Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(11): 228
https://doi.org/10.31083/j.ceog5011228

Original Research

The Normal Body Mass Index (BMI) of Women with Polycystic Ovary Syndrome (PCOS) was Associated with IVF/ICSI Assisted Conception Outcomes

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Academic Editor: Michael H. Dahan
Submitted: 22 May 2023 Revised: 13 July 2023 Accepted: 1 August 2023 Published: 9 November 2023

Abstract

Background: One of the characteristics that is directly linked to polycystic ovary syndrome (PCOS) is body mass index (BMI), and there have been numerous studies that are pertinent to PCOS patients with high BMI. However, further research is needed to determine the precise impacts of normal BMI on PCOS patients' metabolism and chances of becoming pregnant. Achieving a normal BMI may enhance glucose metabolism and lower the risk of gestational diabetes in pregnant PCOS women. By examining the reproductive results of PCOS patients with normal BMI, this study offers fresh suggestions for the management and alleviation of clinical symptoms in PCOS patients. **Methods**: From January 1, 2021 to April 30, 2022, 133 *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) cases with normal body mass index were enrolled in the Reproductive Medical Center of Hainan Women and Children's Medical Centre, including 77 PCOS patients with normal BMI and 46 non-PCOS patients with normal BMI, the ovulation induction regimen was used as an antagonist regimen, and the waist circumference, body mass index, follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH, anti-Mullerian hormone (AMH), blood lipids, homeostasis model assessment of insulin resistance (HOMA-IR), gonadotropin (Gn) dosage between the two groups were compared, Gn days of use, number of eggs obtained, normal fertilization rate, normal cleavage rate, number of available embryos, number of high-quality embryos, embryo implantation rate, clinical pregnancy rate and other indicators. **Results**: The endocrine situation between the two groups showed that the AMH, LH value, LH/FSH value, fasting insulin and HOMA-IR of PCOS group (group 1) were significantly higher than control group (group 2), and the data between the two groups were extremely significant ($p < 0.01$), the basal testosterone value and blood lipid in group 1 were higher than group 2, and the difference between the two groups was statistically significant ($p < 0.05$). The ovulation induction and embryo conditions between the two groups showed that the amount of Gn in group 2 was extremely significant ($p < 0.01$) higher, the number of eggs obtained, normal fertilization, normal cleavage and available embryos in group 1 were higher, the differences were extremely significant ($p < 0.01$), and the differences in other indicators were not statistically significant ($p > 0.05$). The results of kendall analysis showed that BMI, lipids, and AMH, and of PCOS patients with normal body mass index were significantly positively correlated with HOMA-IR ($R > 0$, $p < 0.05$). The basal testosterone (T) values of PCOS patients with normal body mass index were positively correlated with HOMA-IR ($R > 0$, $p > 0.05$), and the clinical pregnancy rate was negatively correlated with HOMA-IR ($R < 0$, $p > 0.05$). BMI was significantly negatively correlated with clinical pregnancy rate ($R < 0$, $p < 0.05$). **Conclusions**: Patients with PCOS with normal BMI should be treated with hyperandrogen control and insulin resistance therapy, and weight loss is recommended despite a normal body mass index. This study found that the Gn dose of PCOS patients with normal BMI should be lower than that of non-PCOS patients, which would be more conducive to pregnancy in PCOS patients.

Keywords: normal BMI; obesity; PCOS; IVF/ICSI; pregnancy outcomes

1. Introduction

Women of reproductive age are frequently affected by the hormonal condition known as polycystic ovary syndrome (PCOS). The hormonal imbalances associated with PCOS can disrupt ovulation, making it harder for women with PCOS to conceive naturally [1]. PCOS has three canonical features: hyperandrogenism/hyperandrogen hirsutism, oligomenorrhagia/anovulation, polycystic ovarian morphology, characterized by an abnormally high antral follicle count (AFC) and increased ovarian volume. One of the most frequent reasons of female infertility, PCOS is a prevalent hormonal disorder that impacts about 7–8% of women of reproductive age [2]. High body mass index (BMI) women are more likely to experience infertility and irregular menstrual cycles, and obesity is one of the reasons that is directly linked to PCOS [3]. The two most prevalent clinical kinds of PCOS are non-obese PCOS with a BMI in the normal range and obese PCOS with a BMI in the overweight or even obese range [4].

Intracytoplasmic sperm injection (ICSI) and conventional *in vitro* fertilization (IVF) are common fertilization techniques in the field of assisted reproduction and are successful in treating infertility in PCOS patients [5]. Age,

BMI, and use of assisted reproductive technologies all independently affect pregnancy outcomes in women with PCOS, according to prior research, but mixed studies of BMI and assisted reproductive technology (ART) have produced conflicting results [6]. To our knowledge, there are many clinical studies on the outcomes of pregnancies in obese women with PCOS and few studies on the outcomes of pregnancies in women with normal BMI using assisted reproductive technology. This is the reason for the restriction on elucidating BMI in conjunction with ART [7]. Therefore, taking into account the potential effects of normal BMI on assisted reproductive technology, this study compares metabolic indicators and IVF/ICSI fertility outcomes in PCOS patients with normal BMI in order to provide guidance for clinical treatment and improve pregnancy success rate.

2. Patients and Methods

2.1 General Information

The retrospective study collected 133 IVF/ICSI cases with normal body mass index who visited the Reproductive Medical Center of Hainan Women and Children's Medical Centre from January 1, 2021 to April 30, 2022, among which patients with normal BMI PCOS infertility were used as the observation group (group 1, n = 77), and non-PCOS patients with normal BMI were included in the control group (group 2, n = 46), all aged $\geq$20 years and $<$35 years old, 18.5 kg/m^2 $\leq$ BMI $<$ 24 kg/m^2, first IVF or ICSI assisted pregnancy. This study has been approved by an ethical review board and all patients provided written or oral informed consent prior to enrollment. This study was approved by the Medical Ethics Committee of Hainan Women and Children Medical Center (HNWCMC). Retrospective studies did not obtain informed patient consent.

The inclusion criteria for infertility refer to the guidelines on diagnostic of infertility [8], and the criteria are as follows: (1) Normal sexual life is not less than 1 year; (2) No gynecological diseases, normal menstruation; (3) All subjects had normal communication skills and voluntarily participated in this study.

The diagnosis of PCOS is based on the 2003 Rotterdam diagnostic criteria as follows: (1) Two years after menarche, menstrual sparse or amenorrhea occurs; (2) Ultrasound showed the morphology changes of the polycystic ovaries; (3) Problems with high androgens or hirsutism [9]. If two of the above three items are met, polycystic ovary syndrome is achieved.

The exclusion criteria were as follows: (1) Patients with endometriosis; (2) Patients who have previously had surgery to remove one ovary; (3) Bilateral or unilateral tubal effusion; (4) Endometrial abnormalities (intrauterine adhesions, endometrial polyps, submucosal fibroids); (5) Diseases of important organs such as heart, liver, kidney, brain, and lungs; (6) Cushing's syndrome, congenital adrenal hyperplasia and other endocrine diseases.

2.2 Investigation Methods

Statistics of basic data such as height, weight, waist circumference, bilateral ovarian sinus follicles and so on. Measure hormones such as anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and so on.

Take the antagonist program as ovulation induction program, collect basic information such as patient age and BMI, clinically select the appropriate gonadotropin (Gn) dose, and perform ovulation induction operation [10]. Gn includes gonadotropin or urogonadotropin, regular vaginal ultrasound examination, observe the development of follicles and adjust the dose of the drug, and add gonadotropin releasing hormone antagonist (GnRH-A) when the diameter of the dominant follicle reaches 12–14 mm.

Pregnancy outcomes were judged as follows, serum β-human chorionic gonadotropin (β-HCG) values were measured on day 14 after embryo transfer, and biochemical pregnancy was measured when HCG $\geq$25 U/L [11]. If vaginal ultrasound shows intrauterine gestational sac 28 days after embryo transfer, it is diagnosed as clinical pregnancy, and the number, size, location, fetal bud and fetal heart rate of the gestational sac are recorded, as well as other abnormalities. Spontaneous abortion occurring within 12 weeks' gestation is defined as early spontaneous abortion. Nuchal translucency was performed at 12 weeks' gestation, and after no abnormalities, he was transferred to the obstetrics department for routine prenatal examination.

2.3 Observation Index

Statistics include patient age, follicle-stimulating hormone (FSH), luteinizing hormone (LH), AMH, blood lipids, homeostasis model assessment of insulin resistance (HOMA-IR), number of embryos transferred, clinical pregnancy rate, moderate to severe ovarian hyperstimulation syndrome (OHSS) rate and other indicators.

2.4 Statistical Analysis

The data were analyzed with SPSS 26.0 statistical software (IBM Corp, Armonk, NY, USA), and the measurement data was expressed as $\bar{x} \pm s$. The rank sum test was used for comparison between the two groups, and the Kendall analysis was used for correlation analysis, and $p <$ 0.05 was statistically significant.

3. Results

The comparison of the basic conditions and endocrine conditions of the two groups is shown in Table 1. There was no significant difference ($p > 0.05$) in basic information such as age, waist circumference and BMI, while endocrine status of two groups was different. The AMH, LH value, LH/FSH value, fasting insulin and HOMA-IR of group 1 (PCOS group) were higher than group 2 (Control group), and the data between the two groups were extremely ($p <$ 0.01) significant. In terms of basal testosterone values and

Table 1. Basic information and endocrine status of the two groups.

Index	PCOS group with normal BMI (Group 1)	Control group (Group 2)	p value
Age (years)	31.21 ± 2.53	30.59 ± 2.49	0.155
Waistline (cm)	78.0 ± 7.0	75.37 ± 8.05	0.051
BMI (kg/m^2)	20.73 ± 1.49	20.94 ± 2.33	0.382
AMH (ng/mL)	6.5 ± 2.91	3.1 ± 1.64	0.000
FSH (mlU/mL)	6.17 ± 1.93	5.91 ± 1.87	0.464
LH (U/L)	7.83 ± 4.52	4.35 ± 1.7	0.000
LH/FSH	1.36 ± 0.93	0.76 ± 0.26	0.000
Testosterone (ng/mL)	0.33 ± 0.25	0.24 ± 0.11	0.044
Blood lipids (cm/s)	1.33 ± 0.83	1.08 ± 0.59	0.047
Fasting blood sugar (mmol/L)	4.95 ± 0.55	5.15 ± 0.56	0.062
Fasting insulin (pmol/mL)	12.83 ± 5.98	7.54 ± 6.23	0.000
HOMA-IR (mmol/L)	3 ± 1.75	1.73 ± 1.48	0.000

Note: $p < 0.01$ indicates that the difference is extremely significant, $p < 0.05$ indicates that there is a statistical difference, $p > 0.05$ indicates that the difference is not significant. PCOS, polycystic ovary syndrome; BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2. Ovulation induction, embryo and pregnancy of the two groups.

Index	Group 1	Group 2	p value
Periodicity (days)	74	45	
Gn dosage (mlU/mL)	1583.12 ± 526.74	1894.02 ± 498.00	0.000
Gn days	9.46 ± 1.63	9.63 ± 1.42	0.151
Daily E_2 of HCG (pg/mL)	3009.53 ± 1743.21	2507.87 ± 1440.85	0.143
Number of eggs obtained (n)	16.54 ± 7.26	10.43 ± 4.15	0.000
Normal number of fertilizations (n)	10.64 ± 5.31	7.96 ± 3.92	0.002
Normal cleavage number (n)	10.37 ± 5.22	7.67 ± 3.90	0.002
Number of embryos available (n)	7.26 ± 3.33	5.72 ± 3.01	0.008
Number of high-quality embryos (n)	7.32 ± 4.98	6.26 ± 5.05	0.219
Number of implanted embryos (n)	0.69 ± 0.61	0.63 ± 0.55	0.693
Clinical pregnancy rate	61.54%	59.38%	0.854

Gn, gonadotropin; E_2, estrogen; HCG, human chorionic gonadotropin.

lipids, group 1 was higher and the difference was statistically significant ($p < 0.05$). And the difference between FSH and fasting blood glucose was not significant ($p > 0.05$).

After IVF/ICSI, relevant indicators of the two groups are shown in Table 2. Analysis of ovulation induction in the two groups showed that the cycle and average daily growth rate of HCG in group 1 were higher, and the amount of Gn dosage and Gn days used were lower, and the difference in Gn dosage was extremely ($p < 0.01$) significant. Statistics on embryo situation showed that the number of eggs gained, normal fertilization, normal cleavage and available embryos in group 1 were higher, and the difference was extremely significant ($p < 0.01$), although the number of high-quality embryos in group 1 was higher, the difference was not significant ($p > 0.05$). The pregnancy outcome statistics showed that the number of implanted embryos and the clinical pregnancy rate in group 1 were higher, but the difference was not significant ($p > 0.05$).

The results of Kendall analysis showed (Tables 3,4) that the BMI, blood lipid, AMH, and basal testosterone of group 1 were positively correlated with the HOMA-IR ($R > 0.00$), and the BMI, lipid and AMH of group 1 were statistically different from the HOMA-IR ($p < 0.05$). Basic LH/FSH and clinical pregnancy rate were negatively correlated with HOMA-IR index, but there was no significant significance ($R < 0.00$, $p > 0.05$). The BMI of patients in group 1 was significantly negatively correlated with the clinical pregnancy rate ($R < 0.00, p < 0.05$), and negatively correlated with the number of high-quality embryos, but not significant ($R < 0.00, p > 0.05$). Overall, with the increase of HOMA-IR, BMI, blood lipid, and AMH significant increased.

4. Discussion

Menstrual disruption, infertility, and clinical and biochemical hyperandrogenemia are important clinical characteristics of PCOS [12]. PCOS is usually diagnosed by in-

Table 3. HOMA-IR correlation analysis in PCOS patients.

Index	*R* value	*p* value
BMI (kg/m^2)	0.278	0.010
Blood lipids (cm/s)	0.264	0.010
AMH (ng/mL)	0.164	0.037
Testosterone (ng/mL)	0.096	0.222
LH/FSH	–0.004	0.957
Clinical pregnancy rate	–0.035	0.795

Note: $R > 0.000$ indicates a positive correlation and $R < 0.000$ indicates a negative correlation.

Table 4. BMI correlation analysis in PCOS patients.

Index	*R* value	*p* value
Clinical pregnancy rate	–0.302	0.043
Number of high-quality embryos (n)	–0.069	0.586

ternationally recognized Rotterdam criteria, the Androgen Excess Society (AES) proposed a simplified diagnostic requirement in 2006 with clinical and/or biochemical hyperandrogenemia simultaneously with oligo/anovulation and polycystic ovaries on ultrasound [13,14]. Since insulin resistance contributes to obesity in patients, which worsens the severity of clinical symptoms in women with PCOS, it is not currently recognized in diagnostic criteria as a major cause of reproductive and metabolic impairment [15,16]. BMI is an important indicator for the judgment of obesity, and BMI is closely related to the clinical symptoms of PCOS patients [17]. At present, PCOS patients can improve endocrine and relieve PCOS symptoms through drug treatment, but the complete cure of PCOS can not be achieved, and drugs can not alleviate the patient's difficulty in conceiving, and there are strong side effects [18]. Therefore, people with PCOS who are of childbearing age still prefer artificial assisted reproductive technology as their first option for getting pregnant. IVF and ICSI are two popular IVF procedures that are currently used to treat infertile women's inability to conceive a child. They are less risky, safer, more cost-effective, and patient-friendly than other IVF procedures [19]. There have been many studies on the treatment of PCOS patients with IVF/ICSI, but most of them focus on the impact of the two techniques on the metabolism of follicles in patients [20], effects on pregnancy in patients with high BMI [21,22], the impact of the two techniques and patients' menstrual manifestations on pregnancy [23]. This study innovatively started from PCOS patients with normal BMI, explored the differences in clinical features of different patients with normal BMI, and clarified the impact of normal BMI on the clinical characteristics and pregnancy of PCOS patients, so as to provide better clinical treatment for PCOS patients.

Through the analysis of the clinical characteristics of the patients in this study, the results showed that the AMH, LH value, LH/FSH value, fasting insulin and HOMA-IR of PCOS patients with normal BMI were higher than those in group 2, and the data were extremely significant ($p < 0.01$). The basal testosterone value and lipid profile of group 1 were higher, and the difference was significant ($p < 0.05$). AMH levels can be used as an alternative tool for PCOS diagnosis, elevated AMH levels correlate with the severity of PCOS, analysis of AMH to predict ovarian response to stimulation has been widely used, PCOS patients tend to have higher AMH levels, which is consistent with our findings [24,25]. LH and FSH play an important role in triggering luteal cell formation and stimulating steroid synthesis, with insufficient FSH levels leading to impaired follicle development, while elevated LH levels increase ovarian androgen production, and the LH/FSH ratio is a typical indicator of PCOS [26]. Fasting insulin and HOMA-IR play a role in the release level and regularity of LH in POCS patients, high insulin will also further promote the production of androgens in follicular membrane cells, and insulin may also directly affect human endocrine homeostasis through the phosphatidylinositol 3 kinase (PI3K) pathway [27,28]. Therefore, high LH, high LH/FSH in the PCOS group in this study all showed that androgen, insulin resistance and follicle development in PCOS patients were worse than non-PCOS patients. In addition, although relevant study has found that endocrine and metabolic variables in patients with high BMI are higher, causing many chronic diseases such as diabetes and dyslipidemia [29]. This study shows that even in POCS patients with normal BMI, their androgens, insulin, etc., are still higher than ordinary infertility patients, and the increase of androgens in turn aggravates abdominal obesity and inflammation, and when abdominal obesity is aggravated, lipid metabolism abnormalities are aggravated, dyslipidemia may continue to worsen obesity in PCOS [30], this leads to a vicious circle. Therefore, even in PCOS patients with normal BMI, BMI is more likely to rise, pregnancy is still more difficult than ordinary infertile patients, and maintaining a low BMI is more necessary for PCOS patients.

The study showed that after IVF/ICSI in the two groups, the dosage of Gn in group 2 was extremely significant ($p < 0.01$) higher. The statistics of embryos showed that the number of eggs obtained, normal fertilization, normal cleavage and available embryos in group 1 were higher, and the differences were extremely significant ($p < 0.01$). Previous study has shown a significant correlation between Gn dose and body weight, with higher Gn doses increasing body weight [31]. In this study, it was found that the amount of Gn used in PCOS patients was lower than that of ordinary infertile patients, which may be related to the normal BMI of PCOS patients themselves, and combined with the number of eggs obtained by PCOS patients, normal fertilization and other indicators, it is not difficult to find that even if the amount of Gn is reduced, the embryo situation of PCOS patients with normal BMI is better. Kamardi *et al.* [22] performed ICSI pregnancy assistance on 170 infertile patients under the age of 38 and there was no significant difference in BMI on clinical pregnancy rate. Patients with nor-

mal BMI had more egg acquisition and fertilization, while there was no significant difference between the number of available embryos and the clinical pregnancy rate. This is consistent with the results of this study, and there were no significant differences in the number of days of Gn use, the daily estrogen (E_2) value of HCG, the number of high-quality embryos and the clinical pregnancy rate. This may be because PCOS patients have a higher ovarian reserve, so they do not need higher doses of Gn to stimulate, too high doses of Gn can obtain a higher number of eggs, and also tend to increase the risk of moderate to severe ovarian hyperstimulation (OHSS). Therefore, we may consider that in the future, for PCOS patients with normal BMI, the dose of Gn can be appropriately reduced for clinical treatment, this not only facilitates the pregnancy of PCOS patients, but also effectively reduces the risk of OHSS in PCOS patients.

Although this study comprehensively elaborates the differences in pregnancy metabolism and other indicators between the two groups, there are still many shortcomings. This study's sample size is still modest, therefore expanding it further is crucial to the study's reliability and applicability in general. The next step in improving this study is to combine it with PCOS patients of various BMIs, despite the fact that it was originally conducted on PCOS patients with normal BMI. At the same time, the mechanism of insulin on PCOS patients still needs further research, which may be an important reason for limiting the further development of PCOS treatment. The treatment of PCOS is still a global problem, and it is believed that through more and more in-depth research by excellent medical workers, the creation of a more complete PCOS treatment system is just around the corner.

5. Conclusions

In summary, during the treatment of PCOS patients with normal BMI, insulin resistance should be treated simultaneously with the control of hyperandrogen, and weight loss is recommended despite a normal body mass index. For PCOS patients with normal BMI, it is recommended to reduce the dose of Gn clinical treatment, which not only benefits the pregnancy of PCOS patients, but also effectively reduces the risk of OHSS in PCOS patients.

Availability of Data and Materials

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

Author Contributions

NM, JZ and WL jointly designed the research content. NM and JZ contributed equally. NM conducted the clinical research and manuscript editing. JZ participated in the clinical research and was responsible for data analysis. WL was the guarantor of the integrity of the entire research, and was responsible for manuscript review and research technical support. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of Hainan Women and Children's Medical Center (HNWCMC) (Approval number: HNWCNC.2023.[33]). Retrospective studies did not obtain informed patient consent.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This project was supported by the Natural Science Foundation of Hainan Province (Grant No.: 820RC771); The Key R&D Projects of Hainan Province (Grant No.: ZDYF2022SHFZ074); Hospital-Level Task Book of Hainan Women and Children's Medical Center (Grant No. 2020YJ01).

Conflict of Interest

The authors declare no conflict of interest.

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