Article

Ovarian stimulation in polycystic ovary syndrome patients: the role of body mass index

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Abstract

In an attempt to examine whether body mass index (BMI) may influence IVF outcome in polycystic ovary syndrome (PCOS) patients undergoing ovarian stimulation with either gonadotrophin-releasing hormone (GnRH)-agonist (agonist group) or antagonist (antagonist group), 100 IVF cycles were studied: 35 in the agonist and 65 in the antagonist groups. In both agonist and antagonist groups, patients with BMI ≤ 25 kg/m^2 had a significantly higher fertilization rate compared with patients with BMI > 25 kg/m^2 ($P < 0.02$ and $P < 0.01$, respectively). Lean patients (BMI ≤ 25) undergoing ovarian stimulation using the GnRH-agonist, demonstrated the highest pregnancy rate. In conclusion, in this series of PCOS patients undergoing IVF-embryo transfer cycles, ovarian stimulation utilizing the midluteal long GnRH-agonist suppressive protocol yielded a higher pregnancy rate in lean patients, probably due to its ability to lower the high basal LH milieu and its detrimental effect on oocyte quality and implantation potential.

Keywords: *body mass index, GnRH agonist, GnRH antagonist, IVF outcome, PCOS, pregnancy*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age (Rotterdam European Society for Human Reproduction and Embryology [ESHRE]/American Society for Reproductive Medicine [ASRM], 2004). The pathophysiology of PCOS is not completely understood and its aetiology remains an enigma. The recognition of the controversies surrounding the treatment has led to the recently published ESHRE/ASRM Consensus that addressed the therapeutic challenges raised in women with infertility and PCOS (Thessaloniki ESHRE/ASRM, 2008).

IVF and embryo transfer is an effective and reasonable option for PCOS patients who are refractory to conventional infertility modalities or who have coexisting infertility factors (Buyalos and Lee, 1996; Thessaloniki ESHRE/ASRM 2008). Many ovarian stimulation strategies have been offered to patients with PCOS undergoing IVF (Dor *et al.*, 1990; Mulders *et al.*, 2003; Griesinger *et al.*, 2006), but no compelling advantage for one stimulation protocol over another has been established (Thessaloniki ESHRE/ASRM, 2008).

Obesity, a common clinical manifestation of PCOS patients (Franks, 2006), is linked to insulin resistance and failure or delayed response to the various ovarian stimulation treatments (Mulders *et al.*, 2003; Rotterdam ESHRE/ASRM, 2004). Health problem are increased with increasing body mass index (BMI). In an unselected population from Alabama, 66% of women with PCOS had BMI > 25 kg/m^2 (Azziz *et al.* 2004). Data regarding the impact of obesity on IVF cycle outcome is controversial, ranging from studies reporting no effect of increasing BMI on IVF success rates (Lashen *et al.*, 1999; Spandorfer *et al.*, 2004; Dechaud *et al.*, 2006; Dokras *et al.*, 2006) to those demonstrating lower cumulative live birth rates in overweight patients (Fedorcsak *et al.*, 2004; Lintsen

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et al., 2005; Ku *et al.*, 2006). There has been a recent attempt to examine the influence of BMI on IVF outcome in patients undergoing ovarian stimulation with either gonadotrophin-releasing hormone (GnRH) agonist or antagonist (Rabinson *et al.*, 2008). This study found that in patients with BMI > 25 kg/m^2, ovarian stimulation with either GnRH agonist or antagonist achieved a comparable outcome, in those with BMI < 25 kg/m^2, the use of GnRH-agonist suppressive protocol revealed a significantly higher pregnancy rate.

These findings have prompted the present study into whether BMI affects IVF cycle outcome in PCOS patients undergoing ovarian stimulation protocols using either the GnRH agonist or antagonist ovarian stimulation protocols. The findings of this study may help to clarify whether patient BMI necessitates a different approach to GnRH analogues in ovarian stimulation. It will also aid fertility specialists in tailoring the appropriate ovarian stimulation protocols to PCOS patients.

Materials and methods

Computerized files were reviewed of all women admitted to the study IVF unit (Barzilai Medical Centre) during a 4-year period, who reached the ovum retrieval stage. Only patients with PCOS, who met the criterion of the recent ESHRE/ASRM Consensus (2004) and underwent ovarian stimulation using either the midluteal long GnRH-agonist suppressive protocol (agonist group) or the flexible multidose GnRH-antagonist protocol (antagonist group) were included. A detailed description of the two GnRH-analogue protocols has previously been presented (Orvieto *et al.* 2006a,b). The selection of type of analogue used was the decision of the treating physician and largely dependent on the fashion at that time and the programme policy (Orvieto, 2005). In the study unit, high-responder patients are offered the use of GnRH-antagonist during their first IVF attempt. With this strategy it is possible to substitute human chorionic gonadotrophin (HCG) with GnRH agonist to trigger ovulation, with the consequent elimination of severe ovarian hyperstimulation syndrome (OHSS).

Data on 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. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

Results are presented as mean ± SD. Differences in variables were statistically analysed with non-parametric Wilcoxon signed rank test, Student's *t*-test and chi-squared test, as appropriate. A *P*-value of less than 0.05 was considered significant.

Results

Fifty-nine patients undergoing 100 IVF cycles were evaluated; 35 in the agonist group and 65 in the antagonist group. Pregnancy was achieved in 10 patients in the agonist group (pregnancy rate, 28.6% per cycle) and 11 patients in the antagonist group (pregnancy rate, 16.9% per cycle); this difference was not statistically significant. No differences were observed in the clinical characteristics of the IVF cycles between the two study groups.

Table 1. Comparison between IVF cycles in the GnRH agonist and GnRH antagonist groups according to the different body mass index (BMI) subgroups.

	Agonist			*Antagonist*		
	BMI ≤ 25 kg/m^2	*BMI > 25 kg/m^2*	P-*value*	*BMI ≤ 25 kg/m^2*	*BMI > 25 kg/m^2*	P-*value*
Number of cycles	18	17	–	24	41	–
Patient age (years)	30.2 ± 3.7	30.9 ± 3.9	NS	29.4 ± 4.0	32.8 ± 4.2	$P < 0.02$
BMI (kg/m^2)	23.9 ± 2.1	30.8 ± 4.7	$P < 0.001$	22.5 ± 2.9	31.1±3.6	$P < 0.001$
Day 3 FSH (IU/l)	6.1 ± 1.4	6.4 ± 2.4	NS	6.3 ± 1.9	5.2 ± 1.8	NS
Number of gonadotrophin ampoules used	32.4 ± 14.3	37.2 ± 13.4	NS	24.5 ± 16.3	33.3 ± 14.5	$P < 0.03$
Length of stimulation (days)	10.1 ± 2.4	12.0 ± 2.9	$P < 0.05$	10.0 ± 2.1	10.8 ± 2.5	NS
Peak oestradiol on day of HCG administration (pg/ml)	1966 ± 875	1729 ± 730	NS	1822 ± 905	1396 ± 1086	NS
Progesterone on day of HCG administration (ng/ml)	0.6 ± 0.4	0.5 ± 0.2	NS	0.6 ± 0.3	0.7 ± 0.7	NS
Number of follicles >14 mm in diameter on day of HCG administration	10.9 ± 4.8	10.3 ± 3.7	NS	9.1 ± 4.2	8.7 ± 4.5	NS
Number of oocytes retrieved	11.5 ± 5.9	13.1 ± 4.9	NS	11.5 ± 7.8	11.0 ± 7.7	NS
Fertilization rate (%)	62 ± 18	44 ± 22	$P < 0.02$	69 ± 16	53 ± 21	$P < 0.01$
Number of embryos transferred	2.2 ± 0.5	2.3 ± 0.8	NS	2.1 ± 0.5	2.3 ± 0.6	NS
Pregnancy rate (%)	8/18 (44.4)[a]	2/17 (11.8)	$P < 0.02$	4/24 (16.7)[b]	7/41 (17.1)[c]	NS

Values are mean ± SD unless otherwise stated. HCG = human chorionic gonadotrophin; NS = not statistically significant.
[a,b]$P < 0.05$; [a,c]$P < 0.04$.

Patients were further divided into two subgroups according to their BMI (A ≤25 kg/m^2; B >25 kg/m^2). In the agonist group, patients in subgroup A required significantly shorter stimulation ($P < 0.05$) and had higher fertilization ($P < 0.02$) and pregnancy rates (44.4% versus 11.8%, respectively; $P < 0.02$), compared with subgroup B. No differences were observed between the subgroups in the other stimulation variables (**Table 1**).

In the antagonist group, patients in subgroup A used significantly fewer gonadotrophin ampoules ($P < 0.03$), had a higher fertilization rate ($P < 0.01$) compared with subgroup B, with no differences between the groups in the other stimulation characteristics, including clinical pregnancy rate (16.7% versus 17.1%, respectively).

Lean patients (BMI≤25) undergoing ovarian stimulation using the GnRH agonist, demonstrated the highest pregnancy rate (**Table 1**).

Discussion

In the present study of PCOS patients undergoing ovarian stimulation for IVF, an apparently higher (but not statistically significantly higher) clinical pregnancy rate was observed in those undergoing the midluteal long GnRH-agonist suppressive protocol than in those undergoing the flexible multidose GnRH-antagonist protocol. This finding is in accordance with previously reported findings (Orvieto *et al*., 2006c) and the recent meta-analysis by Al-Inany *et al*. (2007). These studies found a significantly lower clinical pregnancy rate and ongoing pregnancy/live birth rate in the antagonist group compared with the agonist group.

While overweight/obese PCOS patients equally benefit from ovarian stimulation consisting of GnRH agonist or antagonist, lean PCOS patients demonstrated a significantly higher pregnancy rate while using the GnRH-agonist ovarian stimulation protocol. This might be explained by the well-established observations showing higher LH and sex-hormone binding globulin and lower insulin levels in non-obese compared with obese PCOS women (Insler *et al*. 1993; Morales *et al*. 1996; Pagan *et al*. 2006). The high LH levels in the non-obese PCOS patients might have a detrimental role on oocyte quality (Shoham, 2002). The observed higher implantation rate of oocytes obtained from PCOS patients exposed to GnRH agonist (Ashkenazi *et al*., 1995) is in agreement with the present observation and may suggest that GnRH agonist should be the preferred GnRH analogue used in lean PCOS patients undergoing ovarian stimulation for IVF.

In conclusion, in this series of PCOS patients undergoing IVF-embryo transfer cycles, ovarian stimulation utilizing the midluteal long GnRH-agonist suppressive protocol yielded higher a pregnancy rate in lean patients, probably due to its ability to lower the high basal LH milieu and its detrimental effect on oocyte quality and implantation potential. However, it should be emphasized that the number of cycles involved in the current study is relatively limited, arguing for some caution regarding the conclusions. Moreover, since PCOS patients are at high risk of developing severe OHSS, it would be prudent, in the first IVF cycle attempt, to offer these patients the GnRH-antagonist ovarian stimulation protocol, with its inherently lower risk of OHSS (Al-Inany *et al*., 2007), with the possibility of substituting HCG with GnRH agonist and the consequent elimination of severe OHSS (Orvieto, 2005).

Further large studies are needed to clarify the role of these two GnRH analogues in lean and obese PCOS patients. These studies may help fertility specialists to tailor the ovarian stimulation protocol, to optimize IVF success and reducing the risk of severe OHSS.

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