Article

Impact of isolated obesity on ICSI outcome

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Abstract

The aim of this study was to assess the impact of isolated obesity on the outcome of intracytoplasmic sperm injection (ICSI). A total of 775 patients undergoing 1113 ICSI cycles were categorized on the basis of body mass index (BMI): group 1 (BMI 18.5–24.9 kg/m^2; normal weight; $n = 627$ cycles), group 2 (BMI 25.0–29.9 kg/m m^2; overweight; $n = 339$ cycles) and group 3 (BMI ≥30 kg/m^2; obese; $n = 147$ cycles). Sixty-three (10.0%) cycles in group 1, 53 (15.6%) cycles in group 2 and 26 cycles (17.7%) in group 3 were cancelled ($P < 0.05$ for group 1 versus groups 2 and 3). Despite the significantly higher total gonadotrophin consumption in groups 2 and 3 compared with group 1, the mean serum oestradiol level on the day of human chorionic gonadotrophin administration was significantly higher in group 1 ($P < 0.05$). The number of cumulus–oocyte complexes, metaphase II oocytes, and two-pronucleated oocytes were significantly lower in group 3 compared with group 1 ($P < 0.05$). However, fertilization rate, the mean number of embryos transferred, the mean number of grade 1 embryos transferred, clinical pregnancy, implantation, multiple pregnancy and miscarriage rates were comparable among the three groups. The rate of cycles with cryopreservable embryos was significantly lower in groups 2 and 3 compared with group 1 ($P < 0.05$).

Keywords: *assisted reproduction treatment, body mass index, intracytoplasmic sperm injection, IVF, obesity, overweight*

Introduction

The adverse effect of obesity on natural fecundity has been reported (Harlass *et al*., 1984; Hollmann *et al*., 1996). This negative effect may be due to multiple endocrine and metabolic alterations including steroid metabolism, altered secretion and action of insulin and other hormones, such as leptin, resistin, ghrelin or adiponectin (Poretsky *et al*., 1999; Moschos *et al*., 2002; Pasquali *et al*., 2003; Fedorcsak *et al*., 2004). The effect of obesity on the outcome of IVF/intracytoplasmic sperm injection (ICSI) is not clear. A detrimental effect of obesity on ovarian stimulation response and pregnancy rates has been reported in some studies (Lewis *et al*., 1990; Wass *et al*., 1997; Lashen *et al*., 1999) whereas no such effect has been noted in others (Crosignani *et al*., 1994; Loveland *et al*., 2001). However, there is little data on the impact of isolated obesity on IVF/ICSI outcome without commonly associated disorders such as polycystic ovary syndrome (PCOS).

The aim of this study was to evaluate the effect of isolated obesity on ICSI performance.

Materials and methods

A total of 775 patients undergoing 1113 ICSI cycles were enrolled retrospectively via the computerized IVF database system at the Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine. Exclusion criteria included freeze–thaw cycles, advanced female age (>40 years), history of irregular menstrual cycle, presence of polycystic ovary appearance and/or PCOS and patients suspected of having a poor ovarian response (previous history of poor ovarian response, day 3 FSH >10 mIU/ml, day 3 oestradiol >60 pg/ml or bilateral antral follicle count <6). A diagnosis of PCOS was made in the presence of any two of the following three criteria: polycystic ovaries; oligo- or anovulation; and clinical or biochemical evidence of hyperandrogenism (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop group, 2004).

The height and weight of each patient were obtained to calculate the body mass index (BMI, kg/m^2) immediately prior

to initiating the ICSI cycle. Patients were categorized on the basis of BMI: group 1 (BMI 18.5–24.9 kg/m^2; normal weight; *n* = 627 cycles), group 2 (BMI 25.0–29.9 kg/m^2; overweight; *n* = 339 cycles), group 3 (BMI ≥30 kg/m^2; obese; *n* = 147 cycles).

All patients underwent ovarian stimulation consisting of luteal-long leuprolide acetate (Lucrin; Abbott, Cedex, Istanbul) and recombinant FSH (Gonal-F; Serono, Istanbul) using the step-down protocol. The starting dose of gonadotrophin was determined according to female age, antral follicle count at baseline transvaginal ultrasonography, day 3 FSH, oestradiol concentration, BMI and previous ovarian response, if data available. Ovarian response was monitored with frequent serum oestradiol measurements and transvaginal ultrasonography, as described previously (Bukulmez *et al.*, 2000). The criterion for human chorionic gonadotrophin (HCG, Profasi; Serono, Istanbul) administration was the presence of three or more follicles exceeding 17 mm in diameter. Oocyte retrieval was carried out under local anaesthesia using vaginal ultrasound-guided puncture of follicles 36 h after HCG administration. Standard procedures were carried out for gamete–embryo handling and day-3 embryo transfer was performed in all cases using a soft replacement catheter (Wallace; PM Group, Istanbul, Turkey). The luteal phase was supported by daily vaginal progesterone suppositories (Crinone; Serono, Istanbul) starting one day after oocyte retrieval.

Embryos were graded on day 3 according to a 1 to 4 scoring system (with 1 being the best), which was based on fragmentation, cell symmetry and blastomere number (Hardarson *et al.*, 2001).

Clinical pregnancy was defined as the presence of an intrauterine gestational sac with heartbeat at transvaginal ultrasonography and/or the presence of trophoblastic tissue in a dilatation and curettage pathology specimen.

Statistics

Statistical analyses were performed using Statistics Package for Social Sciences version 12.0 (SPSS Inc., Chicago, IL, USA). The chi-squared test and Fisher's exact test were used to analyse nominal variables in the form of frequency tables. Normally distributed (Kolmogorov–Smirnov test) parametric variables were tested by the analysis of variance (ANOVA) using the Bonferroni test for post hoc analysis. Non-normally distributed metric variables were analysed using the Kruskal–Wallis test and the Mann–Whitney *U*-test. *P* values of <0.05 were considered statistically significant. Values were expressed as mean ± SD, unless stated otherwise.

Results

All three groups were comparable regarding the baseline characteristics, including female age, duration of infertility and proportion receiving ICSI treatment for the first time (**Table 1**).

Sixty-three (10.0%) cycles in group 1, 53 (15.6%) cycles in group 2 and 26 cycles (17.7%) in group 3 were cancelled ($P < 0.05$ for group 1 versus group 2 and 3). Within the cancelled cycles, the rates due to poor ovarian response were 23.8%, 32.1% and 53.8% in groups 1, 2 and 3, respectively ($P < 0.05$ for group 1 versus group 3 only).

Despite the significantly higher total gonadotrophin consumption in groups 2 and 3 compared with group 1 ($P < 0.05$); the mean serum oestradiol concentration on the day of HCG administration was significantly higher in group 1 ($P < 0.05$; **Table 2**).

The number of cumulus–oocyte complexes, metaphase II oocytes and 2-PN oocytes was significantly lower in group 3, compared with group 1 ($P < 0.05$, **Table 3**). However, fertilization rate, the mean number of embryos transferred and the mean number of grade 1 embryos transferred was comparable among the three groups (**Table 3**).

The rate of cycles with cryopreservable embryos was significantly lower in groups 2 and 3 compared with group 1 ($P < 0.05$). The clinical pregnancy rates per embryo transfer were 44.6%, 45.4% and 48.1% in groups 1, 2 and 3, respectively. The implantation rates were comparable among the three

Table 1. Baseline characteristics according to body mass index (BMI).

Parameter	*BMI (kg/m^2)*			P-*value*
	Group 1 18.5–24.9	*Group 2 25.0–29.9*	*Group 3 ≥30.0*	
No. of patients	451	222	102	–
No. of cycles	627	339	147	–
First ICSI treatment (%)	71.9	65.5	69.4	NS
No. of cancelled cycles (%)	63 (10.0)[a]	53 (15.6)	26 (17.7)	<0.05
No. of cancelled cycles due to poor ovarian response (%)	15 (23.8)	17 (32.1)	14 (53.8)[d]	<0.05
Mean age ± SD (years)	31.9 ± 4.2	32.5 ± 4.4	32.5 ± 4.5	NS
Mean BMI ± SD (kg/m^2)	22.1 ± 1.8[a]	26.9 ± 1.3[b]	32.8 ± 2.6[c]	<0.01
Mean duration of infertility ± SD (months)	88.9 ± 53.7	86.3 ± 48.3	92.8 ± 53.1	NS

[a]Statistically different from groups 2 and 3; [b]statistically different from groups 1 and 3; [c]statistically different from groups 1 and 2; [d]statistically different from group 1.
ICSI = intracytoplasmic sperm injection; NS = not statistically significant.

Table 2. Response to ovarian stimulation according to body mass index (BMI).

Variable	*BMI (kg/m²)*			P-*value*
	Group 1 18.5–24.9	*Group 2 25.0–29.9*	*Group 3 ≥30.0*	
Duration of stimulation (days)	10.1 ± 1.7	10.3 ± 2.7	10.6 ± 2.6	NS
Total dose of FSH used (IU)	2516.5 ± 1057.2[a]	2779.1 ± 1160.1[b]	3248.3 ± 1255.1[c]	<0.05
Oestradiol on day of HCG administration (pg/ml)	2472.5 ± 1586.2[a]	2173.2 ± 1295.7	2022.4 ± 1553.7	<0.05
Endometrial thickness on day of HCG administration (mm)	11.1 ± 2.2	11.2 ± 2.4	11.0 ± 2.2	NS

Values are mean ± SD. NS = not statistically significant.
[a]Statistically different from groups 2 and 3; [b]statistically different from groups 1 and 3; [c]statistically different from groups 1 and 2.

Table 3. Embryological data and pregnancy outcome according to body mass index (BMI).

Variable	*BMI (kg/m²)*			P-*value*
	Group 1 18.5–24.9	*Group 2 25.0–29.9*	*Group 3 ≥30.0*	
No. of oocyte–cumulus complexes	11.9 ± 6.2	11.4 ± 6.2	10.0 ± 5.9[a]	<0.05
No. of metaphase II oocytes	10.1 ± 5.8	9.7 ± 5.6	8.6 ± 5.3[a]	<0.05
No. of 2 PN oocytes	7.2 ± 4.7	6.8 ± 4.4	6.0 ± 4.0[a]	<0.05
Fertilization rate (%)	72	69	70	NS
No. of embryos transferred	3.0 ± 1.1	3.1 ± 1.2	3.1 ± 1.1	NS
Mean no. of grade 1 embryos transferred ± SEM	0.7 ± 0.1	0.7 ± 0.1	0.9 ± 0.1	NS
No. of cycles with embryo freezing (%)	128 (22.7)[b]	43 (15.0)	13 (10.7)	<0.05
Clinical pregnancy/embryo transfer (%)	44.6	45.4	48.1	NS
Implantation rate (%)	25	25	26	NS
Multiple pregnancy rate (%)	52	50	41	NS
No. of miscarriages (%)	34 (13.5)	17 (13.8)	11 (19.0)	NS
No. of OHSS cases requiring hospitalization (%)	6 (1.1)	3 (1.1)	1 (0.8)	NS

Values are expressed as mean ± SD, unless stated otherwise. NS, not significant; OHSS, ovarian hyperstimulation syndrome.
[a]Statistically different from group 1; [b]statistically different from groups 2 and 3.

groups. The multiple pregnancy rates were 52%, 50% and 41%, respectively. The respective figures for miscarriage were 13%, 14% and 19% (**Table 3**).

Discussion

In the current study, a trend of higher gonadotrophin consumption, lower serum oestradiol concentration on the day of HCG administration, fewer cumulus–oocyte complexes retrieved and fewer available cryopreservable embryos was noted in obese females undergoing ICSI when compared with normal weight women. However, this did not translate to inferior pregnancy outcome, since fertilization, implantation, clinical pregnancy and miscarriage rates were comparable among the three BMI groups.

There is a paucity of data on the effect of obesity on IVF/ICSI outcome with conflicting results. Fedorcsak *et al.* (2004) in 2660 patients undergoing 5019 cycles, reported a significant linear association between higher BMI (BMI groups: <18.5 kg/m²; 18.5–24.9 kg/m²; 25.0–29.9 kg/m²; and >30.0 kg/m²) and increased dose and longer stimulation with FSH, increased frequency of cycle cancellation, lower number of oocytes retrieved and lower number of embryos transferred. However, embryo quality, implantation and pregnancy rates were comparable among all BMI groups. Higher BMI was associated with increased incidence of early pregnancy loss (before week 6 of gestation), increased miscarriage during 6–12 weeks of pregnancy, lower live birth and cumulative live birth rates (Fedorcsak *et al.*, 2004). Van Swieten *et al.* (2005) reported that obesity is negatively associated with IVF/ICSI outcome. Obese women had a higher risk of cycle cancellation due to poor ovarian response and lower fertilization rates. Loveland *et al.* (2001) noted that females with BMI >25 kg/m² had higher duration of stimulation, higher gonadotrophin requirement, lower pregnancy, implantation rates and higher miscarriage rates. The present findings confirm the results of the studies that reported a detrimental effect of increased BMI on ovarian stimulation response.

A detrimental effect of high BMI on IVF/ICSI outcome, if present, may arise from its effect(s) on the ovary and/or endometrium. Obesity might be detrimental to ovarian stimulation response via mediators, such as leptin and ghrelin (Agarwal *et al.*, 1999; Tena-Sempere *et al.*, 2002). High levels of

leptin in follicles may inhibit ovarian granulosa and thecal cell steroidogenesis, probably through antagonism of stimulatory factors such as insulin-like growth factor-1, transforming growth factor-β, insulin and LH (Spicer and Francisco, 1997, 1998; Agarwal *et al*., 1999). Ghrelin, associated with obesity, may be another putative mediator (Papotti *et al*., 2000; Shiiya *et al*., 2002; Tena-Sempere *et al*., 2002; Druce *et al*., 2005). The impact of obesity on endometrial receptivity was investigated in an oocyte donation model (Bellver *et al*., 2007). A total of 2656 patients undergoing their first oocyte donation cycle were enrolled in this retrospective study. The recipients were stratified based on BMI as <20.0 kg/m^2 (n = 471), 20.0–24.9 kg/m^2 (n = 1613), 25.0–29.9 kg/m^2 (n = 450), and >30.0 kg/m^2 (n = 122). Implantation, pregnancy, miscarriage, and ongoing pregnancy rates were comparable among all BMI subgroups, although there was a trend of inferior outcome with higher BMI subgroups. Ongoing pregnancy rates were significantly lower in the overweight and obese groups compared with the underweight and normal groups. These data imply that endometrial receptivity might be decreased in overweight and obese females.

In contrast, in some studies, a detrimental effect of increased BMI on IVF/ICSI outcomes could not be shown (Wass *et al*., 1997; Nichols *et al*., 2003; Frattarelli and Kodama, 2004). Frattarelli and Kodama (2004) noted that in 41 women undergoing IVF, patients with BMI >24 kg/m^2 demonstrated a significant increase in the number of follicles and a significant decrease in the dose and duration of gonadotrophins used. Nichols *et al*. (2003), in a retrospective study, evaluated IVF outcome in 372 women (465 cycles) who were stratified according to BMI (BMI groups = <20.0 kg/m^2; 20.0–27.9 kg/m^2 and >28.0 kg/m^2); the dose of gonadotrophin used, duration of stimulation, number of oocytes retrieved, number and quality of embryos transferred, and miscarriage rates did not differ among the three groups. However, implantation (20.3% versus 24.7%, $P < 0.05$) and pregnancy rates (35.2% versus 52.1%, $P < 0.05$) were lower in the BMI >28.0 kg/m^2 group when compared with the normal weight women. In 220 patients, Wass *et al*. (1997) did not note any detrimental effect of obesity on IVF outcome.

Recently, Maheshwari *et al*. (2007) reported a systematic review and meta-analysis including 21 studies in which the effect of BMI on IVF outcomes was investigated. They noted that women with a BMI >25 kg/m^2 had a lower chance of pregnancy following IVF [odds ratio (OR) = 0.71, 95% confidence interval (CI): 0.62–0.81], required higher dose of gonadotrophins (weighed mean differences 210.08, 95% CI: 149.12–271.05) and had an increased miscarriage rate (OR 1.33, 95% CI: 1.06–1.68) when compared with the women with a BMI of 25 kg/m^2 or less. They also noted that there was insufficient evidence on the effect of BMI on live birth, cycle cancellation, oocyte recovery and ovarian hyperstimulation syndrome.

It is the authors' view that the main limitation of studies evaluating the effect of BMI on IVF/ICSI outcome is patient inclusion criteria. The majority of the studies in this context do not discriminate isolated obesity from patients with polycystic ovary appearance and PCOS. Since PCOS is frequently associated with increased BMI, it is essential to exclude such patients in order to delineate the impact of isolated obesity on IVF/ICSI outcome. As far as is known, there are only two reported studies accounting for this patient inclusion criterion. Brannian *et al*. (2001), in 139 patients, reported that isolated increased BMI did not correlate with pregnancy outcome. Loh *et al*. (2002) reported significant cycle cancellation but comparable pregnancy outcome with increased BMI (BMI >30 kg/m^2).

It is concluded that isolated high BMI (≥30 kg/m^2) has a detrimental effect on ovarian stimulation response and availability of cryopreservable embryos. However, this does not translate into inferior pregnancy outcome since the mean number and grade 1 embryos transferred, implantation, clinical pregnancy and miscarriage rates were comparable among all BMI subgroups.

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