

## Impact of high body mass index with or without polycystic ovarian syndrome on the outcome of in vitro fertilization

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### Abstract

**Objective:** To investigate the effect of high body mass index and polycystic ovarian syndrome alone or both on the outcome of in vitro fertilisation-embryo transfer.

**Methods:** The retrospective study was conducted at the First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China, and comprised data from August 2015 to November 2016 of infertility patients with polycystic ovarian syndrome or tubal factors who underwent agonist long-protocol in vitro fertilisation-embryo transfer. Group A comprised polycystic ovarian syndrome patients who were further divided into normal weight A1 and overweight A2. Group B had tubal patients who were further divided into normal weight B1 and overweight B2. SPSS 16 was used for data analysis.

**Results:** Of the 428 patients, 153 were in Group A and 275 in Group B. Further, Group A1 had 94(61.44%) patients and Group A2 had 59(38.56%) ( $p < 0.01$ ), while Group B1 had 219(81.64%) and Group B 56(18.36%) patients. The dose of gonadotropins and the duration of stimulation were significantly greater in Group A2 than Group A1( $p < 0.01$ ), but there was no statistically significant difference in the tubal groups ( $p > 0.05$ ). Significantly more retrieved oocytes and high-quality embryos were observed in the Group A1 ( $p < 0.01$ ). The difference of the maturing rate, fertilisation rate, implantation rate, pregnancy rate and early abortion rate were not significant among the groups ( $p > 0.05$ ).

**Conclusion:** Polycystic ovarian syndrome with high body mass index had a negative effect on the ovarian response to gonadotropins. Pregnancy outcomes were not influenced by body mass index in tubal patients.

**Keywords:** Polycystic ovarian syndrome, Body mass index, In vitro fertilisation, Gonadotropin, Oocyte. (JPMA 69: 852; 2019)

### Introduction

Ovarian stimulation with a high concentration of exogenous gonadotropin is an important part of in vitro fertilisation-embryo transfer (IVF-ET). Its outcome is greatly affected by patient's basic endocrine environment. Among the patients who receive IVF treatments, the most common endocrine disorders are obesity and polycystic ovarian syndrome (PCOS), which usually exist alone or together. They may be the direct causes of infertility or may affect infertility treatment efficiency.<sup>1</sup>

PCOS is closely related to obesity. Compared with normal body mass index (BMI) patients, the incidence of PCOS has been shown to be significantly higher in obese patients.<sup>1</sup> While in PCOS patients, the proportion of overweight and obesity could be as high as 50% to 75%.<sup>2</sup> However, PCOS is a heterogeneous disease with a variety of clinical manifestations. That is why not all PCOS patients are obese. Similarly, some overweight individuals

having regular ovulation and regular menstrual cycles are not PCOS patients.

The simultaneous occurrence of obesity and PCOS was considered to be a serious type of PCOS. There were several significant differences in endocrine and metabolic indices between obese and non-obese PCOS patients. The former was more often related to the hyperandrogenism, hyperinsulinaemia, and insulin resistance (IR).<sup>3</sup> Due to the negative effects of these factors, the adverse outcomes of IVF were common in obese PCOS patients. The oocytes fertilisation rate of these patients was low,<sup>4</sup> while the spontaneous abortion rate was high.<sup>5</sup>

Previous research has focussed on the impact of isolated obesity or PCOS on IVF. Researchers found greater use of gonadotrophin (Gn) and higher cancellation rates in obese than that of non-obese patients,<sup>6</sup> which was associated with the release of leptin from the adipose tissue.<sup>7</sup> Nevertheless, the effect of PCOS on IVF was controversial. It was believed that patients with PCOS could achieve similar or even higher pregnancy rates than other patients, as long as the oocytes quality didn't diminish.<sup>8</sup> However, some studies had suggested that the

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oocytes' quality of PCOS was poor and the fertilisation rate was decreased.<sup>9</sup>

Studies comparing the IVF outcomes of PCOS with non-PCOS individuals generally did not consider the effects of BMI,<sup>10</sup> and only a few studies have considered the interaction between obesity and PCOS,<sup>11</sup> exploring if there was any difference in IVF outcome when PCOS and obesity existed simultaneously or separately, or if the outcome was affected by the increased incidence of obesity in PCOS patients or PCOS itself.

The current study was planned to analyse the therapy data of PCOS and non-PCOS patients with different BMIs in order to explore whether obesity with or without PCOS has an impact on the oocyte and embryo quality of IVF, and whether the impact of obesity and PCOS on IVF is dependent on each other.

## Materials and Methods

The retrospective study was conducted at the First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China, and comprised data from August 2015 to November 2016 of infertility patients with PCOS or tubal factors who underwent agonist long-protocol IVF-ET. The sample size was calculated using the relevant computing programme.<sup>12</sup> In order to meet 80% test effectiveness, and 5% difference of clinical pregnancy rate between PCOS group and tubal group, each had to contain at least 118 patients. Given the possibility of treatment cancellation, the study aimed to enrol more than 150 patients for each group. Data of patients with PCOS or tubal factors was studied and analysed, while that of cases with any other reason for infertility, like endometriosis, ovarian dysfunction, male factors and other unknown causes, was excluded.

Among those included, the number of antral follicles was >10 and the level of anti-Müllerian hormone (AMH) was >2ng/ml. PCOS identification was done in line with the 2003 Rotterdam consensus.<sup>13</sup> At the beginning of IVF, the heights and weights of all patients were measured to calculate BMI according to the formula: (weight (kg)/height (m<sup>2</sup>)).

By using the Judging Criteria for Overweight for Chinese Population in 2015 Guideline,<sup>14</sup> the cut-off point of adult BMI was 18.5<BMI<24 kg/m<sup>2</sup> for the normal weight, 24≤BMI<28 kg/m<sup>2</sup> for the overweight, and BMI≥28 kg/m<sup>2</sup> for obesity. Patients with PCOS and tubal factors were divided into 4 groups. Group A1 had PCOS patients with BMI<24, Group A2 had PCOS patients with BMI≥24, Group B1 had patients with tubal factors and BMI<24, and Group B2 had patients with tubal factors and BMI≥24).

Serum basic levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), pituitary prolactin (PRL) and testosterone (T) were measured during the menstrual period before IVF treatment. In case of LH/FSH >2 or T >2.0 nmol/L, oral contraceptive pills (ethinylestradiol and desogestrel, Marvelon, Organon, Netherlands) were administered once daily for 21 days, and pills were used as necessary until the levels of LH and T returned to normal.

All patients received standard gonadotropin-releasing hormone (GnRH) agonist long protocol. Treatment was started from Day 21 of the first menstrual cycle with a 0.012 mg/kg injection of triptorelin (Diphereline, Ipsen, France). Recombinant human FSH (Gonal-F, Serono, Sweden) with an initial dose of 150 IU/day was subcutaneously injected on the third day of the second menstruation cycle. FSH dose was increased or decreased according to the growth of ovarian follicles. Drug use was maintained until at least 2 follicles achieved a diameter of 18mm.

A 5000 IU intramuscular injection of human chorionic gonadotropin (hCG) (inj.hCG, Livzon, China) was given for oocyte maturation trigger. Oocyte retrieval was performed 36 hours later. IVF or intracytoplasmic sperm injection (ICSI) was chosen depending on the semen parameters and previous fertilisation history. Embryo transfer was performed 3 days after oocyte retrieval. The number of transferred embryos per patient was no more than 2. All patients were prescribed 60mg of intramuscular injection progesterone as luteal phase support for 2 weeks. If the patient was pregnant, progesterone was used for another 2 weeks.

The groups were compared in terms of FSH dose, days of ovarian stimulation, number of retrieved oocytes, maturing and fertilisation rate, number of high-quality embryos, number of transferred embryos, implantation rate, clinical pregnancy rate (CPR), and early abortion rate. MII oocyte was considered mature, while embryo quality grading was based on the standards described in literature.<sup>15</sup> The high-quality embryo was defined as at least 6 cells generated from cleavage on day 3, with generally uniform size and morphology and <20% cell debris.<sup>16</sup> Embryo implantation rate was defined as the number of intrauterine gestational sac divided by the number of transferred embryos. Early abortion rate was defined as abortions before 12 weeks of pregnancy.

Data was analysed using SPSS 16. Shapiro-Wilk test was used to test normal distribution. If accorded with normal distribution, data was presented as mean ± standard deviation (SD) and compared by analysis of variance

(ANOVA), while enumeration data was presented as frequencies (n) and percentages (%) and compared by Chi-square test. Tukey Honest Significant Difference (HSD) test was used between every two groups if ANOVA results suggested significant difference. If the data did not conform to normal distribution, nonparametric Kruskal-Wallis H test was used.  $P < 0.05$  was considered statistically significant.

## Results

Of the 428 patients, 153 were in Group A and 275 in Group B. Further, Group A1 had 94(61.44%) patients and Group A2

had 59(38.56%) ( $p < 0.01$ ), while Group B1 had 219(81.64%) and Group B2 had 56(18.36%) patients (Table-1). The gonadotropin dose and stimulation days of high BMI patients were greater than those of patients with normal BMI in both PCOS and tubal groups ( $p < 0.05$ ). Such differences between the two PCOS groups were significant ( $p < 0.05$ ), while the differences between tubal groups had no statistical significance ( $p > 0.05$ ). The number of retrieved oocytes and high quality embryos of PCOS patients with normal body weight was higher than that of any other groups ( $p < 0.05$ ), but there was no significant difference

**Table-1:** The proportion of patients, age, and years of infertility.

	PCOS groups		Tubal groups		P value
	A1: BMI <24	A2: BMI ≥24	B1: BMI <24	B2: BMI ≥24	
Proportion of patients (%)	61.44% (94/153)	38.56% (59/153) *	81.64% (219/275)	18.36% (56/275)	0.037
Mean age (years)	28.51±3.06	28.33±3.95	29.63±3.17	28.59±4.22	0.390
Mean years of infertility (years)	5.14±3.28	4.17±2.81	4.93±3.10	5.31±3.25	0.536

PCOS: Polycystic ovarian syndrome

BMI: Body mass index

Notes: 1. The index marked with \* of group A2 was significantly higher than that of group B2 ( $P < 0.01$ ).

2. There was no statistical difference in other data between different groups ( $P > 0.05$ ).

3. Measurement data was presented as mean ± SD.

**Table-2:** Analysis of variance (ANOVA) test for follicle-stimulating hormone (FSH) dosage, stimulation time, the number of retrieved oocytes, the number of high-quality embryos, maturing rate and fertilisation rate of oocytes.

	PCOS groups		Tubal groups		P value
	A1: BMI <24	A2: BMI ≥24	B1: BMI <24	B2: BMI ≥24	
Gonadotropin dose (IU)	1830.46±733.15	2362.57±849.22*	1791.35±509.26	1825.73±741.23	0.019
Stimulation days (days)	10.51±3.17	13.36±2.49*	10.17±4.51	10.83±3.62	0.028
Number of retrieved oocytes (n)	19.03±9.75**	13.85±8.56	12.07±6.94	10.28±9.31	0.006
Number of high quality embryos (n)	6.34±3.81**	4.09±2.20	5.16±3.95	4.05±2.66	0.014
Maturing rate (×100%)	0.90±0.16	0.88±0.12	0.90±0.28	0.90±0.37	0.185
Fertilization rate (×100%)	0.69±0.15	0.68±0.23	0.70±0.18	0.68±0.17	0.272

PCOS: Polycystic ovarian syndrome

BMI: Body mass index

Notes: 1. The indexes marked with \* of group A2 were significantly higher than those of other groups ( $P < 0.01$ ). The indexes marked with \*\* of group A1 were significantly higher than those of other groups ( $P < 0.01$ ).

2. There was no statistical difference in other data between different groups ( $P > 0.05$ ).

3. Measurement data was presented as mean ± SD.

**Table-3:** Chi-square test for embryo implantation rate, clinical pregnancy rate and abortion rate during early pregnancy.

	PCOS groups		Tubal groups		P value
	A1: BMI <24	A2: BMI ≥24	B1: BMI <24	B2: BMI ≥24	
Embryo implantation rate (%)	33.82% (70/207)	25.37% (34/134)	28.87% (136/471)	30.00% (36/120)	0.352
Clinical pregnancy rate per transfer (%)	55.56% (50/90)	44.64% (25/56)	48.06% (99/206)	42.86% (24/56)	0.580
Abortion rate during early pregnancy (%)	16.00% (8/50)	12.00% (3/25)	12.12% (12/99)	12.50% (3/24)	0.473

PCOS: Polycystic ovarian syndrome

BMI: Body mass index

Notes: 1. There was no statistical difference in every index between the above groups ( $P > 0.05$ ).

2. Enumeration data was presented as percentage (%).

among the other three groups ( $p > 0.05$ ). There was no significant difference in maturing rate or fertilisation rate among the groups ( $p > 0.05$ ) (Table-2).

In Group A1, there were 90 transfer cycles; 4 cycles were cancelled because of ovarian hyperstimulation syndrome (OHSS); and the total number of transferred embryos was 207. In Group A2, the transfer cycles were 56; 3 cycles were cancelled because of OHSS; and the total transferred embryos were 134. For Group B1, the transfer cycles were 206; 12 cycles were cancelled because of OHSS and 1 cycle was cancelled because of abnormal fertilisation; and total number of transferred embryos was 471. For group B2, the transfer cycles were 56; no cycle was cancelled; and the total number of transferred embryos was 120. Embryo implantation rate, CPR, and the rate of abortion during early pregnancy were calculated and there was no significant difference among the groups ( $p > 0.05$ ) (Table-3).

## Discussion

When similar ovarian stimulation drugs were used and the oocytes were cultivated in a laboratory environment, the patient's endocrine environment became the major factor affecting the development of oocytes and embryos. PCOS was characterised by a series of endocrine disorders affecting the pituitary gland, insulin, lipid metabolism, etc.<sup>17</sup> Studies found that the decreased expression of Growth Differentiation Factor 9 (GDF-9) deriving from follicles among PCOS patients inhibits granular cell amplification and oocyte development,<sup>18</sup> and long-term exposure to LH and insulin would result in the abnormal function of granular cells.<sup>19</sup>

However, PCOS patients in the current study showed no obvious differences in maturing rate and fertilisation compared to tubal patients, suggesting that the oocytes from the PCOS patients did not decrease in quality after controlled ovarian hyperstimulation. The process of ovarian hyperstimulation may play a role in promoting oocytes maturation, and we also believe that the fine oocytes quality was associated with the use of oral contraceptives prior to the period. The pre-treatment of contraceptives lowered the abnormal serum level of LH and androgen, and maintained the hormone level within the normal range in the short term,<sup>20</sup> which would significantly improve ovarian environment and promote follicular development during this period, thus generating satisfying oocytes.

Compared with PCOS, obesity seemed to have a more significant impact on ovarian stimulation. Fridstrom et al. proposed as early as in 1997 that, as an independent factor affecting the IVF outcome of PCOS, obesity caused pharmacokinetic changes, leading to the decline of effective Gn concentration and the increase of its

dosage.<sup>21</sup> In line with such finding, the number of retrieved oocytes and high-quality embryos of patients with high BMI were significantly lower than those of normal BMI patients in PCOS. Animal-based studies suggested that excessive Gn stimulation could induce various quality defects and lower implantation ability of oocytes and embryos.<sup>22</sup> This may explain why the oocyte and embryo quality of high BMI patients were poor.

Recent studies discovered that the intrafollicular concentration of adipose tissue-derived leptin, which obviously inhibited the stimulation of FSH on the synthesis of granular cells, was increased among obese patients.<sup>23</sup> Some scholars argued that BMI was always negatively associated with the number of retrieved oocytes,<sup>24</sup> and it could be used as a risk factor for the poor prognosis of ovarian stimulation. However, our results showed that there was no significant difference in ovulation between high BMI and normal BMI in tubal groups. This suggested that the negative effect on ovulation might be more obvious when obesity was combined with PCOS, while obesity alone might not affect the number of retrieved oocytes.

The World Health Organisation (WHO) defined the criterion for overweight as  $BMI \geq 25$ . However, because of the physical characteristics of the Chinese, the criterion in Chinese Center for Disease Control and Prevention (CDC) guidelines was slightly lower than that determined by the WHO.<sup>25</sup> In fact, even by Chinese standards, so-called 'obese' patients whose  $BMI > 28$  were rare, and most of them were 'overweight'. The physical characteristic in China or East Asia may also be responsible for the decrease in the influence of obesity on IVF in this study.

A concept closely related to obesity was IR. Studies had proven that high insulin levels may directly inhibit the growth of follicles in a diameter of 5-10mm.<sup>26</sup> Peripheral IR also resulted in the increase of insulin signalling in the ovaries and generated excessive sex hormones such as androgen. Obesity, IR, and hyper-androgenism interacted with each other in PCOS patients. The WHO epidemiological report pointed out that the incidence of metabolic syndrome (MS) was about 43-47% among PCOS patients, twice that of the general population.<sup>27</sup> This means that compared with general patients, PCOS patients would be more subject to the obesity factor. As shown by the data in our study, obesity played the most prominent role in affecting ovarian stimulation treatment in the PCOS group.

On the contrary, PCOS patients with normal BMI could often obtain more retrieved oocytes and embryos than the fallopian tube group because of the more sinus follicles. Therefore, for obese PCOS patients, their pregnancy-

related outcomes of IVF treatment would be good after the obesity is well controlled. Polycystic ovaries themselves provided more possibility for follicular development, and the contraceptive pre-treatment, when necessary, could improve the quality of oocytes and embryos.

### Conclusion

PCOS with high BMI had a negative effect on the ovarian response to Gn. The presence of PCOS in non-obese patients was a favourable prognostic factor in ovarian stimulation. Pregnancy outcomes were not influenced by BMI in tubal patients.

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**Conflict of Interest:** None.

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