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ORIGINAL RESEARCH

Higher Cumulative Live Birth Rate but Also Higher Late Miscarriage Risk in Non-Obese Women with Polycystic Ovary Syndrome Undergoing the First IVF/ICSI Cycle

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Purpose: To determine the impact of polycystic ovary syndrome on in vitro fertilization/intracytoplasmic sperm injection and embryo transfer outcomes while analyzing the influencing factors.

Patients and Methods: A retrospective cohort study comprised 4839 patients who underwent their first cycle of IVF/ICSI treatment from January 2016 to December 2021. Cumulative pregnancy rates, cumulative live birth rates, and late miscarriage rates compared between the PCOS group and control group. Subgroup analysis and binary regression were used to analyze the influence of BMI on clinical outcomes among individuals diagnosed with PCOS.

Results: Non-obese PCOS patients exhibited higher cumulative pregnancy rates, cumulative live birth rates, and late miscarriage rates compared to the control group with the normal BMI population (84.7% vs71.2%, $P < 0.001$; 74.1% vs 61.6%, $P < 0.001$; 4.1% vs 2.0%, $P = 0.002$), but there was no significant difference in early miscarriage rates between the two groups.

Conclusion: Non-obese PCOS patients demonstrated a notably higher cumulative live birth rate but also a higher risk of late miscarriage compared to non-PCOS females with a normal BMI.

Keywords: body mass index, cumulative live birth rate, in vitro fertilization, intracytoplasmic sperm injection, late miscarriage, polycystic ovary syndrome

Introduction

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder characterized primarily by a combination of clinical features, including hyperandrogenism, anovulation, and the presence of polycystic ovaries.[1] The intricate physiopathology of PCOS remains elusive, with the complexity attributed to the intricate interplay of components, including genetic predisposition, neuroendocrine dysfunction, prenatal influences, and lifestyle factors.[2–5] The global prevalence of PCOS among women of childbearing age varies, ranging from 6% to 21%.[6–9] PCOS represents a significant contributor to ovulatory infertility, carrying substantial implications for those affected by the condition.[10,11] Additionally, PCOS frequently coexists with metabolic disorders such as obesity, hyperlipidemia, insulin resistance, further complicating its clinical landscape.[12,13]

Assisted Reproductive Technology (ART), which includes approaches such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), presents promising prospects for PCOS patients aiming to overcome their fertility challenges.[11,14] The Cumulative Live Birth Rate (CLBR), a metric that considers outcomes from both fresh embryo transfer cycles and frozen embryo transfer (FET) cycles, provides a more comprehensive measure for assessing the

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overall success of IVF/ICSI interventions.[15,16] The substantial response observed during ovarian stimulation in PCOS women contributes to an impressive CLBR of approximately 70%.[17]

It is crucial to acknowledge that although PCOS patients may exhibit enhanced reproductive capacity, the presence of underlying metabolic disorders underscores the potential for an increased vulnerability to pregnancy complications and adverse perinatal outcomes.[18–21] While approximately 40–60% of PCOS patients are overweight or obese,[22,23] a clinically significant subset maintains a normal body mass index (BMI < 25 kg/m²).[24] These metabolic abnormalities extend beyond overweight or obese individuals with PCOS, impacting even those with a normal BMI.[25] Research has emphasized the adverse impact of obesity on IVF outcomes, including live birth rates and the risk of miscarriage.[26] However, there remains a notable scarcity of dedicated investigations specifically aimed at exploring the clinical outcomes of IVF/ICSI in individuals diagnosed with non-obese PCOS.

Accordingly, we conducted a comprehensive evaluation of the clinical outcomes among a cohort of PCOS patients undergoing IVF/ICSI treatment. Our particular emphasis was on comparing these outcomes, especially in relation to non-PCOS patients. The study aimed to provide valuable insights into the potential differences in treatment outcomes that could arise between non-obese and obese PCOS patient groups.

Materials and Methods

Study Design and Population

This retrospective study has undergone a thorough review and received approval from the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. The study initially enrolled PCOS patients (n = 913) who underwent their first IVF/ICSI treatment at our reproductive center between January 2016 and December 2021. According to the Rotterdam Criteria, patients were diagnosed as PCOS if they met two of the three following criteria: oligoovulation or anovulation; hyperandrogenism; and polycystic ovaries.[27] The control group (n = 5553) included patients who underwent first IVF/ICSI treatment due to fallopian tubal factor or male factor infertility. Both the PCOS and control groups were subjected to exclusion criteria encompassed: (1) age > 40 years; (2) diagnosis of recurrent spontaneous abortion, endometriosis, congenital uterine malformation, and intrauterine adhesions; (3) endocrine disorders such as Cushing's syndrome, hyperprolactinemia, pituitary microadenoma, and thyroid dysfunction; (4) autoimmune diseases. Additionally, cases with missing information regarding cycles, embryos, and clinical pregnancy data were excluded from the analysis. The study ultimately comprised 787 PCOS patients and 4052 controls.

Ovarian Stimulation and Laboratory Protocols

All patients underwent ovarian stimulation, oocyte retrieval, and embryo transfers in accordance with standard protocols.[28] Ovarian stimulation protocol was selected and carried out by female age and ovarian reserve function. Human chorionic gonadotropin (hCG) was administered when at least three follicles measured exceeded 18 mm to induce oocyte maturation. Oocyte retrieval was performed 36h later. Different fertilization methods were performed according to sperm quality. Embryo transfers followed a standard protocol, and patients received vaginal and/or intramuscular progesterone for luteal support. Fresh embryo transfers occurred on either day 3 or 5 days after oocyte retrieval. In cases where fresh embryo transfer was deemed unsuitable due to factors such as ovarian hyperstimulation syndrome (OHSS), inadequate endometrial thickness, or abnormal laboratory parameters, a comprehensive strategy involving the freezing of all embryos was adopted. For subsequent FET cycles, endometrial preparation was carried out using either natural cycles or hormone replacement therapy. Following successful embryo transfer and confirmation of clinical pregnancy, the administration of luteal support drugs was continued until the tenth week of pregnancy.

Main Outcome Measures

The clinical pregnancy was defined as the presence of a gestational sac detected via ultrasound examination four weeks after the embryo transfer procedure. Miscarriage events were categorized into early miscarriage, referring to pregnancy loss occurring prior to 12 weeks of gestation, and late miscarriage, defined as pregnancy loss transpiring between 12 and 24 weeks of gestation.[29] The live birth rate was defined as the successful delivery of one or more live infants. The cumulative pregnancy rate was the proportion of at least one pregnancy per started cycle. The cumulative live births

encompassed the live births arising from both fresh cycles and subsequent FET cycles subsequent to the same ovarian stimulation cycle, until the occurrence of one live birth or the exhaustion of all available embryos.

Statistical Analysis

The statistical analysis was conducted using SPSS software (version 26.0, Chicago, USA). Continuous variables that followed a normal distribution were presented as mean ± standard deviation, while continuous variables with non-normal distribution were described using median and interquartile range. Comparisons between continuous variables were performed using either the two tailed *t*-test or the Mann–Whitney *U*-test, depending on the distributional characteristics of the data. Categorical variables were presented as rates and percentages, and differences between groups were assessed using the chi-square test or Fisher's exact test, as appropriate. Odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs) were calculated to evaluate the strength of associations. Univariate analysis and multivariate analysis were performed by binary Logistics regression. Variables with statistical differences in the univariate analysis were included in the multivariate regression equation. Statistical significance was established at $P < 0.05$.

Results

Patient Characteristics

The primary baseline characteristics of the two cohorts are systematically outlined in Table 1. Notably, individuals diagnosed with PCOS displayed a slightly younger mean age in contrast to the control group (29.39 ± 3.53 vs 31.97 ± 4.28, $P < 0.001$). It is pertinent to highlight that patients grappling with PCOS exhibited a notably higher BMI when compared to their counterparts in the control group (22.60 ± 3.43 vs 21.50 ± 2.81, $P < 0.001$). Furthermore, discernible differences were observed in total testosterone levels, with the PCOS group showcasing significantly elevated values as compared to the control group (0.45 ± 0.16 vs 0.29 ± 0.11, $P < 0.001$). Of particular significance is the marked discrepancy in the distribution of infertility types between the two cohorts, with the PCOS group presenting a notably greater proportion of primary infertility cases (65.9% vs 35.3%, $P < 0.001$).

Table 1 Baseline Characteristics of Patients with and without PCOS

	Control	PCOS	*P* value
No. of patients	4052	787	
Female Age (y)	31.97±4.28	29.39±3.53	<0.001
Male Age (y)	34.21±5.44	31.96±4.43	<0.001
BMI (kg/m^2)	21.50±2.81	22.60±3.43	<0.001
Baseline FSH (IU/L)	5.83±2.16	5.04±1.27	<0.001
Baseline LH (IU/L)	3.48±1.93	6.89±4.84	<0.001
bE2 (pg/mL)	36.34±25.10	39.79±31.08	0.003
Baseline total T (ng/mL)	0.29±0.11	0.45±0.16	<0.001
AFC	10.54±6.15	17.47±10.40	<0.001
Duration of infertility (y)	3.70±2.93	3.76±2.44	0.516
Infertility type			<0.001
Primary infertility (%)	35.3	65.9	
Secondary infertility (%)	64.7	34.1	

Abbreviations: BMI, Body Mass Index; AFC, Antral Follicle Count; FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone.

Ovarian Stimulation Results

Cycle characteristics and ART outcomes have been meticulously compiled in Table 2. Compared to the control group, the PCOS cohort exhibited a notably favorable ovarian response, characterized by a diminished total gonadotropin dosage and an augmented count of retrieved oocytes. Parallels were observed in oocyte maturation rates between the two groups. Encouragingly, the rates of both cleavage and blastocyst formation registered a slight elevation within the PCOS group as compared to the control group (97.8% vs 97.4%, P = 0.017 and 67.5% vs 64.3%, P < 0.001, respectively). Nonetheless, it is imperative to note that no significant discrepancy emerged in terms of the rate of high-quality embryos between these two cohorts.

Pregnancy Outcomes

The embryo transfer outcomes are presented in Table 3. In comparison to the control group, the PCOS cohort exhibited notably elevated rates of clinical pregnancy, cumulative pregnancy, and cumulative live birth. Although the overall miscarriage rates in both groups displayed a semblance (15% vs 14.8%, P = 0.891), it is noteworthy that the late pregnant loss rate within the PCOS group surpassed that within the control group, with statistical significance (3.8% vs 2.3%, P = 0.023). Upon scrutinizing the embryo transfer cycle modalities, discernment reveals that the PCOS group registered higher abortion rates than the control group in the context of fresh embryo transfer cycles (21.2% vs 13.5%, P = 0.034). Moreover, while an upward trend in late miscarriage rate during FET cycles was observed within the PCOS group, this escalation did not attain statistical significance (3.4% vs 2.2%, P = 0.058).

Subgroup Analysis

In order to deepen our understanding of the potential influence of BMI on clinical outcomes among individuals diagnosed with PCOS, a meticulous subgroup analysis was conducted. This analysis involved the stratification of women into two distinct categories based on their BMI, as meticulously presented in Table 4. In non-obese people (BMI < 25 kg/m²), our findings illuminated a compelling trend: the PCOS group displayed notably elevated rates in cumulative pregnancy and

Table 2 Oocyte Retrieval Cycle Characteristics of the Patients in the PCOS Group and Control Group

	Control	PCOS	*P* value
No. of patients	4052	787	
Gn initiation dose (IU)	217.73±60.96	163.45±42.10	<0.001
Gn treatment (days)	10.38±2.05	9.11±2.48	<0.001
Gonadotropin dose (IU)	2322.40±914.17	1434.18±550.32	<0.001
P on hCG day (ng/mL)	0.80±0.61	0.85±0.56	0.051
No. of >14-mm follicles on the Trigger day	9.74±4.94	13.65±5.85	<0.001
Number of retrieved oocytes	14.20±7.87	21.37±11.10	<0.001
No. of MII oocytes retrieved	12.62±7.16	18.53±9.69	<0.001
No. Of available embryos	5.25±3.60	7.59±4.59	<0.001
Mature oocyte rate (%)	82.4 (5492/6663)	82.4 (3591/4360)	0.932
Cleavage rate(%)	97.4 (36,867/37,836)	97.8 (10,366/10,594)	0.017
Blastocyst formation rate (%)	64.3 (17,107/26,615)	67.5 (5715/8468)	<0.001
High-quality embryo rate (%)	45.3 (16,711/36,867)	46.2 (4784/10,366)	0.137
Unavailable embryo rate (%)	1.8 (14/787)	3.2 (131/4052)	0.029

Table 3 Pregnancy Outcomes of Patients with and without PCOS

	Control	PCOS	*P* value
No. of patients	4052	787	
Overall pregnancy rate per ET (%)	51.6% (3335/6465)	57.9% (773/1335)	<0.001
Overall miscarriage rate (%)	14.8% (494/3335)	15% (116/773)	0.891
Overall early miscarriage rate (%)	12.5% (417/3335)	11.3% (87/773)	0.340
Overall late miscarriage rate (%)	2.3% (77/3335)	3.8% (29/773)	0.023
Cumulative outcomes			
Cumulative pregnancy rate (%)	70.7 (2866/4052)	82.8 (652/787)	<0.001
Cumulative live birth rate (%)	61.0 (2470/4052)	71.3 (561/787)	<0.001
Fresh cycle outcomes			
Pregnancy rate per ET (%)	49.1 (1014/2066)	48.1 (104/216)	0.794
Miscarriage rate (%)	13.5 (137/1014)	21.2 (22/104)	0.034
Early miscarriage rate (%)	10.8 (110/1014)	15.4 (16/104)	0.164
Late miscarriage rate (%)	2.7 (27/1014)	5.8 (6/104)	0.075
Frozen-thawed cycle outcomes			
Pregnancy rate per ET (%)	52.5 (2321/4418)	59.5 (669/1125)	<0.001
Miscarriage rate (%)	15.4 (357/2321)	14.1 (94/669)	0.397
Early miscarriage rate (%)	13.2 (307/2321)	10.6 (71/669)	0.073
Late miscarriage rate (%)	2.2 (50/2321)	3.4 (23/669)	0.058

Table 4 Subgroup Analysis for the Effect of BMI on Reproductive Outcome Over Multiple IVF/ICSI Cycles in PCOS and Control Group

Variables	BMI<25			BMI≥25		
	Control	PCOS	*P* value	Control	PCOS	*P* value
Cumulative pregnancy rate (%)	71.2 (2565/3601)	84.7 (516/609)	<0.001	67.0 (302/451)	76.4 (136/178)	0.020
Cumulative live birth rate (%)	61.6 (2220/3601)	74.1 (451/609)	<0.001	55.4 (250/451)	61.8 (110/178)	0.146
Early miscarriage rate (%)	12.5 (374/2991)	10.5 (64/608)	0.174	12.5 (43/344)	13.9 (23/165)	0.651
Late miscarriage rate (%)	2.0 (60/2991)	4.1 (25/608)	0.002	4.9 (17/344)	2.4 (4/165)	0.181

live birth compared to the control group. It is of particular significance that the late miscarriage rate among non-obese PCOS patients stood higher compared to the control group (4.1% vs 2.05%, P = 0.002). In the obesity subgroup (BMI ≥ 25 kg/m²), PCOS women also showed a higher cumulative live birth rate than the control group, and there was a trend toward higher late miscarriage rate (4.9% vs 2.4%, P = 0.181), but the difference did not reach statistical significance.

Logistic Regression Analysis

To assess the comparative predictive capacity of variables including PCOS diagnosis, age, type of embryo transfer, BMI, and infertility type with respect to the late miscarriage rate, a logistic regression analysis was undertaken, as detailed in Table 5.

Table 5 Logistic Regression Analysis for the Prediction of Late Miscarriage Rate

	B	Standard Error	*P* value	OR (95% CI)
Diagnosis of PCOS[a]	0.594	0.250	0.018	1.811 (1.110,2.957)
BMI[a]	0.577	0.254	0.023	1.780 (1.081,2.931)
Female age[a]	0.116	0.283	0.595	1.123 (0.732,1.723)
Stage of ET[a]	−0.097	0.208	0.640	0.907 (0.604,1.364)
Infertility type[a]	0.019	0.027	0.481	1.019 (0.966,1.075)

Note: [a]Reference is non-PCOS, BMI<25 kg/m^2, female age<30 y, cleavage-stage embryo, Primary infertility.

The outcomes of this analysis unveiled significant associations between the diagnosis of PCOS and the late miscarriage rate (OR 1.811; 95% CI 1.110–2.957; P = 0.018). Additionally, it was discerned that BMI stands as an independent factor possessing predictive potential for the late miscarriage rate (OR 0.577, 95% CI; 1.081–2.931; P = 0.023).

Discussion

The study's findings reveal a significantly elevated CLBR among women diagnosed with PCOS compared to the control group. This distinction persists even among individuals within the obese subgroup. It is imperative to acknowledge that PCOS patients exhibit an increased susceptibility to late-stage miscarriage. Notably, this heightened risk of late pregnancy loss extends beyond the confines of obesity, affecting non-obese cohorts as well.

Compared to the ovaries of the normal population, those of patients with PCOS exhibit a greater follicle storage capacity,[30] and the number of oocytes obtained plays a pivotal role in cumulative live birth outcomes.[31,32] Numerous studies consistently report that the CLBR among PCOS patients exceeds that of control groups,[33,34] even in women aged ≥ 35.[35,36] Our findings align with prior research, reinforcing the notion that PCOS patients achieve higher CLBR than their non-PCOS counterparts. Obesity is recognized for its adverse impact on oocyte quantity and quality, as well as reduced endometrial receptivity,[37,38] ultimately influencing embryo implantation and clinical pregnancy rates.[39] Remarkably, the obese PCOS group still demonstrated a significantly higher CLBR compared to the control group. This phenomenon may be attributed to the superior oocyte reserve and increased availability of embryos among PCOS patients, surpassing the influence of obesity on patients' internal environments and embryo quality, thus conferring enhanced fertility.

While women with PCOS may indeed exhibit improved reproductive potential, empirical findings emphasize the impact of inherent hormonal dysregulations in PCOS. These, combined with compromised oocyte quality and alterations in endometrial receptivity, exert significant influence on the outcomes of IVF/ICSI cycles.[40,41] It is noteworthy that several comprehensive meta-analyses have rigorously investigated the clinical implications of IVF/ICSI procedures in women with PCOS, consistently revealing a higher propensity for miscarriage when compared to their non-PCOS counterparts.[42–44] Recent research has also pointed towards an association between PCOS and increased rates of preclinical and early-stage pregnancy losses in IVF.[45] In a retrospective study involving 2357 PCOS women who achieved pregnancy through IVF, a heightened incidence of late-stage miscarriage was observed among PCOS patients.[46] Importantly, even after excluding embryo chromosomal anomalies, the frequency of miscarriages among PCOS patients remained notably higher than that within the control cohort.[47] In alignment with these prior investigations, our current study similarly identifies an elevated risk of late miscarriage among PCOS patients compared to the control group.[11,46–50] This consistency with previous research reaffirms the designation of PCOS as a substantive risk factor in relation to late miscarriage rates. Additionally, our study underscores the significance of BMI as a predictive parameter in assessing the likelihood of late miscarriages.

The intricate association between PCOS and miscarriages involves controversial molecular mechanisms. Elevated BMI in PCOS may profoundly impact sex hormone secretion and metabolism, influencing the bioavailability of estrogen and androgens and thereby affecting normal follicular development.[51] Recent studies elucidate altered gene expression of

steroid receptors and reduced expression of Hox10a, integrins, and Mmp9 in the implanted uterus region of PCOS animals.[52] These changes, along with modified expression patterns of key angiogenic molecules in granulosa-lutein cells of women with PCOS and a compromised capacity to sustain vascularization, delineate impaired angiogenesis, potentially resulting in luteal phase insufficiency and and influencing the risk of pregnancy loss.[53]

Numerous studies have extensively investigated the heightened risk of abortion in PCOS patients with elevated BMI.[54,55] However, it is surprising that clinical ART investigations and fertility outcomes in non-obese PCOS patients remain inadequately represented in the literature. A substantial proportion of clinically significant PCOS cases is characterized by normal or lower BMIs.[56] Although PCOS patients with normal weight share certain clinical features with obese PCOS patients, it is believed to arise and develop endocrinopathy under distinct circumstances.[57–59] PCOS patients with a normal BMI exhibit milder metabolic disturbances compared to their overweight counterparts, yet they still contend with metabolic challenges such as insulin resistance, hyperandrogenism, and low-grade chronic inflammation.[60] These factors significantly contribute to the phenotypic expression of PCOS.[61,62] In our study, we observed a higher incidence of late miscarriage among PCOS patients with a normal BMI when compared to the control population. Even after adjusting for obesity, non-obese PCOS patients continued to experience an elevated risk of adverse pregnancy outcomes.

When compared to BMI-matched healthy controls, women diagnosed with PCOS and falling into the emaciated category exhibit a range of pathophysiological abnormalities.[63,64] Study had revealed a 4.4-fold increased prevalence of impaired glucose tolerance among lean PCOS patients.[65] Moreover, there is evidence indicating that insulin resistance or hyperinsulinemia increases the risk of spontaneous abortion.[66–68] Insights from a lean PCOS mouse model emphasize the correlation between reduced oocyte quality and the impairment of mitochondrial ultrastructure and function.[69] Studies have documented aberrant expression of sex hormone receptors and co-expression receptors in the endometrium of PCOS patients.[70] Additionally, there is conclusive evidence supporting the notion that insufficient trophoblast invasion and placental disorders in PCOS patients can lead to abortion and pregnancy complications.[71–73] The mechanism contributing to the heightened risk of late-term abortion in PCOS may also be associated with alterations in endometrial metabolism. These alterations encompass disruptions in glucose metabolism, hyperinsulinemia, and hyperandrogenism, all of which can detrimentally affect endometrial function.[74] The analysis from our study unambiguously demonstrates that even among individuals who are not obese, PCOS patients continue to confront an elevated risk of late-term miscarriage.

Our research is not without its limitations. Firstly, owing to the retrospective nature of the study, we were unable to investigate certain unidentified confounding factors, such as preemptive blood glucose control, lipid metabolism control, exercise, and weight loss, which might have influenced our findings. Secondly, there were varying degrees of missing data in the patients' endocrine-related examinations, preventing further categorization based on blood glucose, insulin, and androgen levels. Additionally, our study did not track or analyze other potential pregnancy complications in patients. Lastly, to obtain a more comprehensive understanding of the relationship between PCOS and miscarriage, a prospective clinical trial is warranted, incorporating comprehensive clinical parameters such as BMI, hormone status, age, phenotype, and other relevant variables.

In conclusion, this study conducted a thorough examination of pregnancy outcomes in a cohort of patients undergoing IVF/ICSI cycles, uncovering an elevated CLBR specific to PCOS patients. Concurrently, a heightened susceptibility to late miscarriages was observed among non-obese PCOS individuals. It is of paramount importance for clinicians to be cognizant of these associations and to offer appropriate counseling and monitoring to mitigate the risk of late miscarriage in non-obese women with PCOS.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University [No. IIT-2023–593]. All procedures were performed in accordance with the Declaration of Helsinki. Since this retrospective study analyzed the medical records obtained in the past clinical diagnosis and treatment, the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University agreed to waive the patient's written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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