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ORIGINAL RESEARCH

Free Androgen Index Might Not Be a Perfect Predictor of Infertility Outcomes in Patients with Polycystic Ovary Syndrome Undergoing Frozen Embryo Transfer:A Retrospective Cohort Study

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Purpose: It is well known that androgen excess impairs oocyte quality, endometrial receptivity and even embryo invasion to some extent. Free androgen index (FAI) is strongly recommended to evaluate active androgen. Previous studies have showed conflicting conclusions on the effect of hyperandrogenism on the pregnancy outcomes in patients with polycystic ovary syndrome (PCOS). This study aims to analyze the influence of hyperandrogenemia based on FAI on frozen embryo transfer (FET) outcomes in patients with PCOS.

Patients and Methods: Patients diagnosed with PCOS who underwent their first FET between January 2017 and April 2022 were stratified into two cohorts using FAI, a highly recommended parameter: PCOS with hyperandrogenemia (n=73) and PCOS without hyperandrogenemia (n=255). Basic and infertility characteristics were analyzed using Student's *t*-test or chi-square ($\chi 2$) statistics. Logistic regression analysis was performed to verify whether FAI was helpful in predicting pregnancy outcomes in women with PCOS.

Results: Body mass index (BMI), total gonadotropin (Gn), basal serum follicle-stimulating hormone (bFSH), basal serum testosterone (bT), sex hormone binding globulin (SHBG), and FAI were significantly different between the two groups. (P=0.005, P<0.001, P<0.001, P<0.001, and P<0.001, respectively). However, clinical pregnancies, abortions, and live births did not differ significantly. Further regression analyses showed that FAI was not related to clinical pregnancy, abortion, or live birth rates (adjusted odds ratio (OR)=0.978, 95% confidence interval (CI)=0.911–1.050, P=0.539; adjusted OR=1.033, 95% CI=0.914–1.168, P=0.604; and adjusted OR=0.976, 95% CI=0.911–1.047, P=0.499, respectively).

Conclusion: FAI was not associated with pregnancy outcomes in patients with PCOS; that is, it did not reflect any negative effects of hyperandrogenemia on pregnancy outcomes in patients with PCOS and was not an informative clinical parameter. Therefore, more attention should be paid to the factors that influence the accuracy of FAI in reflecting androgen levels in vivo, and further discussion is needed.

Keywords: FAI, Hyperandrogenemia, PCOS, Pregnancy, FET

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 8%-13% of reproductive-aged women[1] and accounting for almost 70% of anovulatory infertility cases.[2] It is diagnosed based on the 2003 Rotterdam criteria that generate four phenotypes: hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (Phenotype A); hyperandrogenism and ovulatory dysfunction (Phenotype B); hyperandrogenism and

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polycystic ovarian morphology (Phenotype C); and ovulatory dysfunction and polycystic ovarian morphology (Phenotype D).[3]

Androgen excess is one of the three basic criteria for diagnosing PCOS, underlining its indispensability. It not only affects oocyte quality and endometrial receptivity but also leads to metabolic disorders, which, in turn, further elevate androgen levels, resulting in a vicious cycle.[4,5] This led us to hypothesize that pregnancy outcomes may be reduced in PCOS patients with hyperandrogenism (phenotypes A, B, and C). However, pregnancy outcomes in patients with PCOS with different phenotypes during assisted reproductive techniques treatment have been controversial.

Ramezanali et al reported no significant differences in clinical pregnancy, abortion, and live birth rates between 386 women with PCOS and 350 women without PCOS. However, patients with PCOS and clinical/biochemical hyperandrogenism had a significantly lower implantation rate than patients without PCOS. After adjusting for age and body mass index (BMI), PCOS phenotypes A and B were associated with decreased clinical pregnancy rates, while this association was not observed in phenotype C.[6] The data from our center suggested that PCOS was an independent risk factor for significantly lower clinical pregnancy and live birth rates as well as higher early miscarriage rates in PCOS patients with phenotypes A, B, C, and D.[7] Wang et al studied 1887 women with PCOS and 7016 controls and found that phenotypes A and D were associated with an increased risk of miscarriage after adjusting for confounding factors. However, when comparing PCOS patients with different phenotypes and patients in the control group, the clinical pregnancy rate of phenotype A was significantly higher than that of the control group and phenotype D, while the live birth rate was not statistically different among the groups.[8] Another study did not observe any differences in pregnancy outcomes with different phenotypes after FET.[9]

It is well known that PCOS is a highly heterogeneous disorder. The cutoff level for hyperandrogenemia has been inconsistent in the aforementioned studies, leading to conflicting results. Currently, the free androgen index (FAI) is highly recommended as an indicator of active androgen in vivo even from the latest 2023 International Evidence-based Guideline;[10] however, it has not been used widely in identifying hyperandrogenemia.[11,12] Up to now, cutoff value of hyperandrogenemia based on FAI has not yet reached a consensus internationally. The assay of SHBG is not routinely carried on or approved in some hospitals or doctors do not take it into consideration when it is available. Furthermore, we found that data on FAI especially on PCOS Chinese populations are limited.[13,14] Therefore, in our study, we aim to analyze the influence of hyperandrogenemia based on FAI on FET outcomes in Chinese patients with PCOS.

Materials and Methods

Study Design and Patients

This retrospective study included patients who underwent their first FET between January 2017 and April 2022 at the Reproductive Medicine Center of the First Affiliated Hospital of Sun Yat-sen University and were diagnosed with PCOS based on the 2003 Rotterdam criteria with at least two of the following items: oligoovulation and/or anovulation, clinical or chemical hyperandrogenism, and polycystic ovary morphology (PCOM). The exclusion criteria were as follows: (1) age <18 years or >40 years; (2) other endocrine secretion diseases, including thyroid disease, hyperprolactinemia, adrenal hyperplasia, and androgen-secreting tumor; (3) intrauterine adhesion or thin endometrium (endometrial thickness less than 7 mm); (4) submucosal myoma; endometrial carcinoma or atypical endometrial hyperplasia; (5) endometrial hyperplasia; (6) uterine malformations, including saddle uterus, arcuate uterus, double uterus, etc.; (7) endometriosis; (8) recurrent abortion (spontaneous abortion with the same sexual partner for two or more consecutive pregnancies); (9) repeated implantation failure (two or more instances of high-quality blastocyst or three or more instances of cleavage-stage embryo transfer without pregnancy); (10) adverse pregnancy history, such as fetal malformation; (11) systemic diseases, such as systemic lupus erythematosus, connective tissue disease, Sjogren's syndrome, etc.; (12) incomplete data records or unavailable results of the first FET; and (13) absence of viable embryo formation. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [approval no. Ethics (2020) no. 422–1]. All patients provided written informed consent to participate in the study. PCOS patients were divided into two groups based on FAI: hyperandrogenemia (HA-PCOS; FAI > 6) and non-hyperandrogenemia (NHA-PCOS; FAI < 6). The FAI threshold of 6 was determined by a large-scale national epidemiological survey conducted by the Center for Reproductive

Medicine of Peking University Third Hospital in 2017, which included data from women aged 19–45 years in 10 out of 30 provinces in mainland China [FAI =testosterone (nmol/L)/ sex hormone-binding globulin (nmol/L) × 100].

Controlled Ovarian Stimulation and in vitro Fertilization

The controlled ovarian stimulation (COS) protocol, drug dosage, and maintenance days were determined by a professor at our center according to the patient's age, ovarian reserve, and BMI. Oocytes were retrieved by ultrasound-guided transvaginal puncture 34–36 hours after intramuscular injection of human chorionic gonadotropin. The retrieved oocytes were fertilized by standard insemination or intracytoplasmic sperm injection (ICSI).

Frozen Embryo Transfer Protocol

Only the first cycle of frozen-thawed embryo transfer was included in this study, and the best-quality embryos were selected. The patient's endometrial preparation protocol was determined by a physician at our center according to the patient's menstrual cycle and history, including hormone replacement therapy and ovulation induction cycle. The luteal support protocol used intramuscular progesterone or oral Duphaston and vaginal Crinone according to patient and physician preferences. No more than three embryos were transferred.

Outcome Parameters

Clinical pregnancy, the main outcome, was defined as the presence of one or two gestational sacs and a fetal heartbeat in the uterine cavity on transvaginal ultrasound five weeks after embryo transfer. A live birth was defined as the delivery of a viable newborn after 28 weeks of gestation. An ectopic pregnancy was defined as the presence of a gestational sac outside the uterine cavity. Early miscarriage was defined as pregnancy loss after a clinical pregnancy was visible on pelvic ultrasonography before 12 weeks of gestation. Late miscarriage was defined as pregnancy loss between 13 and 28 weeks of gestation.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS ver. 26.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Numerical data conforming to a normal distribution were presented as mean ±standard deviation ($\overline{x} + s$) and compared using Student's *t*-test. Non-normally distributed data were presented as median (interquartile range [IQR]) and compared using the Mann–Whitney *U*-test. Categorical variables were presented as number (percentage) (n%) and analyzed using the chi-square test or Fisher exact probability test. Bivariate and multivariable logistic regression analysis were all performed to verify whether FAI was helpful in predicting pregnancy outcomes in women with PCOS. Some common cofounders,[15] female age, BMI, embryo stage at transfer, and endometrial preparation were included to multiple regression analysis. $P<0.05$ was considered statistically significant.

Result

Study Population

A total of 692 PCOS patients underwent in vitro fertilization (IVF)/ICSI at our hospital between January 2017 and April 2022. After rigorous screening, 364 patients were excluded for the following reasons: 316 patients did not undergo the SHBG test at our center, 27 patients lacked verified information regarding their menstrual characteristics or PCOM, one patient had incomplete FET records, seven were still pregnant, three had congenital uterine malformation, three had endometriosis, one had cervical insufficiency, two had intrauterine adhesion, one had endometrial complex hyperplasia, one had repeated implantation failure, one had recurrent abortion, and one had an abnormal female chromosome karyotype. Finally, 328 patients were included in this study. Based on the FAI, they were divided into two groups: 73 patients in the HA-PCOS group and 255 patients in the NHA-PCOS group (Figure 1).

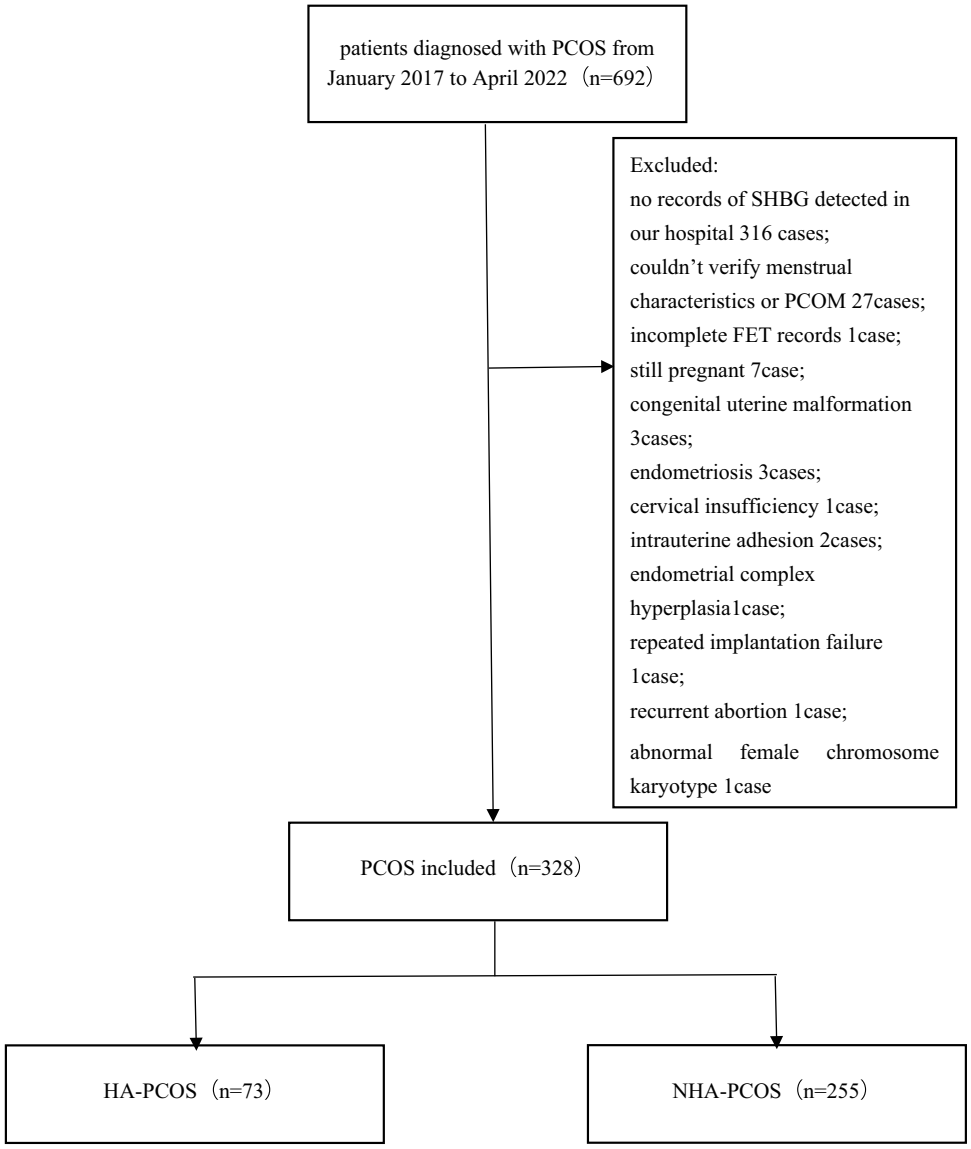

Figure 1 Flowchart of patient recruitment.

Baseline Characteristics

In terms of the baseline characteristics, the HA-PCOS group had a significantly lower basal serum follicle-stimulating hormone level (bFSH) and a significantly higher BMI compared to the NHA-PCOS group. Moreover, FAI and basal testosterone (bT) were significantly higher and SHBG was significantly lower in the HA-PCOS group. Other baseline characteristics, including female age, duration of infertility, indication combined with PCOS, type of infertility, previous spontaneous miscarriage, manual miscarriage, ectopic pregnancy, and basal luteinizing hormone (bLH) and basal estradiol (bE2) levels, were comparable between the two groups (Table 1).

Ovarian Stimulation and FET Characteristics

Among the ovarian stimulation and FET characteristics, a high FAI level was associated with a high Gn dose. Although the NHA-PCOS group tended to transfer a greater number of good-quality embryos, this difference was not statistically significant. There were no significant differences in the remaining ovarian stimulation or FET characteristics (Tables 2 and 3).

Table 1 Baseline Characteristics and Hormonal Profile Between Groups

Characteristic	HA-PCOS (n=73)	NHA-PCOS (n=255)	*P* value
Age (year)	30(28, 31)	29(27, 32)	0.777
Duration of infertility (year)	3(2, 5)	3(2, 5)	0.260
Indication combined with PCOS			0.542
PCOS only	24 (32.9%)	88 (34.5%)	
PCOS + tubal factor	26 (35.6%)	106 (41.6%)	
PCOS + male factor	19 (26%)	52 (20.4%)	
PCOS + other	4 (5.5%)	9 (3.5%)	
Type of infertility			0.483
Primary infertility	49(67.1%)	182(71.4%)	
Secondary infertility	24(32.9)	73(28.6%)	
Previous spontaneous miscarriage	8(11.0%)	27(10.6%)	0.982
Previous manual miscarriage	11(15.1%)	26(10.2%)	0.246
Previous ectopic pregnancy	6(8.2%)	17(6.7%)	0.647
bFSH (IU/L)	4.65(3.93, 5.22)	4.98(4.40, 5.82)	0.005*
bLH (IU/L)	6.18(4.81, 8.25)	6.19(3.87, 9.38)	0.77
bE2 (pg/mL)	32(24, 43)	34(25, 47)	0.119
bT (ng/mL)	0.55(0.49, 0.67)	0.44(0.35, 0.56)	<0.001*
SHBG (nmol/l)	20.90(15.50, 28.20)	58.20(40.50, 93.65)	<0.001*
FAI	8.54(6.94, 11.57)	2.73(1.63, 4.02)	<0.001*
BMI (kg/cm^2)	24.81±2.83b	21.51(19.86, 23.81)	<0.001*

Note: *Indicate significant difference (*P*<0.05).
Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Table 2 Ovarian Stimulation Characteristics Between Groups

Characteristic	HA-PCOS (n=73)	NHA-PCOS (n=255)	*P* value
Fertility method			0.206
IVF	49	188	
ICSI	20	62	
IVF+ICSI	4	5	
COS protocol			0.943
Antagonist protocol	66	225	
Long protocol	6	23	
Other	1	7	
Total Gn (IU)	1500(1200, 1925)	1212(1050, 1530)	<0.001*
Days of Gn use	9(8, 10)	8(8, 10)	0.148
Oocytes retrieved	23(16, 32)	21(16, 29)	0.381
Normal fertilized oocytes	12(10, 22)	13(10, 19)	0.901
Number of viable embryos	7(1, 10)	7(4, 11)	0.931
Number of top-quality embryos of D3	5(2, 9)	5(3, 9)	0.798

Reproductive Outcomes of FET

All the assessed reproductive outcomes were from the first FET cycle. In the logistic regression analysis, FAI was not associated with the outcomes of clinical pregnancy, miscarriage, or live birth. However, an increase in FAI appeared to cause a decline in the clinical pregnancy and live birth rates (adjusted odds ratio [aOR]=0.978, 95% confidence interval [CI] (0.911, 1.050) and aOR=0.976, 95% CI (0.911, 1.047), respectively) and an

Table 3 Characteristics in the First FET Cycle Between Groups

Characteristic	HA-PCOA (n=73)	NHA-PCOS (n=255)	*P* value
Year of FET			0.128
2017–2019	29(39.7%)	127(49.8%)	
2020–2022	44(60.3%)	128(50.2%)	
Endometrial preparation			0.349
Hormone therapy	60	194	
Mild stimulation	11	42	
Other	2	19	
Endometrial thickness(mm)	9.6(8.8, 10.8)	9(8.3, 10)	0.105
E2 level at the time of FET	114(90, 159)	125(93.5, 186)	0.218
Number of embryos transferred			0.131
1	55(75.3%)	212(83.1%)	
2	18(24.7%)	43(16.9%)	
Embryo stage at transfer			0.489
Day 3	13(17.8%)	37(14.5%)	
Day 5/6	60(82.2%)	218(83.5%)	
Number of top-quality embryo	72(78.3%)	255(85.6%)	0.096
Embryo frozen days	91(73, 119)	90(72, 125)	0.735

Note: Number of transferred embryos: HA-PCOS=92; NHA-PCOS=298.

increase in the miscarriage rate (aOR=1.029, 95% CI (0.911, 1.161)); nevertheless, the differences were not statistically significant (Tables 4 and 5). One patient in the NHA-PCOS group was diagnosed with an ectopic pregnancy (Table 4).

Table 4 Reproductive Outcomes in the First FET Cycle Between Groups

Characteristic	HA-PCOS (n=73)	NHA-PCOS (n=255)	*P* value
Implantation	46 (50.0%)	166 (55.7%)	0.337
Clinical pregnancy	44 (60.3%)	162 (63.5%)	0.612
Miscarriage	8 (17.8%)	25 (15.4%)	0.704
Early miscarriage	7 (15.9%)	22 (13.6%)	0.736
Late miscarriage	1 (2.2%)	3 (3.1%)	1.000
Ectopic pregnancy	0 (0.0%)	1 (0.4%)	1.000
Live birth	36 (80%)	136 (84%)	0.532

Table 5 Logistic Regression of FAI as a Continuous Variable on Pregnancy Outcomes

Parameters	OR(95% CI)	P value	aOR(95% CI)	*P* value
Clinical pregnancy	0.975(0.916, 1.039)	0.436	0.978(0.911, 1.050)	0.539
Miscarriage	1.065(0.958, 1.185)	0.244	1.033(0.914, 1.168)	0.604
Early miscarriage	1.062(0.956, 1.180)	0.260	1.029(0.911, 1.161)	0.650
Late miscarriage	0.980(0.719, 1.337)	0.900	0.931(0.653, 1.326)	0.692
Live birth	0.964(0.906, 1.025)	0.242	0.976(0.911, 1.047)	0.499

Note: Analyses were adjusted for female age, BMI, embryo stage at transfer, and endometrial preparation.
Abbreviations: OR, Odds Ratio; aOR, adjusted Odds Ratio; CI, Confidence Interval.

Discussion

In a rigorously defined cohort of patients with PCOS, our research did not find a significant association between FAI and reproductive outcomes such as clinical pregnancy, miscarriage, and live birth. Given that the gold-standard tests for measuring androgen levels, such as equilibrium dialysis and liquid chromatography–tandem mass spectrometry techniques, are time-consuming methodologies and require sophisticated equipment, FAI is recognized as a relatively accurate and informative parameter for assessing hyperandrogenemia according to the Rotterdam consensus[11] and is also highly recommended in China. However, in most studies, hyperandrogenemia depended on total testosterone levels. Therefore, we chose FAI, a superior indicator of androgen activity, to analyze whether hyperandrogenemia affects fertility outcomes in patients with PCOS.

In addition, our findings hold clinical significance. The results demonstrated that bFSH levels in the HA-PCOS group were lower than those in the other group, which is consistent with the recognition that there is a hypothalamic-pituitary-ovarian axis dysfunction in PCOS patients.[16–18] Besides, bLH levels and LH/FSH ratios are similar in the two groups, which is contrary to many studies showing that women with PCOS had elevated serum LH concentrations and LH/FSH ratios that could be caused by androgen.[19–21] However, a clinical study also found that LH levels were lower in obese or overweight patients with PCOS than in patients within a healthy BMI range.[22] This is in line with the findings of this study that show that the BMI of the HA-PCOS group was significantly higher than that of the NHA-PCOS group. Hyperandrogenism, the main hallmark of PCOS, plays a pivotal pathogenic role in metabolic dysfunction.[23] Most studies have demonstrated that total and free testosterone levels are positively correlated with abdominal fat accumulation in women with PCOS. Testosterone facilitates visceral fat accumulation by inhibiting lipolysis and promoting lipogenesis.[24] Higher BMI observed in the HA-PCOS group implies that higher Gn doses based on body weight are required to achieve a therapeutic effect.[25,26] However, higher Gn doses are associated with an increased risk of ovarian hyperstimulation syndrome, a severe complication that should be avoided during COS. In addition, women in the HA-PCOS group not only suffered from psychological stress caused by infertility but also received increased doses of drugs, which inevitably increased the economic burden. Therefore, PCOS patients with hyperandrogenism should be paid more attention.

Our results seem to indicate that FAI had no clinical predictive value for reproductive outcomes in women with PCOS undergoing FET, which was in accordance with the results of a previous study[9] but not with those of another study that showed that patients with PCOS and androgen excess undergoing IVF/ICSI-ET had a lower live birth rate and a higher abortion rate.[27] However, another study also showed similar clinical pregnancy and live birth rates in different phenotypes,[28] indicating that androgen excess did not influence the outcomes, while their hyperandrogenemia depended on total testosterone. In contrast to previous reports showing that a lower FAI in PCOS patients with ovulation induction had a higher chance of pregnancy or live birth,[29,30] clinical pregnancy or live birth in our patients did not seem to be related to the FAI level. This might be attributed to the differences as follows. Firstly, subjects were not the same. They investigated PCOS not responding to clomiphene citrate treatment or oligomenorrhea/amenorrhea was necessary as diagnostic criteria for PCOS. Secondly, endometrium preparations were inconsistent. Thirdly, others' studies contained multiple treatment cycles, ours only included the first cycles in order to reduce confounding factors.

Androgen excess is one of the three fundamental diagnostic criteria for PCOS and plays an indispensable role in its pathophysiology. It not only harms follicular development and oocyte quality but also influences endometrial receptivity, which is detrimental to the development of embryos and the success of live births.

Hyperandrogenism may affect oocytes directly or indirectly through granulosa and theca cells via multiple signaling pathways. An anti-apoptotic protein of the heat shock protein (HSP) family, HSP27, is significantly reduced in the oocytes of women with PCOS.[31] Studies have shown that excessive androgens activate ER stress in granulosa and cumulus cells;[32,33] change autophagy-related markers;[34] and disturb mitochondrial function[35] and many metabolic pathways,[36] impairing oocyte maturation, follicle formation, and ovulation. In a prenatally androgenized animal model, elevated testosterone altered the expression of a series of genes encoding for extracellular matrix components and their signaling pathways[37] in adult ovaries or reduced the expression of CYP17A1[38] in theca cells.

Regarding endometrial receptivity, increasing evidence supports that androgen receptor (AR) in the endometrium is regulated throughout the menstrual cycle and during pregnancy, suggesting its important role in embryo implantation, pregnancy maintenance, and disease incidence.[39] Reduced expression of HOXA-10, a receptivity marker, can also be

detected in the endometrium of PCOS patients. It has been shown that testosterone downregulates the expression of HOXA-10 through the AR pathway[40] and decreases the levels of PRL, IGFBP-1, and other decidualization-related markers.[41] Lee et al found that abnormal glucose metabolism was also detected in the endometrium of patients with PCOS and that both hyperinsulinemia and high androgen levels could lead to abnormal glucose metabolism, suggesting that high androgen levels are not conducive to the establishment of a normal pregnancy.[42]

Interestingly, this study did not observe any negative effects of hyperandrogenemia on pregnancy outcomes. Several factors may contribute to these findings and are worthy of attention: First, there are performance issues with regard to the precision and accuracy of the immunoassay of serum testosterone; therefore, rapid improvements in or simplification of equilibrium dialysis and liquid chromatography–tandem mass spectrometry technique for accurate clinical application is crucial. Second, the level of serum testosterone can be reduced by some medications, such as the contraceptive pill Diane-35, antidiabetics metformin, liraglutide,[43] or traditional Chinese medicine. For example, several studies have shown that metformin lowers testosterone levels in women with PCOS independently as well as in a manner dependent on insulin sensitivity.[44–46] Caution should be undertaken as SHBG concentrations can be easily and dramatically altered, which has a significant impact on FAI. Pathologies such as hyperinsulinemia, obesity, and metabolic syndrome can change SHBG levels.[47–49] Even resistance training[50] or time-restricted feeding increases SHBG.[51] Some studies have shown that vitamin D supplementation might have an effect on FAI,[52] although the evidence is inconclusive. Most patients trying to conceive often consume vitamin D, which might make us notice this kind of situation. Since this was a retrospective study, the menstrual cycle phase during which the blood was collected or the fasting status was unclear, which may affect FAI. It is recommended that specimens be collected during the early follicular phase[53] as androgen levels fluctuate throughout the menstrual cycle.[54] Therefore, it is important to thoroughly inquire and record patient history and collect blood samples when appropriate. In addition, it is possible, although unlikely, that this study included a small proportion of non-PCOS infertile patients who only had a short period of irregular menstruation and may contain unknown or more complex infertility factors that interfered with the results.

Strength and Limitation of the Study

The strength of this study lies in the use of a highly recognized parameter to reflect serum-free testosterone (FAI) and an appropriate FAI threshold to reflect the hyperandrogenemia has not yet been determined so far and the value of FAI in predicting infertility outcomes remains controversial. The limitation of this study is its retrospective design; therefore, confounding bias cannot be completely excluded, and clinical hyperandrogenism cannot be included. Although patients with PCOS were rigorously selected, the sample size was insufficient, decreasing the generalizability of our conclusions and limiting analysis of other critical metabolic parameters. Further studies are needed to determine the extent to which androgen levels require interventions in patients with PCOS.

Conclusion

In a word, FAI did not accurately reflect the potential negative effects of hyperandrogenemia on pregnancy outcomes in PCOS patients. Factors that influence the accuracy of FAI should be paid more attention. Further studies are needed to determine the extent to which androgen levels require interventions in patients with PCOS.

Abbreviations

PCOS, Polycystic ovary syndrome; FAI, Free androgen index; FET, Frozen embryo transfer; BMI, Body mass index; COS, Controlled ovarian stimulation; IVF, In vitro fertilization; ICSI, Intracytoplasmic sperm injection; bFSH, Basal serum follicle-stimulating hormone; bLH, Basal serum luteinizing hormone; bE2, Basal serum estradiol; bT, Basal serum testosterone; HA, Hyperandrogenemia; NHA, Non- hyperandrogenemia; SHBG, Sex hormone binding globulin; Gn, Gonadotropin; HSP, Heat shock protein; AR, Androgen receptor.

Data Sharing Statement

The data that support the finding of this study are available on request from the corresponding author.

Ethics Approval and Consent to Participate

The present study received approval from the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University [approval no. Ethics (2020) no. 422-1]. All procedures were carried out in accordance with the relevant guidelines and regulations. Furthermore, informed consent was obtained from all participants before the study. This study complies with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the reported work in terms of conception, study design, execution, acquisition of data, analysis, and interpretation; took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

Senlan Wang and Jifan Tan are co-first authors for this study. The authors declare that they have no conflicts of interest in this work.

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