0.01).

All patients proceeded at least to oocyte retrieval. Cycle cancellations were therefore equivalent to cancellations of embryo transfer and elective cryopreservation of all embryos. Cycle/embryo transfer cancellations were similar in the agonist and antagonist protocol [five patients (4.5%) versus four patients (3.6%); Table II.

DISCUSSION

The present study evaluated the comparative efficacy of the flexible GnRH antagonist and the long GnRH agonist down-regulation protocol in PCOS patients treated for IVF. Ongoing pregnancy rates were similar in the two protocols, although the GnRH antagonist protocol was associated with significantly lower incidence of Grade II OHSS (requiring monitoring on an outpatient basis but not necessitating hospitalization), as well as significantly higher proportion of women who did not develop OHSS or developed mild hyperstimulation without clinical relevance and did not require monitoring (Grade I). In addition, duration of stimulation and total amount of gonadotrophin units required were significantly lower in the antagonist compared with the agonist protocol.

Figure 4

Table IV Logistic regression of pregnancy outcome in patients with PCOS

Baseline parameter	Total sample	
	b	P-value
Age (years)	-0.018	0.691
BMI (kg/m2)	-0.055	0.039
Duration of infertility (years)	0.070	0.266
Number of previous attempts	-0.160	0.029
FSH (IU/l)	-0.034	0.694
LH (IU/l)	0.125	0.093
E2 (pg/ml)	0.001	0.887
Progesterone (ng/ml)	-0.256	0.438
Type of stimulation protocol	0.218	0.526

b is the value of the coefficient and P-value shows its significance of its entrance in the logistic regression equation. P-values in bold indicate statistical significance

The meta-analysis by Griesinger et al. (2006) compared agonist and antagonist protocols in a total of 305 patients with PCOS and included four studies.

In agreement with the results presented here, pregnancy rates of 41.5 versus 37% in the agonist and in the antagonist groups were reported. It must be noted that the ongoing pregnancy rates reported in the present manuscript (50.9 versus 47.3% for agonists and antagonists, respectively) are higher than the baseline pregnancy rate (35%) used for the power calculation.

Higher pregnancy rates have also been shown in previous studies in patients with PCOS [57 versus 61% (Kurzawa et al., 2008); 58.5 versus 57.6% (Bahceci et al., 2005) for agonists and antagonists, respectively].

It should be noted that the difference observed here in ongoing pregnancy rates between the groups (3.6%) is below that arbitrarily accepted as clinically significant (5%), and is not statistically significant.

However, the 95% CI shows that the current study (although, to the best of our knowledge, the largest performed in patients with PCOS comparing the two GnRH analogues) cannot exclude a difference of 29.6 or þ16.8%, which is clinically important. Thus it is likely that to reject or accept the hypothesis that in PCOS patients the probability of ongoing pregnancy is independent of the analogue used, a meta-analysis of adequate size is necessary.

In the current study it was shown that the flexible GnRH antagonist protocol was associated with a significantly lower probability of Grade II OHSS (requiring monitoring on an outpatient basis but not necessitating hospitalization) compared with the GnRH agonist protocol. Our results corroborate findings from previous studies in the general population (Kolibianakis et al., 2006; Aboulghar et al., 2007; Lainas et al. 2007), which suggested that the use of GnRH antagonists was associated with a lower probability of OHSS as compared with the use of GnRH agonists. These observations suggest that use of GnRH antagonists in the treatment of patients with PCOS results in a safer way of performing ovarian stimulation for IVF. It is not, however, clear what is the basis of the different occurrence of OHSS observed between the two groups: this does not appear to be associated with the number of COCs retrieved (Table II).

However, a significantly lower total dose of gonadotrophins was required and a shorter duration of stimulation was necessary in the antagonist, as compared with the agonist, group. Despite the similar number of COCs retrieved in the

two groups, it cannot be excluded that the number of small follicles, which did not yield COCs but contributed to OHSS occurrence, might be associated with the total rFSH dose administered and/or the duration of stimulation.

The findings of a decreased total dose of rFSH, of shorter duration of gonadotrophin stimulation and of lower E2 levels on the day of hCG administration in the antagonist group, should be read with caution as this study was not double blind. Nevertheless, these results are in agreement with those previously published by other groups (Hohmann et al., 2003; Hwang et al., 2004; Bahceci et al., 2005; Ragni et al., 2005; Griesinger et al., 2006; Kolibianakis et al., 2007 ; Lainas et al., 2007; Kurzawa et al. 2008).

Increased BMI was shown to have a negative effect on ongoing pregnancy rates, as calculated by logistic regression. This finding is in agreement with previous studies that reported lower pregnancy rates in women with high BMI who had been treated with either agonist (Orvieto et al., 2009) or antagonist protocols (Kolibianakis et al.,2003).

Figure 5

Table V OHSS occurrence in the GnRH agonist and antagonist groups

OHSS % (n)	Agonist group (n 110)	Antagonist group (n110)	Difference (95% CI)	P-value (chi-square)
I	34.5(38)	55.5(61)	-21.0(233.8to28.1)	0.006
II	60.0(66)	40.0(44)	20.0(p7.1 to p32.9)	
III	5.5(6)	4.5(5)	1.0(p29.2top11.2)	

I, none or mild OHSS; II, moderate and severe OHSS treated at an outpatient level; III, critical OHSS requiring patient hospitalization. P-values in bold indicate statistical significance.

It should also be noted that the dose of hCG used for triggering final oocyte maturation in the current study was 5000 IU. This choice was made in order to reduce the occurrence of OHSS in this high-risk population. Consequently, regarding OHSS occurrence the conclusions drawn in the current study might not be applicable in patients with PCOS in whom 10 000 IU hCG are used for triggering final oocyte maturation.

CONCLUSIONS

Despite the lack of adequate power that would allow solid conclusions to be drawn, this is the largest study to date comparing GnRH analogues in patients with PCOS. The flexible GnRH antagonist protocol, as compared with the long agonist protocol, appears to offer similar ongoing pregnancy rates, and is associated with a significantly lower incidence of Grade II OHSS, requiring lower gonadotrophin amounts and a shorter duration of stimulation. Considering, in addition, that the antagonist protocol is more patient friendly as compared with the agonist, GnRH antagonists might be the protocol of choice for patients with PCOS. This, however, remains to be verified by a future meta-analysis.

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