

Original Article

Obesity impaired oocyte maturation and embryo implantation rate in Chinese women without polycystic ovary syndrome undergoing *in vitro* fertilization-embryo transfer

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Abstract: This study aimed to evaluate the effect of body mass index (BMI) on the *in vitro* fertilization-embryo transfer (IVF-ET) outcomes in Chinese overweight/obese women without polycystic ovary syndrome (PCOS). A retrospective cohort study was performed in 411 non-PCOS patients aged less than 38 years old undergoing their first IVF-ET treatment between January 2011 and January 2013. According to the criteria of Chinese BMI classification, patients were divided into 3 groups: 47 obese ($BMI \geq 28$ kg/m²), 130 overweight ($24 \leq BMI \leq 27.9$ kg/m²) and 234 normal weight ($18.5 \leq BMI \leq 23.9$ kg/m²). The correlation between clinical treatment characteristics and IVF-ET outcomes in their fresh IVF cycles was analyzed. Obese women suffered a longer infertility duration than normal weight women ($P < 0.01$). Higher doses of gonadotrophin were used in overweight/obese patients than in normal weight patients ($P < 0.001$), but their Estradiol (E2) level on human chorionic gonadotropin (hCG) day was lower in obese patients ($P < 0.01$). There were no significant differences in the number of retrieved oocytes, rate of Good Quality Embryo (GQE), transferred embryos or endometrial thickness, but overweight/obese patients had statistically less mature oocytes, fertilization rate, blast formation rate and embryo implantation rate ($P < 0.05$). Clinical pregnancy rate and live birth rate also showed a decreased trend in overweight/obese patients. Conclusions: Female obesity indeed affected fertility in Chinese women. During IVF-ET treatment, obesity had an adverse impact on gonadotropin (Gn) response, oocyte maturation, blast formation and embryo implantation.

Keywords: BMI, overweight, obesity, IVF-ET

Introduction

Currently, obesity is an epidemic in the world-wide. The report from Dr. Marie Ng and her co-workers indicated that the overweight proportion of adults has increased about 10 percent from 1980 to 2013. China has become the second largest country for obese people [1]. Obesity has been considered one of the risk factors by World Health Organization (WHO) for many diseases, such as type 2 diabetes, cardiovascular diseases, hypertension, stroke and various cancers. Thus, the prevention and control of obesity has become an urgent task [2]. The body mass index (BMI) was a common indicator for the evaluation of overweight and obe-

sity. WHO proposed that BMI higher than 30 kg/m² was considered as obese, and this criteria was accepted by the USA. However, for China this was not a suitable cut-off value. WHO also demonstrated the BMI cut-off points for Asian populations were different from those for European populations [3]. Now, in China, overweight population reached 22.4%, and obese ones were up to 3.01%. The Working Group on Obesity in China (WGOC) has recently developed the cut-off level for overweight (24.0 kg/m²) using BMI for the general Chinese population [4-6]. In the present study, the optimal cut-off values for Chinese men and women adults were found to be 23.53 and 24.25 kg/m² for BMI. These values were very similar compared

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with WGOc definitions in both men and women [7].

In addition to increasing the incidence of the above diseases, overweight and obesity might even result in increased infertility incidence [8]. However there is still controversy over this opinion. Some studies suggested that increased BMI does not affect the outcomes of IVF pregnancy [9], while other studies confirmed that overweight/obese women had reduced number of IVF-ET egg maturation, blastocyst formation rate and pregnancy rate [10]. If the patient's weight reduced to normal after treatment, assisted reproductive technology (ART) outcomes could be improved [11].

This study aimed to reveal whether increased BMI index could affect the quality of embryo or intrauterine microenvironment, and further study the relationship between overweight/obesity and the outcomes of IVF-ET in Chinese infertile women.

Materials and methods

Patients

A retrospective analysis was carried out on the non-polycystic ovary syndrome (PCOS) infertile women undergoing their first IVF-ET treatment between January 2011 and January 2013 in reproductive medical center of Yantai Yuhuangding Hospital and Weifang People's Hospital. The recruited patients met the following criteria: Causes of infertility was simple tubal factor; age less than 38 years; serum FSH values <12 mIU/mL; undergoing their first fresh egg retrieval cycle; ovulation stimulation with the long protocol. Exclusion criteria were infertile male partner, with chromosomal abnormalities, receiving intracytoplasmic sperm injection-embryo transfer (ICSI-ET), and with PCOS or endometriosis. According to criteria proposed by WGOc, all patients were divided into three groups: obese group (group A, 47 cases, $\text{BMI} \geq 28$ kg/m²), overweight group (group B, 130 cases, $24 \leq \text{BMI} \leq 27.9$ kg/m²), and normal BMI group (group C, 234 cases, $18.5 \leq \text{BMI} \leq 23.9$ kg/m²). Clinical data included the patients' height (m), weight (kg), body mass index (BMI) and duration of infertility were collected.

Equation for calculating BMI

Body mass index (BMI) = weight/height² (kg/m²).

Determination of sex hormone level

On the morning from 8:00 to 9:00, 3 mL of venous blood was drawn from regular menstrual patients on days 1-3 of menstruation. The blood serum was isolated to measure the level of testosterone (T), follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P) and estradiol (E2) by means of radio-immunoassay.

IVF protocol

Ovarian stimulation and oocyte retrieval were performed as we previously described [12]. Briefly, when more than two follicles exceeded 18 mm in diameter, 10000 IU of HCG (Merck Serono, Swiss) was injected intramuscular. After 36 hours, oocytes were retrieved.

Outcomes

Parameters during the assisted reproductive process including the patients basal FSH value, duration of gonadotropin (Gn) stimulation, Gn dosage, the total number of retrieved oocytes, the rate of fertilization, the number of transferred embryos, the rate of good quality embryos, blastocyst formation rate, clinical pregnancy rate, miscarriage rate and live birth rate were also collected.

Fertilization were classified into three groups: (i) oocyte exhibiting normal fertilization (2 pronuclei, 2PN) and (ii) oocyte exhibiting abnormal fertilization (1 and more than 2 pronuclei, 1PN, MPN). Oocytes with no pronuclei (OPN) were discarded. On Day 2 (44-46 h post-IVF), individually cultured embryos were evaluated accord, the number of transferred embryos, the number of good quality embryos (On Day 3, embryos containing at least 7 cells, $<10\%$ fragmentation and no multinucleated blastomeres were classified as Good Quality Embryo (GQE). Two or three embryos were transplanted into the uterus of patients on Day 3, whereas the others were cultured to the blastocyst stage. The blastocysts were scored based on the expansion of the blastocoel cavity, the cohesiveness of the inner cell mass, and trophoctodermal cells. The best blastocyst quality on Day 5 were score 1 = BL 3-5, AA or AB (innercell mass/trophoctoderm, ICM/TE) with $\leq 10\%$ fragmentation. Good blastocyst quality on Day 5 were blastocysts core 1 or 2 with score 2 = BL 1, 2 or BL 3-5 with BA or BB (ICM/TE score) with $\leq 20\%$ fragmentation [13]. On day 12 of embryo

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Table 1. Participant characteristics by female BMI

Variable	A group (BMI≥28)	B group (24≤BMI≤27.9)	C group (18.5≤BMI≤23.9)	P Value
Number	47	130	234	n/a
Female Age (years)	34.14±4.58	33.15±4.19	32.6±3.72	0.056
Duration of infertility (years)	6.17±4.48	5.11±3.17	4.47±3.16	0.004 ^a
BMI (kg/m ²)	29.7±1.78	25.4±1.12	21.4±1.65	n/a
Day 3 FSH (pg/mL)	6.60±2.4	6.59±1.85	7.13±2.46	0.055
AFC (n)	14.31±6.86	14.49±6.18	13.26±5.36	0.121

Notes: Data presented as mean ± SD, n (%) or OR (95% CI). ^aPairwise comparison revealed a statistically significant difference between A group and C group; n/a not applicable.

Table 2. IVF cycle clinical treatment and laboratory data

Variable	A group (BMI≥28)	B group (24≤BMI≤27.9)	C group (18.5≤BMI≤23.9)	P value
Duration of stimulation (days)	9.44 ± 1.38	8.99 ± 1.44	9.12 ± 1.48	0.233
Total dose of gonadotropins	2636.43 ± 673.99	2216.71 ± 517.91	1982.93 ± 566.38	0.000 ^{a,b,c}
E2 on hCG day (pg/mL)	2845.01 ± 1327.89	3256.57 ± 1214.18	3525.64 ± 1124.59	0.005 ^a
P on hCG day (pg/mL)	0.97 ± 0.75	1.07 ± 0.48	1.13 ± 0.43	0.122
Retrieved oocytes (n)	10.91 ± 6.41	11.42 ± 5.99	11.53 ± 6.01	0.815
MII (n)	6.72 ± 4.09	7.91 ± 4.24	8.91 ± 4.67	0.004 ^a
Fertilization rate (%)	394/513 (76.8%)	1183/1487 (79.6%)	2190/2699 (81.1%)	<0.05 ^a
Good quality embryos rate (%)	183/322 (56.8%)	579/980 (59.1%)	1148/1920 (52.3%)	>0.05
Embryos transferred (n)	2.19 ± 0.74	2.26 ± 0.58	2.27 ± 0.61	0.775
Endometrial Thickness on hCG day (cm)	1.12 ± 0.23	1.17 ± 0.24	1.18 ± 0.25	0.314
blastocyst formation rate (%)	68/173 (39.3%)	250/555 (45.9%)	689/1152 (59.8%)	<0.01 ^{a,b}

Notes: Data presented as mean ± SD, or proportion (%). ^aPairwise comparison revealed a statistically significant difference between A group and C group; ^bPairwise comparison revealed a statistically significant difference between B group and C group; ^cPairwise comparison revealed a statistically significant difference between A group and B group. E2: estradiol; P: progesterone.

transfer, each patient had her β -hCG level assessed. Pregnancy was defined by serially increasing serum β -hCG titres to at least 25 IU/l within 12 days after the cleavage stage ET. All of the patients underwent transvaginal ultrasounds at 5 to 6 weeks of gestation, or when the β -hCG exceeded 2,000 IU/L, in order to determine the location and number of fetus. Biochemical pregnancy was defined as a transient pregnancy that spontaneously resolved before the ultrasonographic confirmation. Clinical pregnancy was documented by ultrasonographic evidence of the fetal cardiac activity at 6-7 weeks of gestation. Spontaneous abortion was defined as the loss of a clinical pregnancy. Additionally, ongoing pregnancy was defined as progression beyond 12 weeks of gestation. The calculation methods of relative indexes were as following:

Fertilization rate (%) = $\frac{2PN+1PN+MPN}{\text{retrieved oocytes}} \times 100\%$

Good quality embryos (GQE) rate (%) = $\frac{\text{number of GQE}}{2PN} \times 100\%$

Blastocyst formation rate (%) = $\frac{\text{the number of blastocyst formation on Day 5-6}}{\text{the number of culture embryos}} \times 100\%$

Clinical pregnancy rate (%) = $\frac{\text{the cycle of clinical pregnancy}}{\text{the cycles of transfer}}$

Miscarriage rate (%) = $\frac{\text{the cycle of miscarriage}}{\text{the cycle of clinical pregnancy}}$

Live birth rate (%) = $\frac{\text{the cycle of live birth}}{\text{the cycles of transfer}}$

Statistics

Data were represented as mean ± sd. One-way ANOVA was used to compare mean value among groups. After the means for oocyte maturation rate, embryo Implantation rate, clinical pregnancy rate, and live birth rate were calculated, the correlation among the means of the BMI groups were analyzed using a simple linear regression model. χ^2 tests were used to compare the fertilization rates, good quality embryos rates, blastocyst formation rates, embryo implantation rates, clinical pregnancy rates,

miscarriage rate, live birth rates among groups. $P < 0.05$ was considered to be significant. SPSS17.0 (Chicago, USA) was used to analyze the data.

Results

This study selected a total of 411 cases in their first fresh IVF autologous cycle. These patients were divided into three groups according to the BMI standard of China. Group A was the obese group, Group B was the overweight group, and Group C was normal weight group. The basic characteristics of infertile women in each group were shown in **Table 1**.

Among the three groups, we found no significant difference in the age of patients, the FSH level on day 3, or the AFC (basal follicle count). However the duration of infertility of the obese group was significantly higher than that of the normal group ($P = 0.004$). IVF cycle clinical treatment and laboratory data was represented in **Table 2**.

From **Table 2**, we could see the amount of Gn used by obesity group and overweight group was higher than did by normal group. However, compared with the normal weight group, P level on hCG day, the number of oocytes retrieved, the number of transferred embryos and endometrial thickness on HCG day declined in the overweight/obesity group, although with no significance. A significantly decreased number of mature oocytes was found in the obese patients, which resulted in an obviously lower fertilization rate and blastulation rate.

The pregnancy outcomes were summarized in **Table 3**, which showed that clinical pregnancy rate, live birth rate, and gestational age all tended to be lower in the obesity group than the normal weight group or overweight group. In comparison to normal weight patients, obese women had a significantly lower embryo implantation rate (24.5% versus 35.0%) in the IVF outcomes. As shown in **Table 4**, linear regression analyses showed that the means of oocyte maturation and embryo implantation rate both decreased with the increase in BMI ($P < 0.05$).

Discussion

This study was the first to evaluate the effects of obesity and overweight on the outcomes of ART in infertile women with Chinese BMI stan-

dard. Our study showed that there was no age difference among the obese group, the overweight group and the normal group, but the duration of infertility in obese group was higher than that in normal weight group, which indirectly indicated that obesity was an important risk factor for infertility. Previous retrospective researches have indicated that overweight or obese patients accounted for 67% of all PCOS patients. PCOS is a condition clinically closely related to insulin metabolism which seriously affects female fertility [14, 15]. Therefore, in order to avoid the interference of PCOS on the analysis between obesity and infertility, PCOS patients were excluded from this cohort study.

Under the same length protocol, the Gn dosage for ovulation induction was calculated based on the patients' weight. Obese and overweight patients received higher dosage of Gn, but the E2 level on the day of hCG in the obese group was significantly lower. Ozekinci's research also reported similar results [16]. This phenomenon might be related to a decreased ovarian reactivity in obese patients [17, 18]. Among the three groups there were no differences in the FSH level, basal follicle number, or the number of retrieved oocytes, but obesity group showed significantly decreased number of mature egg and greatly reduced fertilization rate. These outcomes perhaps were related to the arrested development potential of oocytes in the obese patients [19]. In this study, all the patients were less than 38 years old, and without PCOS. The reason for IVF-ET treatment was a simple female tubal factor. Therefore, our research design could confirm whether obesity could affect women oocyte maturation.

There was no significant difference in GQE rate among the three groups, but blastocyst formation rate severely declined, which indicated that the evaluation of GQE based on the morphology features could not fully represent the development potential of embryos, sometimes the lower-score embryo could also form a blastocyst [20]. In comparison with GQE rate, the formation rate of blastocyst would be a better indicator to interpret the embryonic development potential in the laboratory [21]. Now, majority of the reproductive centers have chosen blastocyst transplantation, which greatly improved the clinical pregnancy rate, reduced the abortion rate, and increased the take-home baby rate [22]. This study has revealed that

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Table 3. Pregnancy outcomes by female BMI

Variable	A group (BMI≥28)	B group (24≤BMI≤27.9)	C group (18.5≤BMI≤23.9)	p value
Embryo implantation rate (%)	25/102 (24.5%)	93/294 (31.6%)	184/525 (35.0%)	<0.05 ^a
Clinical pregnancy rate (%)	21/47 (44.7%)	65/128 (50.8%)	131/233 (56.2%)	>0.05
Miscarriage rate (%)	4/21 (19.0%)	9/65 (13.8%)	25/131 (19.1%)	>0.05
Live birth (%)	17/47 (36.2%)	56/128 (43.8%)	106/233 (45.4%)	>0.05
Gestational age (weeks)	37.27 ± 2.25	37.71 ± 1.97	37.83 ± 2.18	0.626
Birth weight (g)	2974.00 ± 694.21	3007.03 ± 683.70	2968.00±651.28	0.927

Notes: Data presented as mean ± SD, or proportion (%). ^aPairwise comparison revealed a statistically significant difference between A group and C group. No statistical difference was observed for the other reported outcomes across different BMI categories.

Table 4. Relationship between BMI groups and embryonic development by linear regression analysis

Variable	A group (BMI≥28)	B group (24≤BMI≤27.9)	C group (18.5≤BMI≤23.9)	R ²	p value
MII (n)	6.72±4.08	7.91±4.24	8.91±4.67	0.995	0.032*
Embryo Implantation rate (%)	17.8±10.6	26.2±7.76	35.5±2.58	0.998	0.019*
Clinical pregnancy rate (%)	39.1±16.5	46.4±12.0	56.8±5.66	0.980	0.064
Live birth (%)	26.3±17.1	33.7±6.19	45.7±2.59	0.963	0.087

*P<0.05.

although there were no significant difference on the endometrial thickness and serum progesterone lever on hCG day among the three groups, these two indexes tended to decrease in the overweight and obese patients.

Over whether overweight/obesity affected female clinical outcome there were still different views. A retrospective study analyzed the data of 308 women undergoing IVF cycles, and considered increase in body mass index in women did not have a negative effect on IVF outcome [23]. Another retrospective analysis showed obesity only adversely affected embryo quality, and the oocyte quality was not negatively affected [24]. Petersen's work indicated increased female BMI negatively influenced live birth during IVF treatments [25].

Compared with the above results, our results found the clinical pregnancy rate, live birth rate, and abortion rate had a downward trend in overweight group and obesity group. Obesity could affect the quality of eggs and the subsequent development of the embryo in Chinese women without PCOS, which indicated that obesity might become a potential risk factor for the occurrence of infertility in Chinese women.

In the future, larger sample sizes and multi-institutional analysis are needed to further reveal the effect of BMI on cumulative pregnancy rate, and to discover their correlation.

Nevertheless, this study still drew some instructive conclusion. For Chinese women, once their BMI reached higher than 28, there will be a risk to reduce the quality of eggs, affect the egg fertilization, impair the formation of the blastocyst, and ultimately decline the embryo implantation rate. Therefore, in the clinical practice, Chinese women with high BMI should be suggested to control their diet and strengthen physical exercise before IVF-ET treatment. At the same time, blastocyst transplantation is a better way for obese patients, which will not only improve the success rate of IVF-ET treatment, but also reduce the patient's psychological burden as well as their financial pressure.

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Disclosure of conflict of interest

None.

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