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Hyperandrogenism increases late spontaneous miscarriage in polycystic ovary syndrome women due to cervical insufficiency? A propensity-score matching study

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Abstract

Background The potential effects of hyperandrogenism (HA) on pregnancy outcomes among polycystic ovary syndrome (PCOS) patients are still unknown. The aim of this study was to explore the impact of HA on miscarriage rate after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment in PCOS patients.

Methods Women diagnosed with PCOS who underwent the first autologous IVF/ICSI cycles using gonadotropin-releasing hormone agonist (GnRH-a) protocols for ovarian stimulation during the period from January 2016 to December 2022 were included. Women were divided into the HA and non-HA group according to Hyperandrogenemia (serum testosterone level > 0.48 ng/mL), and/or the presence of hirsutism. Pregnancy outcomes were compared before and after propensity-score matching (PSM). Multiple logistic regression models were performed to demonstrate the independent impact of HA on pregnancy outcomes.

Results A total of 3066 patients were included. PCOS women with HA experienced a notably higher rates of late spontaneous miscarriage (LSM) as compared to those without HA before and after PSM (8.8% versus 3.5%, $P < 0.001$; 8.9% versus 3.9%, $P = 0.001$, respectively), but comparable rates of clinical pregnancy, early spontaneous miscarriage, and live birth. After adjusting for possible confounding factors, the logistic regression confirmed that HA was independently associated with the increased risk of LSM (adjusted OR: 2.540, 95% confidence interval: 1.326–4.672, $P = 0.003$). For the specific reasons for LSM, cervical insufficiency accounted for a larger proportion in women with HA than their counterparts without HA (15/32 versus 7/33, $P = 0.029$).

Conclusions Androgen excess is postulated to play a role in late miscarriage via increased likelihood of cervical insufficiency.

Trial registration N/A.

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Keywords Polycystic ovarian syndrome, Hyperandrogenism, Late spontaneous miscarriage, Cervical insufficiency, Propensity score matching

Introduction

Polycystic ovary syndrome (PCOS) is a chronic complex, polygenic and multifactorial syndromic disorder that significantly impacts health and well-being for childbearing women [1]. The participation of genetic and environmental factors is considered in the etiology of PCOS development. PCOS is connected with different metabolic disorders, such as insulin resistance, vitamin D deficiency, metabolic disturbances, and hyperandrogenism (HA) [2]. The diagnostic criteria for PCOS have been grouped in different classifications that have been conflicting for many years, and the classification of Rotterdam is the most widely used, among which HA is the main criterion in the diagnostic work-up of PCOS [3].

To date, numerous clinical studies have established the correlation between PCOS and infertility, as well as between PCOS and pregnancy complications during in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment. In was speculated that reduced fertility potential in women with PCOS may be caused by altered oocytes, embryo and endometrial competence [4–6]. It is shown in some studies that compared with those without PCOS, women with PCOS are at an increased risk of suffering from miscarriage and pregnancy-related complications [7]. In addition, PCOS was also shown to be an independent risk factor for several pregnancy complications, such as gestational diabetes, hypertensive disorders of pregnancy, pre-labour rupture of membranes, ect [8–10]. However, the potential effects of HA on pregnancy outcomes among PCOS patients are still unknown. In 2018, De Vos et al. found that in IVF/ICSI cycles, hyperandrogenic PCOS phenotypes confer significantly lower cumulative live birth rates compared with their normoandrogenic counterparts [11]. However, a more recent meta-analysis involving 3037 PCOS patients showed that PCOS women with HA exhibited increased miscarriage rates but comparable rates of ongoing pregnancy and live birth as compared with PCOS women without HA [12].

Based on the existing controversy regarding pregnancy outcomes in PCOS patients with different HA status, the aim of this study was to evaluate the effect of HA on IVF/ICSI treatment outcomes in PCOS patients, and also to explore possible explanations for increased miscarriage rates in PCOS women with HA.

Materials and methods

Study population

From January 2016 to December 2022, all patients diagnosed with PCOS undergoing IVF/ICSI treatment for their first cycles at the Reproductive Medicine Center of the First Affiliated Hospital of Zhengzhou University were included. Data collection was from the Clinical Reproductive Medicine Management System/Electronic Medical Record Cohort Database (CCRM/EMRCD) of our center. This study was approved by the Ethics Review Committee of the hospital (2023-KY-1049-002) and written informed consent was waived due to the retrospective nature of the study.

The main inclusion criteria included: (1) PCOS women; (2) the first IVF/ICSI treatment cycles; (3) Gonadotropin-releasing hormone (GnRH)-agonist (GnRH-a) protocols for ovarian stimulation; (4) female age < 40 years old. Exclusion criteria were: (1) preimplantation genetic testing cycles; (2) oocyte donation cycles; (3) uterine malformation, endometrial polyps, intrauterine adhesion and other uterine disease compromising embryo implantation; cervical surgery or cervical insufficiency history; (4) using medication that may affect the level of sex hormones and glucose metabolism in the last 3 months; (5) other diseases leading to androgen excess; (6) artificial multifetal pregnancy reduction cycles.

The diagnosis of PCOS was based on modified Rotterdam criteria [13], which met at least two of the three criteria: oligo-/anovulation; clinical or biochemical hyperandrogenism; ultrasound diagnosis of polycystic ovary morphology (PCOM). Oligo-/anovulation was diagnosed based on the presence of oligo-/amenorrhea (menstrual cycle > 35 days). Hyperandrogenism was defined as a testosterone (T) level > 0.48 ng/mL, which is in accordance with our laboratory normal ranges, and/or the presence of hirsutism. At the beginning of treatment, hirsutism was determined based on Ferriman–Gallwey scoring system (≥ 6 for Asian women) and/or severe acne and alopecia at physical examination. PCOM was defined as the presence of either an ovary containing ≥ 12 antral follicles (2–9 mm in diameter) or an increased ovary volume (> 10 cm^3) [14].

Study protocols

All patients included were treated with GnRH-a protocols for ovarian stimulation. Briefly, pituitary down-regulation was commenced using long-acting GnRH-a in early follicular phase. Around 30 days later, follicle growth was regularly monitored, and the gonadotropin dose was adjusted accordingly. When at least two follicles reached a diameter of 18 mm, human chorionic gonadotropin (hCG) was administrated for oocyte maturation. Afterward, oocyte retrieval, fertilization, and embryo culture were performed as described previously [15].

At the end of oocyte retrieval cycles, patients were divided into three types: (1) No embryos available, mainly due to fertilization failure, embryo developmental arrest; (2) freeze-all embryos, such as high risk for ovarian hyper-stimulation syndrome, progestogen elevation; (3) fresh embryo transfer with cleavage or blastocyst embryos. For those with embryo transfer, luteal phase support was given as routine practice [15].

Main outcome measures

Positive pregnancy test was defined as a serum hCG > 5 mIU/mL 14 days after embryo transfer. Clinical pregnancy was defined as the presence of a live fetus and/or a gestational sac in ultrasonography 5 weeks after embryo transfer. Implantation rate was calculated as the ratio of the number of gestational sacs over the number of transferred embryos. Ectopic pregnancy was defined as the implantation of a pregnancy outside the normal uterine cavity. Early spontaneous miscarriage was defined as miscarriages that occurred before 12 weeks of gestation. Late spontaneous miscarriage occurred 12–28 weeks of gestation. Live birth was defined as delivery of any viable infant at 28 weeks or more of gestation [16].

More specifically, reasons for late miscarriage were further categorized as follows: (1) cervical insufficiency; (2) fetal factors; (3) trauma factors; (4) unexplained factor and others. Cervical insufficiency was diagnosed based on clinical symptoms and ultrasound findings. Physical examination-based: painless cervical dilatation or prolapsed fetal membranes has been detected on manual or speculum examination before 24 weeks of gestation regardless of whether a history of mid-trimester pregnancy loss or preterm birth exists. Ultrasound-based: one or more pregnancy losses or preterm births of 14–36 weeks in the past and the cervical length CL < 25 mm measured by transvaginal ultrasound before 24 weeks of gestation [17, 18]. However, cervical changes attributable to infection were excluded. Fetal factors were mainly chromosomal abnormalities, congenital malformations, infections, and placental insufficiency. Trauma-related causes included physical injury to the abdomen or uterus, surgical interventions, and excessive physical strain. Unexplained factor and others mainly included maternal health conditions (diabetes, hypertension, ect), environmental exposures, and idiopathic causes, subtle genetic issues, or immune incompatibilities that remain undetected by current diagnostic methods.

Statistical analysis

The basic characteristics and treatment outcomes of all PCOS patients were analyzed according to their hyperandrogenism status (HA, or non-HA). Given that baseline parameters were significantly different between the HA group and non-HA group, propensity-score matching (PSM) was performed to identify non-HA patients who were most comparable with the patients with HA. The propensity score was calculated by using a multiple logistic regression model, with HA versus non-HA serving as the dependent variable, and female age, body mass index (BMI), serum anti-Mullerian hormone (AMH), antral follicle count (AFC), and fertilization method serving as independent variables. To optimize the precision of the study, patients with HA were matched to patients with non-HA in a 1:2 ratio.

Firstly, baseline parameters were compared between HA and non-HA groups before and after PSM. Multivariate logistic regression analysis was performed to explore possible relationship between HA status and treatment outcomes (positive pregnancy test rate, implantation rate, clinical pregnancy, ectopic pregnancy, early miscarriage, late miscarriage, and live birth). Adjusted variables included female age, BMI, infertility type, fertilization method, stage of embryos transferred, and number of embryos transferred.

Data were examined for normal distribution before analysis using Shapiro-Wilk test. For normal distribution and non-normal distribution data, Student's t test and nonparametric test (Kruskal-Wallis test) was performed, respectively. Chi-square test was used to detect difference between categorical variables. Statistical analysis was performed with SPSS (Statistical Package for Social Science, SPSS Inc, Chicago, IL, USA) version 21.0. A $P < 0.05$ was considered statistically significant.

Results

A total of 3066 PCOS women undergoing their first IVF/ICSI treatment cycles with GnRH agonist protocol were firstly included. Except for 148 cycles with important data missing, 891 HA patients and 2027 non-HA patients were included for final analysis. A detailed flow chart of patient selection is presented in Fig. 1.

As shown in Table 1, basic characteristics were significantly different between HA and non-HA groups. Patients in HA group were younger (28.1 vs. 28.7 years; $P < 0.001$), with higher AMH level (8.7 vs. 6.6 ng/mL; $P < 0.001$) and higher BMI (24.4 vs. 23.2 kg/m^2; $P < 0.001$) on average as compared with patients in non-HA group. In addition, compared with patients from non-HA group, more patients from HA group were diagnosed with primary infertility (69.0% vs. 59.7%; $P < 0.001$), and used IVF for fertilization (86.6% vs. 80.0%; $P < 0.001$).

As for patients undergoing embryo transfer, there were 473 cycles in HA group, and 1314 cycles in non-HA group. Similarly, before PSM, baseline characteristics were also significantly different between women in HA and non-HA groups. Moreover, positive pregnancy test rate (81.4% vs. 76.8%; $P = 0.038$), and implantation rate (59.9% vs. 55.8%; $P = 0.049$) were higher in HA women as

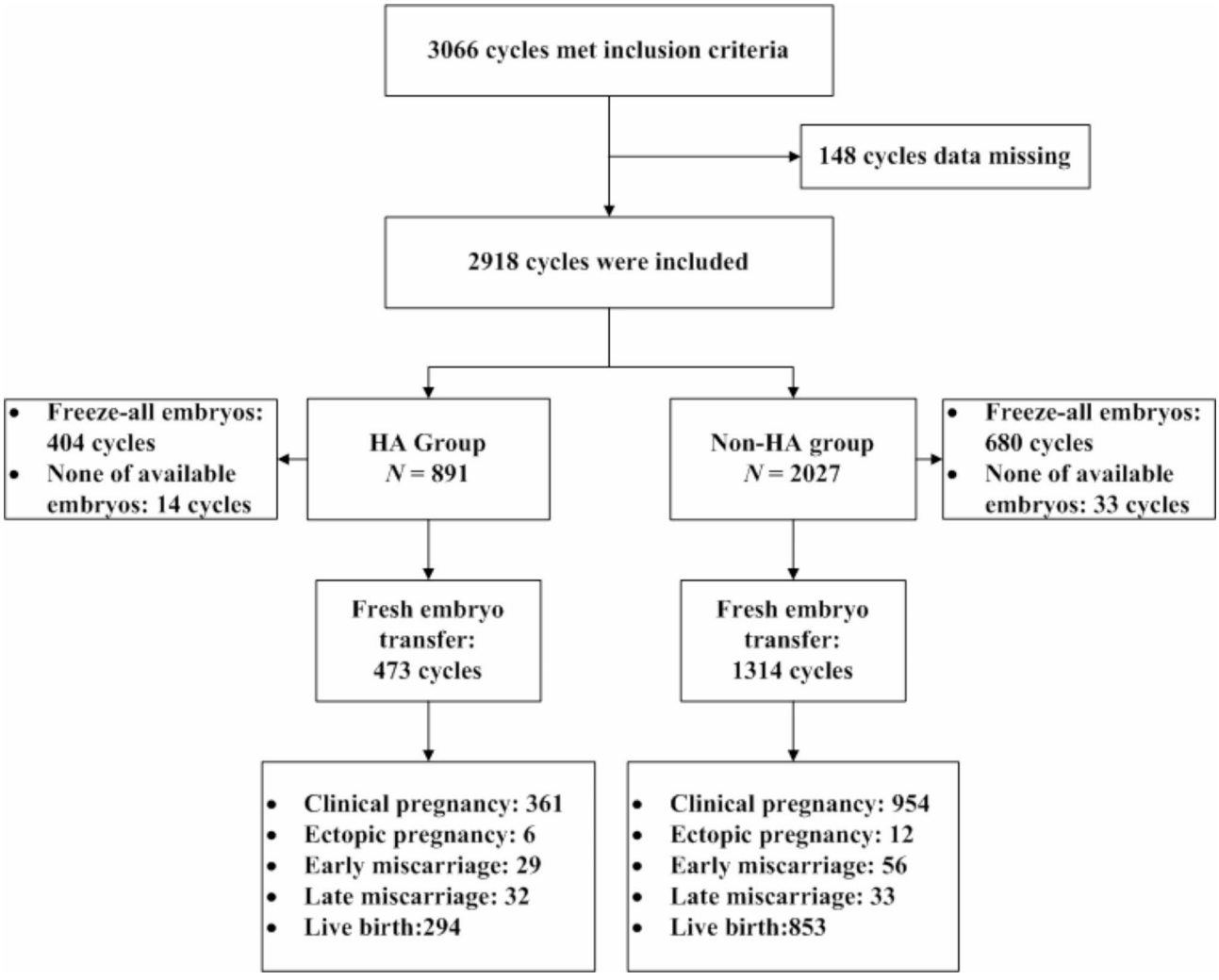

Fig. 1 Flowchart of the retrospective cohort study
Note: HA = hyperandrogenism

compared with non-HA women. As for other pregnancy outcomes, clinical pregnancy rate, ectopic pregnancy rate, and live birth rate were all comparable between patients from two groups. While there was no difference between HA and non-HA patients regarding to early miscarriage rate (8.0% vs. 5.9%; $P = 0.155$), late miscarriage rate in HA women was significantly higher (8.8% vs. 3.5%; $P < 0.001$). After PSM, baseline characteristics and pregnancy outcomes were comparable between two groups, except for late miscarriage rate, which was still higher in HA women (8.9% vs. 3.9%; $P = 0.001$) (Table 2). Furthermore, the relationship between HA status and pregnancy outcomes was also explored by multivariate logistic regression analysis. As shown in Fig. 2, HA was an independent risk factor for both positive pregnancy test [adjusted odd ratio (aOR): 1.264, 95% confidence interval (CI): 1.141–1.487; $P = 0.042$), and late miscarriage (aOR: 2.540, 95% CI: 1.326–4.672; $P = 0.003$).

In order to further explore the possible reasons for late miscarriage in HA and non-HA patients. Detailed information of these 65 women ended with late miscarriage was shown in Table 3. Baseline parameters were comparable between HA and non-HA late miscarriage women. However, specific reasons for late miscarriage were significantly different between the two groups. In the 32 HA women suffering from late miscarriage, 15 of them were attributable to cervical insufficiency. This proportion was higher than that in non-HA group (46.9% vs. 21.2%; $P = 0.029$).

Discussion

This retrospective cohort study focused on the association between hyperandrogenism and pregnancy outcomes in PCOS patients undergoing the first fresh embryo transfer. Within the PCOS population, individuals were categorized into the HA and non-HA groups

Table 1 Basic characteristics in patients with PCOS in their first autologous IVF/ICSI cycles

Characteristics	HA	non-HA	*P*
No. of cycles	891	2027	
Female age (y)	28.1 ± 3.2	28.7 ± 3.8	< 0.001
< 35 (%)	852 (95.6)	1825 (90.0)	< 0.001
≥ 35 (%)	39 (4.4)	202 (10.0)	
BMI (Kg/m^2)	24.4 ± 3.5	23.2 ± 3.2	< 0.001
< 25 (%)	475 (53.3)	1420 (70.1)	< 0.001
≥ 25 (%)	416 (46.7)	607 (29.9)	
Infertility duration (y)	3 (2, 5)	3 (2, 5)	0.349
Infertility type (%)			< 0.001
Primary infertility	69.0 (615/891)	59.7 (1210/2027)	
Secondary infertility	31.0 (276/891)	40.3 (817/2027)	
Basal FSH (mIU/mL)	5.7 ± 1.4	5.8 ± 1.5	0.067
Basal T(ng/mL)	0.58 ± 0.13	0.29 ± 0.08	< 0.001
AMH (ng/mL)	8.7 (5.9, 12.4)	6.6 (4.8, 8.4)	< 0.001
AFC (n)	24 (24, 24)	24 (22, 24)	< 0.001
No. of oocytes retrieved	19 (13, 24)	18 (13, 23)	0.034
Fertilization method (%)			< 0.001
IVF	86.6 (772/891)	80.0 (1622/2027)	
ICSI	13.4 (119/891)	20.0 (405/2027)	
Outcomes (%)			< 0.001
Fresh embryo transfer	53.1 (473/891)	64.8 (1314/2027)	
Freeze-all embryos	45.3 (404/891)	33.5 (680/2027)	
None of available embryos	1.6 (14/891)	1.7 (33/2027)	

Note: PCOS, polycystic ovary syndrome; HA, hyperandrogenism; BMI, body mass index; FSH, follicle stimulation hormone; T, testosterone; AMH anti-Müllerian hormone; AFC antral follicle count; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Data presented as means ± SD, median (25th, 75th percentile), n or n (%). Differences were analysed by Student's t-test, Mann-Whitney U-test or chi-squared test

based on their serum total T levels and/or the presence of hirsutism before COH. The findings of this study revealed a notable link between HA status and an increased risk of late spontaneous miscarriage (LSM). Furthermore, HA were identified as a potential predictive factor for LSM in PCOS patients possibly due to higher incidence of cervical insufficiency. However, the rates of clinical pregnancy, early spontaneous miscarriage and live birth exhibited no significant differences between the HA and non-HA groups.

Although controversial, some scholars suggested that PCOS is linked to an increased risk of miscarriage, and increased risk of pregnancy complications in IVF/ICSI treatment cycles [19]. However, the underlying mechanisms remain still limited and unclear. Embryonic chromosomal abnormality is regarded as a primary cause of early miscarriage, potentially accounting for 50–60% of spontaneous miscarriage during the first trimester. Weghofer et al. first reported a similar rate of embryonic aneuploid in day 3 embryos using embryo biopsy and fluorescence in situ hybridization between PCOS and control groups undergoing IVF treatment [20]. Recently, Wang et al. conducted a secondary analysis of a multi-center randomized controlled trial that initially explored the efficacy of preimplantation genetic test for aneuploidy (PGT-A) using next-generation sequencing (NGS) in improving live birth rates compared with IVF [21]. A total of 1118 embryos, derived from 190 PCOS patients and 190 age-matched patients without PCOS, were analyzed. The study revealed that PCOS did not lead to an increased risk of aneuploid embryos, and no significant differences in embryonic aneuploid rate were observed among the four phenotypes. Nevertheless, in 277 PCOS patients and 1221 patients without PCOS after a single frozen-thawed euploid blastocyst transfer, we previously indicated that PCOS status independently increased the risk of ESM (aOR 1.649, 95% CI 1.032–2.635, $P = 0.036$) [16], which was consistent with the findings of Luo et al., suggesting that factors other than embryonic aneuploidy may contribute to the PCOS-related higher risk of early miscarriage [22].

In the study including 4083 patients without HA undergoing the first single frozen-thawed blastocyst transfers, Hu et al. did not observe an independent effect of PCOS without HA on the incidence of pregnancy loss (11.5% vs. 11.7%, $P = 0.879$) [23]. Androgen excess is widely considered as an essential criterion for PCOS diagnosis and a pivotal factor in the pathogenesis of reproductive and metabolic alterations in patients with PCOS. Whether HA plays a contributory role in the increased risk of miscarriage in PCOS women remains insufficiently substantiated by existing evidence.

Yang et al. divided 583 young PCOS women with GnRH-antagonist protocols into four groups based on androgen level [T level ≥ 2.2 nmol/L or basal androstenedione (AND) level ≥ 12 nmol/L] and BMI and found that HA had a positive effect on good-quality embryos. Among the 406 PCOS patients subsequently undergoing fresh ET, clinical pregnancy rates were comparable among four groups, but basal AND was identified to be an independent risk factor for miscarriage (odds ratio:1.071, 95% CI: 1.005–1.141) and showed a significant predictive value on miscarriage [24]. In the subgroup analysis of a PSM study involving PCOS patients who conceived following single thawed blastocyst transfer, Jie et al. observed a higher rate of early miscarriage in PCOS women with total T levels > 0.7ng/mL than those with low T levels (29.4% vs. 12.3%, $P = 0.032$) [25]. Li et al. recently investigated 876 PCOS patients who achieved single clinical pregnancies after fresh IVF/ICSI-ET treatments, and they demonstrated HA status (serum T ≥ 2.53 nmol/L or AND ≥ 11.5 nmol/L) was independently related to higher risks of early miscarriage (aOR: 1.869, 95% CI: 1.329–2.630) and preterm birth (aOR: 0.403, 95% CI: 0.240–0.675) but lower live birth rates (aOR: 2.248, 95% CI: 1.641–3.080) [26], which was not observed in our study. The differences in these findings may be

Table 2 Baseline characteristics and pregnancy outcomes of patients with PCOS in the first fresh embryo transfer cycles before and after propensity-score matching (PSM)

Characteristics	Before PSM			After PSM		
	HA	non-HA	*P*	HA	non-HA	*P*
No. of cycles	473	1314		470	940	
Female age (y)	28.2 ± 3.4	28.9 ± 3.8	0.001	28.2 ± 3.4	28.3 ± 3.5	0.157
< 35 (%)	450 (95.1)	1190 (90.6)	< 0.001	447 (95.1)	880 (93.6)	0.263
≥ 35 (%)	23 (4.9)	124 (9.4)		23 (4.9)	60 (6.4)	
BMI (Kg/m^2)	24.5 ± 3.5	23.1 ± 3.3	< 0.001	24.5 ± 3.5	24.2 ± 3.4	0.350
< 25 (%)	240 (50.7)	875 (66.6)	< 0.001	243 (51.7)	494 (52.6)	0.763
≥ 25 (%)	233 (51.3)	439 (33.4)		227 (48.3)	446 (47.4)	
Infertility duration (year)	3 (2, 5)	3 (2, 5)	0.420	3 (2, 5)	3 (2, 5)	0.679
Infertility type (%)			0.142			0.532
Primary infertility	64.5 (305/473)	60.7 (797/1314)		64.3 (302/470)	62.6 (588/940)	
Secondary infertility	35.5 (168/473)	39.3 (517/1314)		35.7 (168/470)	37.4 (352/940)	
Basal FSH (mIU/mL)	5.8 ± 1.4	5.9 ± 1.5	0.280	5.8 ± 1.4	5.8 ± 1.5	0.807
Basal T(ng/mL)	0.56 ± 0.11	0.28 ± 0.08	< 0.001	0.55 ± 0.11	0.34 ± 0.09	< 0.001
AMH (ng/mL)	6.8 (4.9, 10.0)	5.0 (3.6, 6.9)	< 0.001	6.8 (4.9, 10.0)	6.7 (4.8, 9.7)	0.072
AFC (n)	24 (24, 24)	24 (22, 24)	< 0.001	24 (24, 24)	24 (24, 24)	0.251
No. of oocytes retrieved	16 (12, 19)	15 (12, 18)	0.012	16 (12, 19)	16 (12, 19)	0.364
Insemination method (%)			0.516			0.874
IVF	402 (85.0)	1100 (83.7)		399 (84.9)	801 (85.2)	
ICSI	71 (15.0)	214 (16.3)		71 (15.1)	139 (14.8)	
Stage of embryos transferred (%)			0.061			0.843
Cleavage	308 (65.1)	917 (69.8)		308 (65.5)	621 (66.1)	
Blastocyst	165 (34.9)	397 (30.2)		162 (34.5)	319 (33.9)	
No. of embryos transferred	1.63 (1, 2)	1.67 (1, 2)	< 0.001	1.63 (1, 2)	1.63 (1, 2)	0.752
Pregnancy outcomes						
Positive pregnancy test rate, %	81.4 (385/473)	76.8 (1009/1314)	0.038	81.4 (383/470)	77.1 (725/940)	0.060
Implantation rate, %	59.9 (462/771)	55.8 (1229/2200)	0.049	59.9 (458/765)	57.1 (875/1532)	0.207
Clinical pregnancy rate, %	76.3 (361/473)	72.6 (954/1314)	0.116	76.3% (359/470)	73.4 (690/940)	0.227
Multiply pregnancy rate, %	28.8 (104/361)	30.9 (295/954)	0.423	29.0 (104/359)	30.6 (211/690)	0.594
Ectopic pregnancy rate, %	1.7 (6/361)	1.3 (12/954)	0.573	1.7 (6/359)	1.4 (10/690)	0.781
Early miscarriage rate, %	8.0 (29/361)	5.9 (56/954)	0.155	8.1 (29/359)	6.2 (43/690)	0.262
Late miscarriage rate, %	8.8 (32/361)	3.5 (33/954)	< 0.001	8.9 (32/359)	3.9 (27/690)	0.001
Live birth rate, %	62.1 (294/473)	64.9 (853/1314)	0.283	62.1 (292/470)	64.9 (610/940)	0.308

Note: PCOS, polycystic ovary syndrome; HA, hyperandrogenism; BMI, body mass index; FSH, follicle stimulation hormone; AMH anti-Müllerian hormone, AFC antral follicle count; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Data presented as means ± SD, median (25th, 75th percentile), n or n (%). Differences were analysed by Student's t-test, Mann-Whitney U-test or Chi-squared test

ascribed to the variations in design and subjects among these studies, and the inconsistent criteria for HA classification. The study conducted by Li et al. and Jie et al. began with PCOS cases with single clinical pregnancies, whereas we included those undergoing the first fresh ET cycles. And our study cohort appears to exhibit a younger age distribution, with a higher proportion of PCOS women under 35 years of age.

Given the multifaceted etiologies of miscarriages during the entire pregnancy, we distinguished the timing of miscarriage occurring. And to our knowledge, there is little research focusing on the relationship between HA and late miscarriage within the PCOS population. In Jie et al.'s study, it was observed that the late miscarriage rates were lower in PCOS patients with higher T levels (0/34 vs. 11/302) [25]. Conversely, in our study with a larger sample size, PCOS women with HA were found to be confronted with an increased risk of late miscarriage compared with those without HA. Considering the significant differences of baseline parameters between HA and non-HA women, we investigated the link between HA status and late miscarriage using PSM to minimize possible biases. In addition, multivariate logistic regression analysis was also performed. Notably, this association also persisted.

Several prior studies have recognized PCOS as an independent risk factor for late miscarriage [25, 27], yet the underlying mechanisms behind that have not been fully elucidated. Based upon above background, we postulate that PCOS might increase the risk of late miscarriage via the effect of androgen excess. An experiment on pregnant primates has shown that exogenous addition

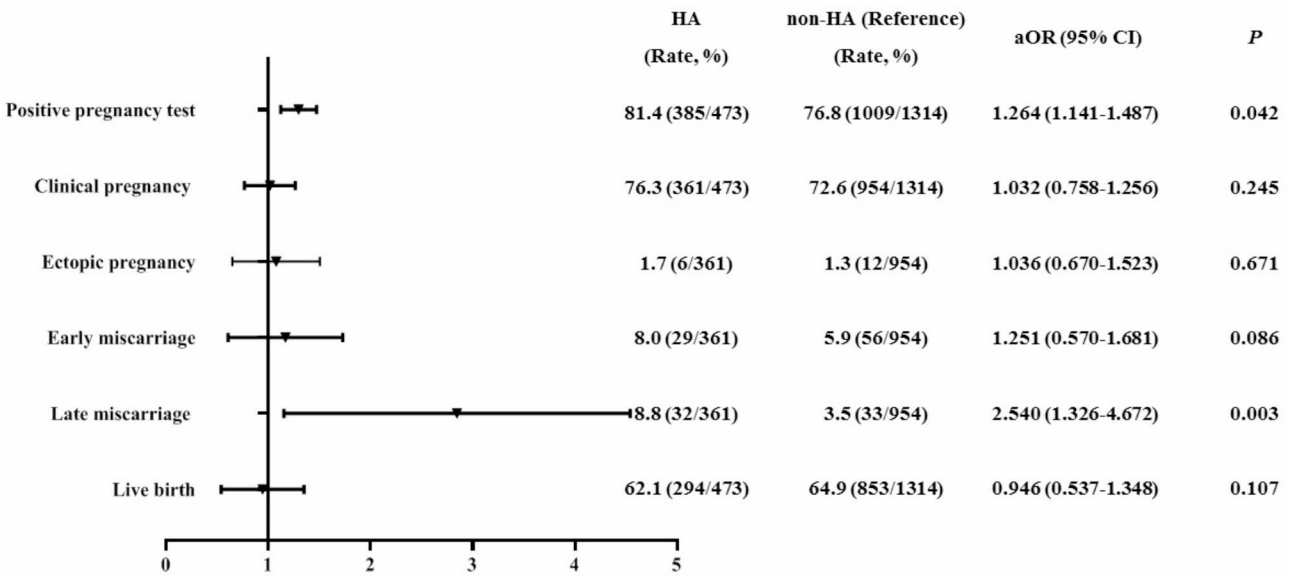

Fig. 2 Relationship between HA status and IVF/ICSI outcomes in PCOS women
Note: HA = hyperandrogenism; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; aOR = adjusted odds ratio; CI; confidence interval. Adjusted variables included female age, BMI, infertility type, fertilization method, stage of embryos transferred, and number of embryos transferred

Table 3 Baseline characteristics and specific reasons for late miscarriage in patients with PCOS

	HA *N* = 32	None-HA *N* = 33	*P*
Female age (y)	30.0 ± 3.0	30.8 ± 3.7	0.076
BMI (Kg/m^2)	24.1 ± 3.9	24.0 ± 3.6	0.163
Infertility type (%)			0.536
Primary infertility	53.1 (17/32)	45.5 (15/33)	
Secondary infertility	46.9 (15/32)	54.5 (18/33)	
Insemination method (%)			0.804
IVF	81.3 (26/32)	78.8 (26/33)	
ICSI	18.7 (6/32)	21.2 (7/33)	
Stage of embryos transferred (%)			0.378
Cleavage	62.5 (20/32)	72.7 (24/33)	
Blastocyst	37.5 (12/32)	27.3 (9/33)	
Multiple pregnancy (%)			0.875
No-Singleton	62.5 (20/32)	60.6 (20/33)	
Yes-Twin	37.5 (12/32)	39.4 (13/33)	
Reasons for late miscarriage			0.003
Cervical insufficiency	46.88 (15/32)	21.21 (7/33)	0.029
Fetal factors	15.63 (5/32)	18.18 (6/33)	0.783
Trauma factors	6.25 (2/32)	15.15 (5/33)	0.427
Unexplained factor and others	31.25 (10/32)	45.45 (15/33)	0.239

Note: PCOS, polycystic ovary syndrome; HA, hyperandrogenism; BMI, body mass index; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Data presented as means ± SD, n or n (%). Differences were analysed by Student's t-test or chi-squared test

of androgens could change patterns of myometrial contractility and lead to premature cervical dilatation, potentially triggering premature delivery [28]. Other previous studies have also suggested a potential role of androgen on cervical remodeling [29], and a higher prevalence of cervical insufficiency in pregnant women with PCOS [30, 31]. Thus, we propose a plausible mechanistic explanation for our findings: HA may exert an adverse influence on the incidence of late miscarriage via increasing the risk of cervical insufficiency in fresh IVF/ICSI-ET cycles. This hypothesis is supported by Wu et al.'s research that demonstrated the predictive value of basal serum T on the incidence of cervical insufficiency during IVF/ICSI treatment [32].

The strength of this study is an adequate sample size from a real-world single center, which could lessen potential biases and ensure the reliability of our findings. Moreover, we differentiated between early and late miscarriage, and adjusted multiple confounding variables, complementing the existing clinical evidence for the independent effect of HA on late miscarriage within the PCOS cohort. However, some limitations should also be noted. First, in this study, hyperandrogenemia was defined solely according to the serum basal T levels before COH and the cut-off values of our center, without combining with AND or other parameters, which may cause some potential biases in the diagnosis of "true HA". However, these additional parameters are not measured in our routine clinical practice, rendering them unavailable in the database. Second, the retrospective nature of the study design means that not all potential confounders related to late miscarriage, such as the history of parity, could be collected and controlled. In addition, although the proportion of singleton and twin pregnancies in HA and non-HA late miscarriage women was similar, future prospective studies should, if possible, include only singleton pregnancies. Third, even total sample in this study

is relatively large, only 65 women were included in late miscarriage group. Interpretation of results from this study should be caution due to the limited number of patients. Fourth, PCOS is known as a complex and heterogenous syndrome. Insulin resistance status, lipid metabolic status, may also play roles in cervical remodeling processes. In addition, PCOS phenotypes could not be accurately distinguished. This important information is lacking currently. Last, the prevalence and degree of HA may vary among different races. This study only included Chinese women with PCOS who underwent the first IVF/ICSI-ET treatment. Therefore, whether our findings can be extrapolated to the general infertile women with PCOS or the potential impact of HA on late miscarriage among non-PCOS women or the necessity of preconception anti-androgen therapy warrants further prospective, large-cohort studies for investigations and discussion in the future.

Conclusions

In conclusion, HA status was an independent risk factor for late miscarriage in patients with PCOS undergoing the first fresh IVF/ICSI embryo transfer. Androgen excess is postulated to play a role in late miscarriage via increased likelihood of cervical insufficiency. These results suggest that PCOS patients with HA should be better informed about their risks of late miscarriage before IVF treatment, and such individuals might benefit from enhanced awareness, close targeted surveillance, and, if necessary, interventions during pregnancy.

Abbreviations

IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
PCOS	Polycystic ovarian sydnrome
HA	Hyperandrogenism
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotrophin
PSM	Propensity-score matching
BMI	Body mass index
AMH	Anti-Mullerian hormone
AFC	Antral follicle count

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Author contributions

KY.W, ZQ.B, XF.G, F.W, MH.Z and YH.G were responsible for the conception of study. ZQ.B and KY.W contributed to design this study, statistical analyses, and write this manuscript. KY.W revised the manuscript. All the authors read and approved the final manuscript.

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Data availability

The datasets analysed during the current study are not publicly available due to ethical consideration but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study adhered to the Declaration of Helsinki regarding medical protocol and ethics, and the Ethics Review Committee of the First Hospital of Zhengzhou University approved the study(2023-KY-1049-002). Written informed consent was waived due to the retrospective nature of the study, in accordance with the national legislation and institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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