Effect of female increased body mass index on intracytoplasmic sperm injection outcome

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Background BMI is calculated by dividing the weight in kilograms by height in meters squared (kg/m^2). It is known that the reproductive potential in obese women is decreased and to be associated with suboptimal outcomes after assisted reproductive technologies.

Objective The aim of this study was to evaluate the effect of increased BMI on pregnancy outcome in women undergoing intracytoplasmic sperm injection (ICSI) cycle.

Patients and methods This retrospective study was conducted on 200 Women at Assisted Reproductive Technology Unit, International Islamic Centre for Population Studies and Research (IICPSR), Al-Azhar University. Data were recruited from patient files at IICPSR from January 2013 to December 2015, who had ICSI trial during this period. Patients who were included in the study were subdivided into two groups according to BMI – first group: normal-weight women with BMI between 18 and 24.9 kg/m^2 (100 cases); secondgroup: overweight and obese women weighing at least 25 kg/m^2 (100 cases). The outcomes in the two groups were demonstrated in all stages of ICSI.

Results The duration of infertility was progressively higher as BMI increased. Basal luteinizing hormone, follicle-stimulating hormone, and estradiol levels were higher in group 2 than in group 1. Higher total doses of gonadotropin were required in group 2 to obtain equivalent ovarian response than in group 1. No significant difference was observed on ovarian response and embryonic parameters. Serum estradiol level on ovulation triggering day was significantly higher in group 2. Ovarian hyperstimulation and cycle outcome were not significantly different between both groups.

Conclusion Overweight and obesity appear to have independent adverse effects on ovarian response to stimulation and outcomes in women undergoing ICSI.
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Introduction

BMI is calculated by dividing the weight by height (kg/m^2). The normal range is considered to be 18.5–24.9 kg/m^2. Obesity is widely regarded as a major global pandemic that has far-reaching implications well beyond the ramifications of the patient's health [1].

Obesity is a major contributor to a variety of underlying etiologies associated with infertility. It is no longer controversial, as most of the recent evidence categorically demonstrates that obese women are at an increased risk of subfecundity and infertility. This is mediated by the interplay between derangements in the hypothalamic pituitary ovarian axis, oocyte quality, and endometrial receptivity [2].

Obesity has a significant negative effect on Assisted Reproductive Technology (ART) outcomes. Patients with a BMI more than 30 have up to 68% lower odds of having a live birth following their first ART cycle compared with women with a BMI less than 30 kg/m^2 [3].

Concerning controlled ovarian stimulation, some authors have shown increased duration of stimulation, higher total dose of gonadotrophin administered. Lower ovarian response to ovarian stimulation, with reduced oocytes retrieval, poorer embryo quality and lower fertilization rate, was observed in obese women undergoing in-vitro fertilization (IVF) compared with normal-weight infertile women. However, other authors found no differences in IVF outcome according to female BMI. In addition, obese women who achieve conception after IVF are likely to present higher risks of spontaneous abortion and obstetrical complications [4]. Early research suggested that an increased BMI has a deleterious effect on fertility. These included cycle cancellation, clinical pregnancy, and live birth rates in various BMI groups, followed by a multivariant analysis adjusting to confounders such as age, presence of polycystic ovary syndrome, and duration of infertility [5].

A different means of investigating this issue is by focusing on the impact of weight loss on fertility. Weight reduction by any mean, for example diet or bariatric surgery, is without doubt the most significant variable that markedly improves fertility, menstrual cyclicity, and reproductive outcomes [6].

Patients and methods

This retrospective study was conducted on 200 Women at ART Unit, International Islamic Centre for Population Studies and Research (IICPSR), Al-Azhar University. Data were recruited from patient files at IICPSR from January 2013 to December 2015, who had ICSI trial during this period.

Inclusion criteria

Inclusion criteria were as follows:

(1) Age 20–40 years.
(2) BMI>18 kg/m^2.
(3) Type of infertility: 1 year.
(4) Male factor: normal semen analysis.
(5) Underwent long agonist protocol.

Exclusion criteria

Exclusion criteria were as follows:

(1) BMI<18 kg/m^2.
(2) Age >40 years.
(3) Women with pelvic disease (e.g. fibroid, pelvic inflammatory disease, endometriosis, ovarian mass).
(4) Women with a medical history (e.g. diabetes mellitus, hypertension, hyperthyroidism, and hypothyroidism).
(5) Abnormal hysterosalpingography (hydrosalpnix, pyosalpinx, septate, bicorniate uterus).

Methods

Patients who were included in our study were subdivided into two groups according to BMI.

First group: normal-weight women with a BMI between 18 and 24.9 kg/m^2 (100 cases).

Second group: overweight and obese women weighing ≥25 kg/m^2 (100 cases).

So the following items demonstrate the following in both groups:

(1) Age, weight, height, BMI.
(2) Duration of infertility.
(3) Infertility workup results such as:
  (a) Recent semen analysis.
  (b) Recent hysterosalpingography.
  (c) Basal hormonal assay on third day of cycle [serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin, and thyroid-stimulating hormone].
  (d) Baseline transvaginal ultrasound.
(4) Duration of stimulation.
(5) Total dose and number of ampoules of gonadotrophin administered.
(6) Ovarian response. The size and numbers of the follicles.
(7) The numbers and quality of oocyte retrieved.
(8) The numbers and quality of the embryo transferred (either fresh or cryopreserved).
(9) Pregnancy rate.
(10) Miscarriage and live birth rate.

Statistical analysis

Collected data are analyzed, organized, presented in tables and suitable graphs, and analyzed according to standard statistical methods.

Data were analyzed with SPSS (version 21; SPSS Inc., Chicago, Illinois, USA). The normality of data were first tested with one-sample Kolmogorov–Smirnov test.

Qualitative data were described using number and percent. The association between categorical variables was tested using χ^2-test.

Continuous variables were presented as mean±SD for parametric data and median for nonparametric data. The two groups were compared with Student's *t*-test (parametric data), whereas Mann–Whitney test was used to compare two medians (nonparametric data).

Results

In this study, with regard to demographic data, the mean age of patients was 28.43 years in group 1 and in group 2 the mean age was 27.43 years. According to BMI, they were divided into two groups:

(1) First group: normal-weight women with a BMI between 18 and 24.9 kg/m^2 (100 cases), with a mean BMI of 22.83 (SD: 1.44, range: 19.03–24.92), and a mean age of 28.4 years, with an SD of 4.92 years.

(2) Second group: overweight and obese women with BMI of at least 25 kg/m^2 (100 cases) (mean BMI: 28.31, SD: 3.39, range: 25.56–44.30), and mean age of 27.4 years with SD of 5.49 years, with a significant difference between the two groups ($P \leq 0.001$).
(3) The duration of infertility was progressively higher as BMI increased. In group 1 the median duration was 4.50 years, whereas in group 2 the median infertility duration was 5 years; there was a significant difference with a *P* value of 0.034 (Table 1).

As shown in Table 2, basal hormonal status on day 3 showed that group 2 patients had a higher FSH level than group 1 patients, but this difference is minimal, belonging to reference interval, and thus without clinical significance; LH levels were significantly higher ($P=0.02$) in group 2 than in group 1.

However, significantly lower day 3 E2 (*P*0.032) was observed in group 2 than in group 1.

ICSI cycle outcomes are reported in Table 3. Overweight and obese patients in group 2 received significantly higher doses of induction ampoules when compared with group 1 ($P=0.041$), leading to comparable ovarian response, although no significant difference of mature oocytes retrieved between the two groups. Duration of stimulation, number of follicles, and endometrial thickness was not statistically different between group 1 and group 2. Serum estradiol level on ovulation triggering day was significantly higher in group 2.

As shown in Table 4, oocyte number and quality are found to be poorer in group 2 than in group 1 (although not significant). Number and quality of transferred embryo is higher in group 1 than in group 2 ($P=0.003$).

As shown in Table 5 subsequently, cycle outcomes such as pregnancy test, abortion, and live birth rate were found to be poorer in group 2 than in group 1, without any statistical significance.

As shown in Table 6, coasting is more in group 1 (27%) than in group 2 (22%), and those in group 2 are at an increased risk of ovarian hyperstimulation than in group 1.

Table 1 Comparison of demographic data and duration of infertility of the studied groups ($n=100$)

Items	Group 1 (BMI 18–25)	Group 2 (BMI>25)	Test of significance	*P* value
Age (mean±SD) (years)	28.43±4.92	27.43±5.49	$t=1.34$	0.179 (NS)
Weight (mean±SD) (kg)	57.23±5.21	69.59±9.88	$t=11.05$	≤0.001**
Height (mean±SD) (m)	1.58±0.06	1.56±0.05	$t=1.81$	0.071 (NS)
BMI				
Mean±SD	22.83±1.44	28.31±3.39	$t=14.85$	≤0.001**
Range	19.03–24.92	25.56–44.30		
Duration of infertility (median)	4.50	5	$Z=2.118$	0.034*

t, Student's *t*-test; *Z*, Mann–Whitney test; *Statistically significant at $P\leq 0.05$.

Table 2 Comparison of basal hormonal profile in the two groups ($n=100$)

Items	Group 1 (BMI 18–25)	Group 2 (BMI >25)	Test of significance (*Z*)	*P* value
FSH (median) (mIU/l)	6.30	6.35	0.187	0.852 (NS)
LH (median) (mIU/l)	4.30	4.80	2.332	0.02*
PRL (median) (ng/ml)	14.40	14.70	0.709	0.479 (NS)
Basal E2 [median (minimum–maximum)] (pg/ml)	48.00	37.40	2.150	0.032*

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; *Z*, Mann–Whitney test; *Statistically significant at $P\leq 0.05$.

Table 3 Ovarian stimulation, ovarian response in the studied groups ($n=100$)

Items	Group 1 (BMI 18–25)	Group 2 (BMI >25)	Test of significance	*P* value
Number of ampoules median)	33.00	36.00	$Z=2.04$	0.041*
Duration of stimulation (mean±SD) (days)	12.37±1.93	12.56±2.31	$t=0.630$	0.529 (NS)
Number of follicles (US) (median)	9	8	$Z=0.385$	0.70 (NS)
Endometrial thickness (mm)				
Mean±SD	11.18±2.27	11.07±2.16	$t=0.323$	0.747 (NS)
Minimum–maximum	6–17	6–18		
Level of E2 on trigger (pg/ml)				
Median	2358	2852.5	$Z=2.015$	0.044*

t, Student's *t*-test; US, ultrasonography; *Z*, Mann–Whitney test; *Statistically significant at $P\leq 0.05$.

Table 4 Outcomes of ovarian stimulation, oocyte, and embryo quality

Items	Group 1(BMI 18–25)	Group 2 (BMI >25)	Test of significance	*P* value
Number of oocytes collected (median)	6	7	Z=1.615	0.106 (NS)
Number of GV oocytes (median)	2	1	Z=1.309	0.191 (NS)
Number of metaphase 1 oocytes (median)	2	1	Z=2.051	0.040*
Number of metaphase 2 oocytes (median)	4	4	Z=0.884	0.377 (NS)
Number of transferred embryos (mean±SD)	2.56±0.59	2.21±0.81	t=3.49	0.001*
Quality grade A [*n* (%)]	97 (97)	85 (85)	χ^2=8.79	0.003*
Quality grade B [*n* (%)]	29 (29)	36 (36)	χ^2=1.11	0.291

t, Student's *t*-test; *Z*, Mann–Whitney test; *Statistically significant at $P \leq 0.05$.

Table 5 Cycle outcome according to the studied groups

Outcomes	Group 1 (BMI 18–25) [*n* (%)]	Group 2 (BMI >25) [*n* (%)]	χ^2	*P* value
Pregnancy test				
Negative	49 (49.0)	62 (62.0)	3.42	0.064 (NS)
Positive	51 (51.0)	38 (38.0)		
Aborted				
Yes	8 (15.7)	10 (26.3)	1.525	0.217 (NS)
No	43 (84.3)	28 (73.7)		
Live birth				
Yes	38 (88.4)	25 (89.3)	0.014	0.905 (NS)
No	5 (11.6)	3 (10.7)		

Table 6 Coasting and risk of ovarian hyperstimulation syndrome among the studied groups (n=100)

Items	Group 1 (BMI 18–25) [*n* (%)]	Group 2 (BMI >25) [*n* (%)]	χ^2	*P* value
Coasting				
Yes	27 (27.0)	22 (22.0)	0.676	0.411 (NS)
No	73 (73.0)	78 (78.0)		
OHSS				
Yes	1 (1.0)	3 (3)	0.432	0.512 (NS)
No	99 (99.0)	97 (97)		

OHSS, ovarian hyperstimulation syndrome.

Discussion

The development and refinement of ART over the past decades has coincided with a rapid increase in the prevalence of obesity among women of reproductive age [7].

In this study group, the duration of infertility was progressively higher as BMI increased. In group 1 it ranged from 1 to 17 years with a mean duration of 4.50, whereas in group 2 it ranged from 1 to 25 with a mean duration of 5 years; there was a significant difference with a *P* value of 0.034.

This agrees with study carried out by Bellver *et al.* [8], which is a larger retrospective study of over 6,000 women, which found A delayed spontaneous conception has been reported in obese women, mainly caused by ovulatory infertility, but also in women with regular ovarian cycles in whom the probability of pregnancy is reduced by 5% for every unit of BMI that exceeds 29 kg/m^2 with *P* value (0.024*).

It was shown that overweight and obese infertile women had a higher basal serum FSH, LH, and estradiol levels than normal-weight women (Table 2).

This observation is in harmony with previous studies that also found impaired pulsatile secretion of pituitary gonadotrophin in obese women, leading to impaired folliculogenesis [9].

However, some authors disagree with our finding [10].

In addition, the important observation drawn from our study is the need for higher doses of gonadotrophin for ovarian stimulation in overweight and obese women compared with normal-weight women. This highlights a special state of 'gonadotropin resistance'. This state leads to longer periods of ovarian stimulation.

Most studies conducted in obese women undergoing IVF cycles agree with us and reported the same observation [8,11].

This raised several hypotheses. First, this increased dose requirement of gonadotrophin may be related to altered pharmocodynamics characteristics of drugs administered subcutaneously in obese women having increased subcutaneous fat thickness. Indeed, changes in absorption, metabolism, bioavailability, and clearance have been reported in these women [4].

In addition, this study noted that E2 levels in the day of human chorionic gonadotropin administration are significantly higher in patients with higher BMI when compared with women with lower BMI.

This in harmony with the study done by [12], but disagrees with the study done by Moragianni *et al*. [3] and Caillon *et al*. [4], who aimed to provide ART outcome rates per BMI category. In their study, higher BMI was associated with lower E2 levels of human chorionic gonadotropin in the day.

Several hypotheses have been raised, involving the relative hyperoestrogenemia state or hyperinsulinemia and some proinflammatory cytokines (interleukin-6, tumor necrosis factor-α), which could create an unfavorable uterine environment for embryonic implantation. This low-grade inflammatory state has also been related to polycystic ovarian syndrome, independently of obesity [13].

In this study, embryo quality and implantation rates are higher in normal-weight women than in obese women. This remains controversial in the literature, but conversely some authors did not find any effect of obesity upon implantation in IVF cycles [14].

This study found that oocyte number and quality are poorer in group 2 than in group 1 (although not significant). Number and quality of transferred embryo is higher in group 1 than group 2 (P=0.003), and subsequently live birth rate tended to be poorer in group 2 than in group 1 (although not significant).

In a retrospective study conducted by Nichols *et al.* [15], it was shown that the dose of gonadotrophin used, the number of oocytes retrieved, the number and quality of embryos transferred, and the miscarriage rate did not differ between the BMI groups. However, implantation and pregnancy rates were lower in the BMI more than 25 kg/m^2 group than in the normal-weight group [15].

Contrarily, other studies reported a detrimental effect of increased female BMI on ovarian response to stimulation, lower number of oocytes retrieved, and lower number of embryos transferred [12].

As many variables can impact IVF success rates, our observations on obesity must be interpreted in light of other factors, such as age, to establish treatment strategy. Some authors demonstrated that BMI had a minimal impact on fertility compared with age in women aged 35 years or more. Beyond these biological and clinical implications, treatment of infertile overweight and obese women has a deep medico-economic impact [16]. Nevertheless, to our knowledge, there is not enough evidence to determine BMI threshold permitting or delaying care of infertility. It is essential to stress losing weight in obese women younger than 35 years by physical activity and hypocaloric diet or medical treatment. It has already been shown that weight loss from 5% can improve menstrual cyclicity and reproductive outcomes [6].

The controversy over ART outcome in obese patients may be due to different cutoff values used to define obesity, inclusion of patients with different infertility etiologies, and/or varying focus of outcome measures [17].

Conclusion

Female overweight and obesity appear to have deleterious effects on ovarian response to stimulation in women undergoing ICSI. Moreover, female obesity compromises ICSI outcomes.

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Conflicts of interest

There are no conflicts of interest.

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