



# Effects of body mass index on the outcomes of in vitro fertilization in Chinese patients with polycystic ovary syndrome: a retrospective cohort study\*

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**Abstract:** Objective: To investigate the effects of body mass index (BMI) on the outcomes of in vitro fertilization (IVF) in Chinese patients with polycystic ovary syndrome (PCOS). Methods: In the retrospective cohort study, a total of 1074 patients with PCOS undergoing IVF between April 2010 and May 2017 in two reproductive medicine centers, respectively in eastern China (Women's Hospital, School of Medicine, Zhejiang University, Zhejiang Province) and in southern China (Maternal and Child Health Care Hospital of Liuzhou, Guangxi Province), were included. The patients were divided into four groups according to the recommended Chinese BMI cut-off points: underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5 kg/m<sup>2</sup> ≤ BMI < 24.0 kg/m<sup>2</sup>), overweight (24.0 kg/m<sup>2</sup> ≤ BMI < 28.0 kg/m<sup>2</sup>), and obese (BMI ≥ 28.0 kg/m<sup>2</sup>). The basic characteristics of the PCOS patients, the details of IVF treatment, and the pregnancy outcomes were collected. Main results: There were no significant differences among the normal weight, overweight, and obese PCOS patients undergoing IVF on the biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate, live birth rate, or term delivery rate (*P* > 0.05), although the overweight and obese PCOS patients required more gonadotropin (Gn) (*P* < 0.001) as well as longer stimulation period (*P* < 0.001), and got less retrieved oocytes (*P* < 0.05) and fertilized oocytes (*P* < 0.05). The underweight PCOS patients required less Gn (*P* < 0.05) and achieved higher live birth rate and term delivery rate (*P* < 0.05), compared with the normal weight PCOS patients. Conclusions: High BMI had no negative effects on the outcomes of IVF in Chinese patients with PCOS; however, the conclusion may seem a little limited due to the retrospective design and the potential bias.

**Key words:** Body mass index; In vitro fertilization; Polycystic ovary syndrome

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## 1 Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women, affecting approximately 5%–10% women of reproductive age (Beydoun et al., 2009). It is characterized by oligomenorrhea and ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovary morphology (Teede et al., 2011; Szydlarska et al., 2017). This disorder is often associated with insulin resistance, hypertension, infertility, obesity, and weight-related

disorders (Bentley-Lewis et al., 2011; Stepto et al., 2013; Joham et al., 2015; Balen et al., 2016; Bergh et al., 2016). The treatment of PCOS was diversified, which included lifestyle intervention, menstrual cycles regulation, anti-androgen therapy, reproductive promotion, and Chinese traditional treatment. As part of Chinese traditional treatment, acupuncture (WU et al., 2016; Robinson, 2017) and transcutaneous electrical acupoint stimulation (Qu et al., 2017a, 2017b) played an important role in treating PCOS, which is increasingly recognized by clinicians.

Approximately 50% of women with PCOS are overweight or obese, and most of them have the abdominal phenotype (Chen et al., 2010). Overweight and obesity are definitely risk factors for adverse pregnancy outcomes (Mantakas and Farrell, 2010; Deshmukh et al., 2016), which may be induced by the altered metabolic conditions (Meenakshi et al., 2012), and the lifestyle intervention can improve the pregnancy outcomes (Oteng-Ntim et al., 2012; Martin et al., 2015). Although some previous studies associated body mass index (BMI) with in vitro fertilization (IVF) outcomes in PCOS women (Jungheim et al., 2009; Ozgun et al., 2011; Bailey et al., 2014; Huang et al., 2014), they had some limitations for these data to be clinically employable to our daily practice. First, these previous studies mainly targeted Caucasian populations. Clinical characteristics of PCOS and also infertility frequently show racial differences (Wang et al., 2018). Second, previous researches defined overweight and obese at different BMI cut-off points according to the study populations, which were 25 and 30 kg/m<sup>2</sup>, respectively. This does not accord with the present Chinese criteria, which are 24 and 28 kg/m<sup>2</sup>, respectively. Thus, these previous data were not available to Chinese or Asian populations. In the retrospective cohort study, a total of 1074 patients with PCOS undergoing IVF in two Reproductive Medicine Centers, respectively in eastern China and southern China, were included to investigate the effects of BMI on the outcomes of IVF in Chinese patients with PCOS.

## 2 Materials and methods

The retrospective cohort study was performed in two Reproductive Medicine Centers, respectively in eastern China (Women's Hospital, School of Medi-

cine, Zhejiang University, Zhejiang Province) and in southern China (Maternal and Child Health Care Hospital of Liuzhou, Guangxi Province). Data were collected from the clinical records between April 2010 and May 2017. A total of 1074 patients with PCOS were chosen using the Rotterdam criteria (Chang et al., 2004). To minimize the bias, the age of all the included patients was ≤42 years, and only the first fresh treatment cycle of IVF was included.

The patients were excluded if they underwent oocyte or sperm donation, in vitro maturation (IVM), preimplantation genetic diagnosis (PGD), intracytoplasmic sperm injection (ICSI), testicular sperm aspiration, frozen embryo transfer (FET), blastocyst transfer, or have severe endometriosis (III and IV stages) which was diagnosed by laparoscopic surgery.

The BMI was defined as weight in kilograms divided by the square of height in meters. Based on the recommended Chinese BMI cut-off points (Barba et al., 2004), patients were divided into four groups: underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5 kg/m<sup>2</sup> ≤ BMI < 24.0 kg/m<sup>2</sup>), overweight (24.0 kg/m<sup>2</sup> ≤ BMI < 28.0 kg/m<sup>2</sup>), and obese (BMI ≥ 28.0 kg/m<sup>2</sup>).

All the included patients underwent controlled ovarian hyperstimulation (COH) using the standard long agonist protocol. Recombinant follicle-stimulating hormone (FSH; Gonal-F, Serono, Switzerland) was administered with or without highly purified human menopausal gonadotropin (HMG; Lizhu, China). Ovulation was induced with 10000 IU human chorionic gonadotropin (HCG) or 250 µg recombinant HCG (Ovitrelle, Merck KCaA, Germany) when at least two follicles had reached 18 mm in diameter. Oocytes were retrieved 34–36 h after HCG administration by guidance of vaginal ultrasound. Conventional fertilization was performed in all patients.

Embryos were transferred on Day 3, except in cases with few embryos (≤2), which were transferred on Day 2. Although one or two embryos were transferred usually, in women over 35 years old, after counseling the risk of multiple gestation, three embryos were also allowed to transfer.

Fertilization rate was calculated as the ratio of number of embryos obtained over the number of oocytes retrieved. Implantation rate was calculated as the ratio of the number of gestational sacs over the number of transferred embryos. Biochemical pregnancy was diagnosed by a rising concentration of serum β-HCG 14 d after embryo transfer (ET). Clinical

pregnancy was confirmed by the presence of a gestational sac and fetal cardiac activity on vaginal ultrasound examination six weeks after ET. Ectopic pregnancy was confirmed by positive HCG without evident product of conception within the uterus. Miscarriage was defined as a pregnancy loss before 28 full weeks of gestation (Xie and Gou, 2013). Live birth was defined as any deliveries in which at least one baby was born alive. Premature delivery was defined as delivery between 28 to 37 completed weeks of gestation. Term delivery was defined as delivery after 37 completed weeks of gestation.

Statistical analysis was performed using SPSS Version 22.0 (SPSS, Chicago, IL, USA). The distribution of continuous data was tested by one-sample Kolmogorov-Smirnov test. The continuous variables were tested by one-way analysis of variance (ANOVA) tests. If ANOVA testing indicated a significant difference among four groups, post-hoc comparisons were performed using the least significant difference (LSD) test. Categorical variables were compared using Chi-square test and logistic regression analysis. Results were presented as mean±standard deviation (SD) or frequency (%). *P* values less than 0.05 were considered to be significant.

### 3 Results

#### 3.1 Descriptive characteristics of the included PCOS patients

As shown in Table 1, the underweight group was younger than the normal weight group ( $P<0.05$ ), while there were no significant differences in age among the normal weight, overweight, and obesity groups ( $P>0.05$ ). The duration of infertility was longer in the overweight and obesity groups than in the normal weight group ( $P<0.05$ ). There were no

significant differences in primary infertility rate or the luteinizing hormone (LH)/FSH ratio on the 3rd day of menstruation among the four groups ( $P>0.05$ ).

#### 3.2 Effects of BMI on the characteristics of IVF treatment of PCOS patients

As shown in Table 2, compared with the normal weight women with PCOS, overweight women with PCOS required higher dose of gonadotropin (Gn) ( $P<0.001$ ) and longer days of COH ( $P<0.001$ ), retrieved less oocytes ( $P<0.05$ ), got less fertilized oocytes ( $P<0.05$ ), transferred more embryos ( $P<0.05$ ), and froze less embryos ( $P<0.05$ ). As BMI increased, it was the same situation in obese women when compared with the normal weight women. Underweight women required lower dose of Gn ( $P<0.05$ ) than normal weight women, with other variables not significantly different ( $P>0.05$ ).

We also conducted comparisons between the obese PCOS women and overweight PCOS women, and found that obese women required higher dose of Gn ( $P<0.001$ ) and longer days of COH ( $P<0.001$ ), retrieved less oocytes ( $P<0.001$ ), got less fertilized oocytes ( $P<0.05$ ), transferred more embryos ( $P<0.05$ ), and froze less embryos ( $P<0.05$ ). Although the fertilization rate decreased with BMI increasing, the difference was not statistically significant.

#### 3.3 Effects of BMI on the pregnancy outcomes of PCOS patients undergoing IVF

As shown in Table 3, the clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate, and preterm delivery rate were comparable in the four groups ( $P>0.05$ ). Although the biochemical pregnancy rate, implantation rate, live birth rate, and term delivery rate decreased with BMI increasing ( $P<0.05$ ), no significant differences were found in overweight women or obese PCOS women when compared with

**Table 1 Descriptive characteristics of the PCOS patients according to BMI**

Variable	Normal weight ( <i>n</i> =606)	Underweight ( <i>n</i> =51)	Overweight ( <i>n</i> =315)	Obesity ( <i>n</i> =102)
Age (year)	29.08±3.23	27.78±3.17*	29.45±3.53	29.77±3.56
BMI (kg/m <sup>2</sup> )	21.44±1.50	17.72±0.66**	25.62±1.08**	30.01±2.19***
Duration of infertility (year)	3.75±2.50	3.67±2.25	4.46±3.05**	4.56±2.90*
Primary infertility	343 (56.6%)	36 (70.6%)	177 (56.2%)	52 (51.0%)
Day 3 LH/FSH	1.46±0.97	1.51±1.25	1.40±0.86	1.26±0.74

PCOS: polycystic ovary syndrome; BMI: body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone. Data are expressed as mean±standard deviation or number (percentage). \*  $P<0.05$ , \*\*  $P<0.001$ , compared with the normal weight group; \*\*\*  $P<0.001$ , compared with the overweight group

the normal weight PCOS women. The live birth rate and term delivery rate in the underweight group were significantly higher than those in the normal weight group ( $P<0.05$ ).

#### 4 Discussion

In the present study, we found that the underweight PCOS patients were much younger, required less Gn, achieved higher live birth rate and term delivery rate when compared with the normal weight patients, while the other pregnancy outcomes were not significantly different. However, other studies found that underweight had a deleterious effect on the pregnancy outcomes such as preterm delivery (Sebire et al., 2001; Hoellen et al., 2014). As the prevalence of underweight in patients with PCOS was very low (Anastasiou et al., 2017), only 51 underweight PCOS patients were included in our study. It needed to be examined whether the inconsistency was caused by the lower sample size of the underweight group.

Overweight and obese PCOS patients required more Gn and days of COH, retrieved less oocytes, got

less fertilized oocytes, transferred more embryos, froze less embryos than the normal weight patients, which were even more obvious in the obese PCOS patients when compared with overweight PCOS patients. Although the fertilization rate, implantation rate, clinical pregnancy rate, miscarriage rate, live birth rate, preterm delivery rate, and term delivery rate were all lower than those of the normal weight patients, the differences were not statistically significant. Our conclusions were consistent with some studies which showed that BMI was negatively associated with ovarian response, but did not remain for implantation rate (McCormick et al., 2008) and live birth rate in PCOS patients (Mulders et al., 2003; Ozgun et al., 2011; Huang et al., 2014). However, our conclusion was contrary to other studies which reported BMI having an adverse effect on the clinical IVF outcomes (Jungheim et al., 2009; Bailey et al., 2014; Cui et al., 2016; Kalem et al., 2016). BMI was also found to have a negative relationship with anti-Müllerian hormone levels (Salmassi et al., 2015; Bernardi et al., 2017; Lefebvre et al., 2017), which is one of the widely recognize markers of ovarian reserve (Fleming et al., 2013).

**Table 2 Effects of BMI on the characteristics of IVF treatment of PCOS patients**

Variable	Normal weight (n=606)	Underweight (n=51)	Overweight (n=315)	Obesity (n=102)
Total dose of Gn (IU)	1716.16±630.85	1427.70±513.08*	2118.73±801.48**	2574.61±1049.49***
Duration of COH (d)	10.60±2.19	10.35±1.53	11.84±2.91**	12.94±3.48***
Number of retrieved oocytes	17.14±8.37	16.75±6.54	15.59±7.64*	11.86±7.53***
Number of fertilized oocytes	10.33±6.89	9.78±5.35	8.85±6.24*	6.58±4.84**
Fertilization rate (%)	59.78±25.37	60.43±24.88	56.45±26.43	56.63±26.10
Number of transferred embryos	1.01±0.94	1.06±0.86	1.17±0.95*	1.42±0.87**
Number of frozen embryos	5.52±5.58	4.82±4.34	4.54±4.90*	3.15±3.46**

BMI: body mass index; IVF: in vitro fertilization; PCOS: polycystic ovary syndrome; Gn: gonadotropin; COH: controlled ovarian hyperstimulation. Data are expressed as mean±standard deviation. \*  $P<0.05$ , \*\*  $P<0.001$ , compared with the normal weight group; #  $P<0.05$ , ##  $P<0.001$ , compared with the overweight group

**Table 3 Effects of BMI on the pregnancy outcomes of PCOS patients undergoing IVF**

Variable	Normal weight (n=606)	Underweight (n=51)	Overweight (n=315)	Obesity (n=102)
Number of patients who had embryos transferred	355 (58.6%)	34 (66.7%)	203 (64.6%)	78 (76.5%)
Biochemical pregnant rate	180 (50.7%)	22 (64.7%)	87 (42.9%)	33 (42.3%)
Clinical pregnant rate	162 (45.6%)	21 (61.8%)	80 (39.4%)	31 (39.7%)
Implantation rate	35.92±43.83	50.00±44.38	28.98±40.23	29.70±41.58
Miscarriage rate	31 (8.7%)	0 (0%)	15 (7.4%)	6 (7.7%)
Ectopic pregnancy rate	3 (0.8%)	1 (2.9%)	5 (2.5%)	0 (0%)
Live birth rate	133 (37.5%)	20 (58.8%)*	65 (32.0%)	25 (32.1%)
Preterm delivery rate	28 (7.9%)	0 (0%)	11 (5.4%)	3 (3.8%)
Term delivery rate	105 (29.6%)	20 (58.8%)*	54 (26.6%)	22 (28.2%)

BMI: body mass index; PCOS: polycystic ovary syndrome; IVF: in vitro fertilization. Data are expressed as mean±standard deviation or number (percentage). \*  $P<0.05$ , compared with the normal weight group

We found that the fertilization rate and implantation rate in overweight and obese PCOS patients were not significantly different from those of the normal weight patients. As obesity is a state of chronic inflammation and metabolic disorder, markers of inflammation and oxidative stress are increased in the serum and ovarian follicular fluids (Merhi et al., 2015; Buyuk et al., 2017), which may have a negative impact on the IVF outcomes (Cakiroglu et al., 2016). The aberrant serum metabolic changes, such as the increased cholesterol, triglycerides, and apolipoprotein A, were often observed in obesity, which were usually reflected in the follicular fluids (Valckx et al., 2012). The studies above suggested that obesity induced an adverse maternal endocrine and metabolic environment both local and general, which then negatively affected the interaction of granulosa cell-oocyte, the maturation of oocyte, and the potential developmental competence of embryo, contributing to unsuccessful outcomes for patients with PCOS (Qiao and Feng, 2011). In our study, all the oocytes were fertilized in vitro, and embryos were transferred after 2 to 3 d culture in vitro, which made the adverse effects of in vivo environment smaller, contributing to the comparable fertilization rate and implantation rate between different BMI groups. Consequently, the increased BMI did not play an adverse role on the general clinical pregnancy outcomes of PCOS patients undergoing IVF.

## 5 Conclusions

BMI had no negative effects on the outcomes of IVF in the overweight and obese Chinese patients with PCOS; however, the conclusion may seem a little limited due to the retrospective design and the potential bias. To minimize the bias as much as possible, only the first IVF treatment cycles were included, so we were not able to find the relationship between the elevated BMI and cumulative pregnancy outcomes of IVF. More studies should be focused on the incidence of ovarian hyperstimulation syndrome, perinatal and neonatal outcomes of PCOS women undergoing IVF with different BMI levels.

## Contributors

Fan QU designed the research, Xiao-ming PAN and Fan QU performed data analysis and wrote the paper. Zhong LIN,

Nan LI, Jia-qi WU, Dan-qing CHEN, and Yi-min ZHU collected and explained the data.

## Compliance with ethics guidelines

Xiao-ming PAN, Zhong LIN, Nan LI, Jia-qi WU, Dan-qing CHEN, Yi-min ZHU, and Fan QU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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## 中文概要

**题目:** 体重指数对中国多囊卵巢综合征患者体外受精胚胎移植结局的影响: 一项回顾性队列研究

**目的:** 探讨体重指数对中国多囊卵巢综合征(PCOS)患者体外受精胚胎移植结局的影响。

**创新点:** 本研究是一项多中心大样本研究, 纳入了华东、华南两家生殖中心的患者; 本研究根据中国体重指数(BMI)分界点进行分组, 而非国际BMI分界点, 得出的结论更加适合中国或者亚洲人群。

**方法:** 此项回顾性研究纳入2010年4月到2017年5月分别在华东、华南两家生殖中心进行体外受精胚胎移植的患者共1074例。根据推荐的中国BMI分界点, 患者被分成四组: 低体重组( $BMI < 18.5 \text{ kg/m}^2$ ), 正常体重组( $18.5 \text{ kg/m}^2 \leq BMI < 24.0 \text{ kg/m}^2$ ), 超重组( $24.0 \text{ kg/m}^2 \leq BMI < 28.0 \text{ kg/m}^2$ )和肥胖组( $BMI \geq 28.0 \text{ kg/m}^2$ )。比较各组间的基本信息、体外受精情况和妊娠结局。

**结论:** 高BMI对中国PCOS患者的体外受精胚胎移植结局没有不利影响。因为本研究是回顾性研究及一些潜在的偏差, 所以此结论可能存在一定的局限性。

**关键词:** 体重指数; 体外受精胚胎移植; 多囊卵巢综合征