

Association analysis of body mass index on ovarian response and pregnancy outcomes during IVF / ICSI treatment: a retrospective study in Southern Han Chinese Women

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Abstract

Background: The purpose of the present study is to evaluate the effect of body mass index (BMI) on cycle characteristics and in vitro fertilization / intracytoplasmic sperm injection (IVF / ICSI) outcomes of a long down-regulation protocol in Southern Han Chinese women.

Methods : This retrospective, observational study included 5279 infertile women undergoing IVF / ICSI cycle with a long down-regulation protocol. All the patients were divided into four subgroups by the recommended Chinese BMI cut-off points: underweight, BMI < 18.5 kg/m² ; normal-weight, 18.5 kg/m² ≤ BMI < 24.0 kg/m² ; overweight, 24.0 kg/m² ≤ BMI < 28.0 kg/m² ; obese, BMI ≥ 28.0 kg/m² . The demographic data and biochemical tests of patients, the parameters related to the ovarian responsiveness to gonadotrophin stimulation, IVF / ICSI treatment characteristics and pregnancy outcomes (clinical pregnancy rate, spontaneous abortion rate and lived birth rate) were compared among BMI categories.

Results: The overweight patients had lower ovarian sensitivity index (OSI) (P < 0.05) and higher spontaneous abortion rate than women in the normal-weight (13.59% vs. 10.28%, OR = 2.37, 95% CI: 1.35 – 4.16, P = 0.003). The overweight and obese patients seemed to have lower clinical pregnancy rate and live birth rate, but the difference was not statistically significant (P > 0.05).

Conclusion: This study provides new epidemiological clues that the elevated BMI might increase the risk of spontaneous abortion and impair ovarian response to gonadotropin stimulation during IVF / ICSI treatment.

Introduction

Elevated body mass index (BMI), the most common medical condition in women at a reproductive age[1], has rapidly become an important global public health problem[2]. The prevalence of obesity has continued to rise, with the most recent estimate indicating that 35.2% of men and 40.4% of women are obese[3]. Overweight and obesity, especially abdominal obesity is known to be associated with an increased risk of a variety of chronic diseases, such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), asthma and cancer[4, 5]. Women who become pregnant while obese are at a higher risk of developing pregnancy specific complications, poor neonatal and maternal pregnancy outcomes, such as gestational hypertension, gestational diabetes mellitus, preeclampsia, fetal macrosomia, congenital anomalies, and stillbirths[6-8].

Obesity-related infertility is another critical problem for reproductive age women[9, 10]. In the last decades, the trend of delaying marriage and childbearing has further exacerbated the burden of infertility[11]. As consequence, more and more infertility women are seeking for treatment, assisted reproductive technology (ART) has become an important option for patients with infertility who wish to become pregnant and contributed to the birth of over 5 million live born babies worldwide[12, 13]. Over the past decades, with the rapid popularity of ART for infertility treatment, a growing number of babies were born from in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)[14]. Controlled ovarian hyper-stimulation (COH) is a fundamental part and the key to the success and safety of ART, while the gonadotropin-releasing hormone agonist (GnRH-a) long protocol is one of the common regimens for ovarian stimulation[15]. The use of GnRH-a has been found to be associated with a reduction in cancellation rates, an increase in multiple follicular growth, and a potentially better timing of the treatment cycle[16].

The adverse effect of overweight / obesity on IVF / ICSI outcome (such as oocyte, embryo quality and pregnancy outcomes) has been extensively investigated in numerous studies [17, 18]. However, most of these previous studies was carried out in Caucasian women, as the racial differences in clinical characteristics and infertility frequency, these previous data were not available to be clinical practice in Chinese or Asian populations[19]. In addition, with the full implementation of the Chinese universal two-child policy, more and more infertile women of childbearing age choose to have two children by ART treatment[5], it is not surprising that an increasing number of women seeking infertility treatment to achieve a pregnancy are overweight or obese[20, 21].

As the low success rate of the ART treatment and the increased incidence of overweight / obese, it is still very important to update the data and explore the various potential factors associated with ART treatment outcome. Respecting these concerns, this study aims to determine the effect of elevated BMI on the cycle characteristics and IVF / ICSI outcomes of a down-regulation GnRH-a long protocol in Southern Han Chinese women.

Methods

2.1 Study design and subjects

This was a retrospective cohort study of patients undergoing their first IVF / ICSI cycle, using a down-regulation GnRH-a long protocol, in the center for reproductive medicine of The Third Affiliated Hospital of Guangzhou Medical University from August 2012 to November 2017.

Inclusion criteria were: patients with unexplained infertility or only male infertility, undergoing first IVF / ICSI cycle, using a down-regulation GnRH-a long protocol within the study period. Exclusion criteria were: preimplantation genetic diagnosis (PGD), invitro maturation, oocyte or sperm donation, frozen embryo transfer, gestational surrogacy cycles, patients with oophoritic cyst, operation on ovary, ovarian tumor, oophoroma, polycystic ovary syndrome (PCOs), endometriosis, operation on uterus, hysteromyoma, uterine adenoma, uterine tumors, cervical carcinoma, precancerous lesions of uterine cervix, hydrosalpinx, thyroid dysfunction, hypertension, diabetes, and other severe diseases. In total, 5279 patients undergoing their first IVF / ICSI cycle with fresh, autologous embryos were analyzed with age under 35 years old. All the patients were divided into four subgroups by the recommended Chinese BMI cut-off points[22]: underweight, $BMI < 18.5 \text{ kg/m}^2$; normal-weight, $18.5 \text{ kg/m}^2 \leq BMI < 24 \text{ kg/m}^2$; overweight, $24.0 \text{ kg/m}^2 \leq BMI < 28 \text{ kg/m}^2$; and obese, $BMI \geq 28 \text{ kg/m}^2$. Normal-weight patients were used as the reference group for all comparisons.

2.2 Treatment

In preparation for pituitary desensitization, all the patients were treated with a standard mid-luteal phase GnRH-a long protocol with Triptorelin (Dipherelin, 3.75 mg Ipsen, Pairs, France) at a dose of 0.1 mg daily.

Once pituitary suppression (the serum concentrations of estradiol (E2) $< 50 \text{ pg/mL}$ and endometrial thickness (EMT) $< 5 \text{ mm}$) was achieved, Recombinant follicle-stimulating hormone (rFSH; Gonal-F, Serono, Switzerland) was given for ovarian stimulation until the day of human chorionic gonadotrophin (HCG) administration.

The follicular growth was monitored by using transvaginal three-dimensional (3D) ultrasonography, oocyte maturation and ovulation was induced with 10000 IU urinary HCG (u-HCG) or 250 ug recombinant HCG (r-HCG; Ovitrelle, Merck KCaA, Germany) injection when the number of leading follicles ($> 18 \text{ mm}$ in diameter) was 2 or more. Oocyte retrieval was performed by transvaginal ultrasound 34-36 hours after injection of HCG, and sperm samples were collected on the same day with sperm morphology evaluated according to the Kruger criteria, which followed by IVF / ICSI treatment.

2.3 Assessments

All patients had their height and weight measured at time of cycle start. BMI was determined by the ratio of weight (in kilograms) divided by the squared of height (in meters). The patients' age, duration of infertility, anti-Mullerian hormone (AMH) level, antral follicle count (AFC), baseline serum FSH, LH, estradiol (E2), testosterone (T) and progesterone (P) level were collected. The parameters related to the ovarian responsiveness to gonadotrophin stimulation and cycle characteristics (such as the gonadotrophin dose, duration of stimulation, sex hormone levels (estradiol and progesterone levels) on the day of HCG administration, the number of oocytes retrieved, the number of transferred embryos), and pregnancy outcomes including clinical pregnancy rate, spontaneous abortion rate and live birth rate were compared among BMI subgroups.

2.4 Statistical analyses

Continuous data were summarized as mean and standard deviation (SD), while categorical variables summarized as n (%). Statistical analysis was performed using the Statistical Package for Social Science software (SPSS 21.0, Chicago, IL, USA). Differences between continuous variables were analyzed with One-way analysis of variance (ANOVA) test, and the Student-Newman-Keuls (SNK) test was used to analyze post-hoc comparisons; categorical variables were compared using χ^2 tests and logistic regression was used to calculate the ORs and 95% CI. $P < 0.05$ were considered to be statistical significant.

Results

3.1 Population characteristics

In total, 5279 patients under 35 years old undergoing their first IVF / ICSI cycle with fresh, autologous embryos were subjected to analysis. Among the 5279 patients, 728 (13.79%) were considered underweight, 3650 (69.14%) normal-weight, 735 (13.92%) overweight, and 166 (3.14%) obese.

The general characteristics and biochemical test of all patients according to the BMI categories are detailed in Table 1. Compared with the normal-weight patients, the obese patients had the bigger body surface area (BSA), increased AFC and decreased baseline serum FSH, LH level, while the overweight patients had the older age, bigger BSA and decreased baseline serum FSH and LH level ($P < 0.05$). The underweight patients had the younger age, increased baseline serum FSH, LH level compared with the normal-weight ($P < 0.05$). There were no significant differences in the infertility duration, baseline serum testosterone, progesterone level of the patients among the BMI categories.

Table 1 Demographic data and biochemical tests of patients by BMI category

Variables	Underweight (N = 728)	Normal-weight (N = 3650)	Overweight (N = 735)	Obesity (N = 166)	Total (N = 5279)
Years of infertility	3.64±2.23	3.83±2.48	4.01±2.66	4.65±2.76	3.85±2.49
Women's age (year) ##	28.88±3.05*	29.75±2.88	30.34±2.78*	30.07±2.90	29.72±2.92
BMI (kg/m ²) ##	17.62±0.70*	20.89±1.44	25.51±1.11*	30.13±2.22*	21.37±2.96
BSA (m ²) ##	1.51±0.06*	1.61±0.08	1.75±0.09*	1.89±0.12*	1.62±0.11
Baseline FSH (U/L) ##	5.99±1.61*	5.59±1.78	5.18±1.40*	5.10±1.45*	5.57±1.71
Baseline LH (U/L) ##	4.11±1.82*	3.54±2.03	3.01±1.64*	2.85±1.80*	3.52±1.97
Baseline E2 (pmol/L) ## #####	150.07±70.87	139.79±120.40	123.06±99.12	130.98±83.04	138.61±111.12
Baseline T (nmol/L)	1.75±6.48	1.91±7.93	1.66±2.28	1.64±0.94	1.85±7.07
Baseline P (nmol/L)	1.60±5.03	1.15±2.72	1.02±1.45	0.83±0.42	1.18±2.98
AMH (ng/ml) #	3.99±3.06	3.89±2.69	3.55±2.52	3.62±2.60	3.84±2.72
AFC ##	14.56±4.39	15.30±4.92	16.05±5.51	18.25±6.38*	15.39±5.03

BMI = body mass index; BSA = body surface area; FSH = follicle stimulating hormone; LH = luteinizing hormone; E2 = estradiol; T = testosterone; P = progesterone; AMH = anti-Mullerian hormone; AFC = Antral follicle count;

Data are shown as the means ± standard;

$P < 0.05$, ## $P < 0.001$, significantly different across the four BMI categories;

* $P < 0.05$, compared with normal-weight group.

3.2 IVF / ICSI treatment cycle characteristics

Regarding the response to the ovarian stimulation and cycle characteristics, we found that the overweight and obese women required more priming gonadotropin dose, total gonadotropin dose, administered dosage per unit of BSA and longer duration of stimulation compared with the patients with normal-weight ($P < 0.05$). On the other hand, we also found that the overweight and obese women had lower serum progesterone and estradiol on the day of HCG administration, lower increase of increase of E2, lower increase of E2 per unit of drug use and lower ovarian sensitivity

index (OSI) compared with normal-weight patients ($P < 0.05$). In addition, requirement for less gonadotropin dose and shorter stimulation duration ($P < 0.05$) were found in the underweight infertile patients, with other variables were not significantly different ($P > 0.05$) (Table 2).

There were no significant differences in the number of oocyte retrieved, endometrial thickness on the day of HCG, high quality embryos rate, IVF-fertility rate, ICSI-fertility rate and the number of transferred embryos between the groups (Table 2).

Table 2 Characteristics of IVF / ICSI treatment by BMI category

Variable	Underweight (N = 728)	Normal-weight (N = 3650)	Overweight (N = 735)	Obesity (N = 166)	Total (N = 5279)
Gonadotropin dose (IU)					
Priming for cycle ##	154.81±48.95*	166.59±49.46	181.34±51.23*	191.42±54.32*	167.80±50.45
Total for cycle ##	2189.60±801.50*	2397.08±848.81	2779.17±933.81*	3118.22±1053.12*	2444.34±884.83
Duration of stimulation (days) ##	12.39±1.73	12.50±1.97	13.04±2.48*	13.28±2.65*	12.59±2.06
The day of HCG administration					
P (nmol/L) ##	2.39±1.01	2.30±1.02	2.12±0.95*	1.93±0.83*	2.27±1.01
E2 (pmol/L) ##	11909.57±4097.27	11357.90±5293.88	9904.67±3879.56*	9223.48±4240.02*	11164.53±4978.45
Number of follicles > 16 mm in diameter#	3.50±3.76	3.88±3.95	4.05±4.01	4.04±4.09	3.86±3.94
Endometrial thickness (mm)	10.73±1.98	10.88±1.93	10.82±2.01	10.58±2.09	10.84±1.95
Administered dosage per unit BSA (IU/ml) ##	1452.05±531.63	1489.53±526.62	1588.73±530.46*	1650.48±541.71*	1503.23±530.25
The increased of E2 (pmol/L) ##	11939.69±4172.69	11354.88±5440.85	9819.43±3891.13*	8975.26±4301.26*	11152.27±5108.47
Increase of E2 per unit of drug use[(pmol/L)/IU] ##	6.39±3.56*	5.49±3.45	3.98±2.33*	3.32±2.19*	5.34±3.39
Number of oocytes retrieved	11.48±4.94	11.56±4.81	11.25±4.56	10.81±4.65	11.48±4.79
ovarian sensitivity index (OSI) ##	6.16±3.81*	5.63±3.44	4.59±2.69*	3.95±2.47*	5.50±3.41
High quality embryos (%)	45.10±29.65	43.66±29.87	43.87±28.77	41.38±28.84	43.82±29.66
IVF-fertility rate (%)	82.14±17.85	82.65±18.44	82.97±18.63	83.25±15.75	82.65±18.31
ICSI- fertility rate (%)	64.13±20.53	62.63±19.31	62.15±21.09	66.85±23.61	62.95±19.89
Number of transferred embryos	1.91±0.29	1.92±0.27	1.93±0.25	1.93±0.26	1.92±0.27

HCG = human chorionic gonadotropin; P = progestogen; E2 = estradiol; BSA = body surface area;

Data are shown as the means ± standard;

$P < 0.05$, ## $P < 0.001$, significantly different across the four BMI categories;

* $P < 0.05$, compared with normal-weight group.

3.3 IVF / ICSI treatment outcomes

We analyzed the effects of BMI on pregnancy outcomes of IVF / ICSI. As shown in Table 3, the overweight patients had the higher spontaneous abortion rate than normal-weight women (13.59% vs. 10.28%, OR = 2.37, 95% CI: 1.35 - 4.16, $P = 0.003$) compared with normal-weight patients. The overweight and obese women seemed to have lower clinical pregnancy rate and live birth rate, but the difference was not statistically significant ($P > 0.05$).

Table 3 Pregnancy outcomes of IVF / ICSI treatment by BMI category

variable	Underweight (N = 728)	Normal-weight (N = 3650)	Overweight (N = 735)	Obesity (N = 166)
Clinical pregnancy rate	462(63.46%)	2227(61.01%)	434(59.05%)	91(54.82%)
OR (95% CI) ^a	0.80 (0.60,1.08)	Ref.	0.86 (0.64,1.14)	1.25 (0.66,2.36)
<i>P-value</i> ^a	0.142		0.286	0.498
Spontaneous abortion rate	42(9.09%)	229(10.28%)	59(13.59%) [#]	16(17.58%) [#]
OR (95% CI) ^a	0.86 (0.41,1.82)	Ref.	2.37 (1.35,4.16)	1.96 (0.63,6.13)
<i>P-value</i> ^a	0.694		0.003*	0.249
Lived birth rate	345(47.39%)	1623(44.47%)	310(42.18%)	61(36.75%)
OR (95% CI) ^a	0.81 (0.55,1.20)	Ref.	0.83 (0.57,1.20)	0.73 (0.53,1.02)
<i>P-value</i> ^a	0.290		0.306	0.365

$P < 0.05$, compared with the normal-weight group;

^a OR, *P-values* were from logistic regression analysis after adjusting age, basal FSH, basal LH, basal E2, AMH, AFC, standardized total gonadotropin dose, duration of infertility, estradiol on HCG day, progesterone on HCG day, endometrial thickness on HCG day, number of oocytes retrieved, and number of embryos transferred, * $P < 0.05$.

Discussion

Over the recent decades, the effect of BMI on the cycle characteristics and IVF / ICSI outcome of ART has been investigated in numerous studies. As the low success rate of the ART and the increased incidence of overweight / obese, it is still very important to explore the various potential factors associated with ART outcomes. In this retrospective study, we focused on the effect of elevated BMI on the ovarian responsiveness to gonadotrophin stimulation and IVF / ICSI outcomes of a down-regulation long GnRH-a protocol in southern Han Chinese women.

It has been established that both underweight and overweight / obesity influence reproductive function of women[23, 24]. Ovarian reserve reflects the potential of reproduction and had been reported to be associated with success of ART in infertile women[25, 26]. Higher gonadotropin consumption (both priming and total gonadotropin dose) and longer stimulation duration were observed in the overweight and obese patients, when compared with the normal-weight. In order to exclude the influence of body surface area (BSA), we calculated the administered dosage per unit of BSA and found that the overweight and obese women also had the higher administered dosage per unit of BSA. Similar to our results, requirement for higher dose of gonadotropin and longer ovarian stimulation duration in elevated BMI women were also reported in previous investigations[27, 28]. As the dose of gonadotropin use is usually modified according to the woman's age, BMI, and ovarian reserve markers (such as AMH and AFC), it has been considered that ovarian sensitivity index (OSI; the number of retrieved oocytes × 1000 / total dose of gonadotropin) as a better representation of ovarian responsiveness[29]. Our study found that elevated BMI patients had the lower OSI, which also indicated that raised BMI impaired ovarian responsiveness. Irene et al^[30] demonstrated that the

inhibitory effect of elevated leptin (a major secretory product of the white adipose tissue) or the increased clearance of the drugs by the excess of fat tissue might induce gonadotrophin resistance, ultimately affect ovarian response. However, the molecular mechanism still remains unclear and needed to be elucidated in future studies.

In the analysis of the relationship between elevated BMI and pregnancy outcomes, although a decreasing trend in the clinical pregnancy rate and live birth rate were observed in overweight and obese patients, the differences were not statistically significant. This finding was consistent with previous studies, which reported that raised BMI has no adverse effect on clinical pregnancy rate and live birth rate^{20,[28]}. In addition, our finding confirmed the previous investigations of an increased risk of spontaneous abortion in raised BMI women following treatment of ART[31-33]. The reasons for an increased risk of abortion among overweight / obese women are still not well understood. It has been reported that both disorders (such as hyperandrogenemia, insulin resistance or altered leptin levels) share endocrine alterations may be responsible for pregnancy loss[34]. María et al's[35] study reported that leptin might induce the inflammation of placental stromal layer, leading to production of pro-inflammatory cytokines (such as IL-6 and TNF- α by activated macrophages), which might play critical roles in placental damage and dysfunction, ultimately affecting pregnancy outcomes. However, abortion susceptibility could be influenced by the multiple factors, including genetic, immunological, infectious, endocrine and environmental factors, further investigation should be performed.

Our study indicated that raised BMI might increase the spontaneous abortion risk during IVF / ICSI treatment and impair response of ovarian stimulation. As the negative effect of overweight / obesity on IVF / ICSI outcomes and the additional economic burden caused by the infertility treatment and pregnancy complications, attaining normal BMI by lifestyle modifications (such as a healthy diet and exercise) before and during the IVF / ICSI treatment should be encouraged whenever possible. However, this study have some limitation, the most important of which is that it was retrospective study, a well-designed and powerful prospective randomized trial are needed to verify this result.

Conclusions

This study demonstrate that raised BMI might impair ovarian response to gonadotrophin stimulation and increase spontaneous abortion risk, suggesting that elevated BMI might have negative effects on the IVF / ICSI outcomes.

Abbreviations

3D: three-dimensional; AFC: antral follicle count; AMH: anti-Mullerian hormone; ANOVA: analysis of variance; ART: assisted reproductive technology; BMI: body mass index; BSA: body surface area; COH: Controlled ovarian hyper-stimulation; CVD: cardiovascular disease; E2: estradiol; EMT: endometrial thickness; GnRH-a: gonadotropin-releasing hormone agonist; HCG: human chorionic gonadotrophin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; OSI: ovarian sensitivity index; P: progesterone; PCOs: polycystic ovary syndrome; PGD: preimplantation genetic diagnosis; rFSH: Recombinant follicle-stimulating hormone; r-HCG: recombinant HCG; SD: standard deviation; SNK: Student-Newman-Keuls; T: testosterone; T2DM: type 2 diabetes mellitus; u-HCG: urinary HCG.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Ethics Committee of The Third Affiliated Hospital of Guangzhou Medical University with written informed consent from all subjects. All procedures performed in studies involving human participants were in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants for being included in the study.

Authors' contributions

LL contributed to writing of this article and provided all sample of this study. YC, CZ, WO, ZL, WL and YL carried out data collection. LK carried out whole design. All authors aided in the design of the study, the interpretation of the data and the critical revision of the manuscript, and all authors approved the final version to be published.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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