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ARTICLE

HORMONAL PROFILE AND REPRODUCTIVE POTENTIAL OF POLYCYSTIC OVARY SYNDROME (PCOS) WOMEN IN INDONESIA

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ABSTRACT

Our study aims to scrutinize the hormonal and laboratory profile of women with polycystic ovary syndrome (PCOS) in Indonesia. A computerized database of 120 diagnosed PCOS women and 120 controls was retrospectively reviewed and analyzed. According to analysis, the concentration of anti-Müllerian hormone (AMH) and basal luteinizing hormone (LH) were significantly more elevated in the PCOS group than in the control group (6.77 vs. 2.05, P<0.001; and 6.8 vs. 5.3, P<0.001, respectively). The level of basal follicle-stimulating hormone (FSH) was significantly lower in the PCOS group (5.83 vs. 7.86; P<0.001). After an IVF cycle, PCOS women had a significantly higher number of retrieved oocytes and the number of mature oocytes compared to controls (18 vs. 8, P<0.001; 12 vs. 6, P<0.001). The number of fertilizations, number of cleavages, and number of top-quality cleavages were also higher in the PCOS group than in the control group (10 vs. 4, P<0.001; 10 vs. 4, P<0.001; 4 vs. 2, P<0.001). At the blastocyst stage, patients with PCOS had a higher number of blastocysts and top-quality blastocysts than control (9 vs. 4, P<0.001); 4 vs. 1, P<0.01). However, the clinical pregnancy was significantly higher in the control group than in the PCOS group (52.6% vs. 16.7%; P = 0.045).

Keywords: Hormonal profile; Laboratory profile; Polycystic ovary syndrome

АБСТРАКТ

Цель нашего исследования - тщательно изучить гормональный и лабораторный профиль женщин с синдромом поликистозных яичников (PCOS) в Индонезии. Была ретроспективно изучена и проанализирована компьютеризированная база данных 120 женщин с диагностированным PCOS и 120 контрольных женщин. По данным анализа, концентрация антимюллерова гормона (АМГ) и базального лютеинизирующего гормона (ЛГ) была значительно выше в группе PCOS, чем в контрольной группе (6,77 против 2,05, P<0,001; и 6,8 против 5,3, P<0,001, соответственно). Уровень базального фолликулостимулирующего гормона (ФСГ) был значительно ниже в группе ПКОС (5,83 против 7,86; P<0,001). После проведения цикла ЭКО у женщин с PCOS было значительно выше количество извлеченных ооцитов и количество зрелых ооцитов по сравнению с контрольной группой (18 против 8, P<0,001; 12 против 6, P<0,001). Количество оплодотворений, количество расщеплений и количество расщеплений высшего качества также было выше в группе PCOS, чем в контрольной группе (10 против 4, P<0,001; 10 против 4, P<0,001; 4 против 2, P<0,001). На стадии бластоцисты у пациенток с ПКОС количество бластоцист и бластоцист высшего качества было выше, чем в контроле (9 против 4, P<0,001; 4 против 1, P<0,01). Однако клиническая беременность была значительно выше в контрольной группе, чем в группе ПКОС (52,6 % против 16,7 %; P = 0,045).

Ключевые слова: Гормональный профиль; Лабораторный профиль; Синдром поликистозных яичников

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women of childbearing age. According to the Rotterdam criteria, PCOS was diagnosed by the presence of two out of three features of androgen excess, ovulatory dysfunction, and polycystic ovaries.[1] Common symptoms of women with PCOS include anovulatory menstrual cycles, infertility, hirsutism, and obesity. The global prevalence of PCOS is estimated between 4% and 20%. In Indonesia, more than seven million cases were reported in early 2000 and are projected to increase every year.[2] The exact pathogenesis of the disease remains unknown. However, a large amount of evidence signifies that PCOS might be a multigenic disorder with a complex genetic, epigenetic, and environmental interaction.[3] Dysregulation in the hypothalamic-pituitary axis is recognized as a critical pathophysiology underlying PCOS that plays a role in the evolution of the disease and is associated with the development of the syndrome.[4,5]

The gonadotropin-releasing hormone (GnRH) is normally secreted in the pulse by the hypothalamus and stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on the theca cells to induce androgen synthesis while FSH promotes aromatase production in the granulosa cells for androgen conversion into estradiol. In the PCOS state, the GnRH release is enhanced due to poor negative feedback suppression of GnRH pulsatility by estradiol and progesterone. Consequently, the LH pulse is raised, and ovarian androgen production is elevated. Due to this neuroendocrine dysregulation, PCOS patients have a significantly elevated level of LH and decreased FSH compared to controls.[6] Moreover, the anti-Müllerian hormone (AMH) level in PCOS women is significantly higher as compared to the control group.[7,8] The deficiency of FSH subsequently disrupts follicle selection and accumulates small and pre-antral follicles leading to an anovulatory cycle. As a result, women with PCOS had a lower natural pregnancy rate and therefore often underwent assisted reproductive technology such as IVF to conceive.[9]

Although PCOS is highly related to reproductive morbidity, PCOS women are known to have a higher risk of developing insulin resistance, diabetes mellitus, hypertension, lipid abnormalities, metabolic syndrome, cancer, and cardiovascular disease.[3] It was also revealed that 75% of PCOS women remain undiagnosed when visiting their doctor.[10] Moreover, women with PCOS have a reduced IVF success rate than a normal healthy woman.[11] Therefore, early recognition of PCOS and evaluation of IVF outcomes of PCOS women are crucial to prevent those life-threatening complications and to depict the reproductive potential after the IVF cycle. However, there is a lack of reports on that information in Indonesia's population. As such, this present study aims to evaluate the hormonal profile and laboratory outcomes of women with PCOS in Indonesia.

The present study has several advantages over previously published retrospective studies of the same area which has a large number of samples and involves subjects from multiethnicity. This solid data set will make it relatively representative of PCOS women in Indonesia thus envisioned to become a reliable basis for improved diagnosis and treatment strategy of PCOS.

MATERIAL AND METHODS

Study population

This retrospective cohort study was conducted using a computerized database in Morula IVF Jakarta Clinic, Jakarta, Indonesia. PCOS patients were selected based on the Rotterdam criteria[12], by which the disease was diagnosed by the presence of two out of three following criteria: oligo-anovulation, hyperandrogenism, and polycystic ovaries. Individuals with a record of under medications or with a condition that has a significant impact on the endocrine system were excluded from the study. 120 PCOS patients (n=120) who underwent in vitro fertilization cycle between 1 January 2020 and 30 June 2023 were randomly selected and their medical

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records were reviewed. 120 healthy women control group (n=120) was also selected. The sample size was calculated using Cochran's formula as described previously.[13]

Blood sample collection, hormone measurement, and ovarian stimulation

On the third day of the menstrual cycle, a blood sample was collected following standard phlebotomy protocol to evaluate the baseline hormone levels. Hormone concentration was measured by the electrochemiluminescent immunoassay. Following hormone level determination, patients underwent mild, agonist, or antagonist ovarian stimulation protocol as described previously.[14] In all protocols, rhCG was given when the diameter of at least two leading follicles reached a size of ≥18 mm.

Oocyte retrieval and maturation check

Oocytes were retrieved by transvaginal ultrasound-guide at 36 hours after hCG trigger. After aspiration, cumulus-oocyte complexes (COCs) were washed in G-MOPS Plus medium (Vitrolife, Sweden) and incubated in culture medium for 3 hours under 6% CO2 at 37°C covered with paraffin oil (Ovoil; Vitrolife). Upon incubation, cumulus cells were mechanically removed by pipetting with 80 IU hyaluronidase (Hyase™-10x, Vitrolife, Sweden). The denuded oocytes were then analyzed under an inverted microscope at 200x magnification to determine the nuclear maturation stage. Mature oocytes were identified by the presence of the first polar body in the perivitelline space.

Insemination

All mature oocytes were inseminated by ICSI or IMSI as described previously.[14] Briefly, oocytes were placed in a 5 µL drop of G-MOPS Plus medium (Vitrolife, Sweden) covered with mineral oil (Ovoil, Vitrolofe, Sweden) on a petri dish (ICSI: Nunc IVF Dish, Thermo Scientific, USA; IMSI: Fluorodish, WPI, USA). A single motile spermatozoon was immobilised by contacting its tail with an injection pipette (TPC; CooperSurgical Fertility). The irreversibly immobilised spermatozoon was then aspirated into the pipette and injected into the oocyte with the 12 o'clock polar body orientation, starting from the 3 o'clock position.

Fertilization assessment, embryo grading, and transfer

After 17+2 hours after the insemination, fertilization was assessed by the appearance of two distinct pronuclei. Only oocytes that showed two pronuclei and the extrusion of the second polar body were considered normally fertilized. Inseminated oocytes were then cultured in G1 medium (Vitrolife, Sweden) for three days and transferred into G2 (Vitrolife, Sweden) medium for another two or three days in a humidified incubator at 37°C, 6% CO2, and 5% O2. The quality of cleavage-stage embryos was determined by the degree of fragmentation, the quantity of blastomeres, and the symmetry of the blastomeres. The quality of blastocyst-stage embryos was judged based on blastocyst cavity expansion, trophectoderm, and inner cell mass.[15] Good-quality embryos were then transferred to the uterus and the clinical pregnancy was determined by 2 weeks after a positive biochemical pregnancy test.

Statistical analysis

The statistical analysis was carried out with a 95% confidence level using IBM Statistical Package for Social Sciences (SPSS) software version 20 (Chicago, USA). Descriptional statistics were used to summarise the sample population. The Chi-square test was used to examine categorical data, which were represented by the number of individuals (n) and the percentage (%). The Mann-Whitney test was employed to evaluate numerical variables, which were presented as mean ± SD or, if relevant, median and interquartile range (Q1 and Q3). To adjust for possible confounders, we used multiple linear regression.

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RESULT

A total of 120 women diagnosed with PCOS and 120 healthy women were enrolled in this study. The clinical parameters of the subjects are summarized in Table 1. The mean age of participants was 33 (30,35) in the PCOS group and 36 (33,40) in the control group (P<0.001). The infertility duration and body mass index in the PCOS and the control group were 5 years and 6 years (P = 0.008) and 22.80 and 24.57 (P=0.017), respectively. In terms of type of infertility, 101 (84.20%) women had primary infertility, and 19 (15.80%) women had secondary infertility in the PCOS group. In the control group, 99 (82.50%) women were diagnosed with primary infertility, and 21 (17.50%) women were secondary infertility sufferers (P = 0.863). Women in the PCOS group had significantly higher antral follicle count (AFC) than in the control group (19 (16,23) vs. 10 (6,12); P<0.001).

Table 1. Clinical characteristics of study participants

Characteristics	Study Group		P-Value
	PCOS	Control	
Female age (years)	33 (30,35)	36 (33,40)	<0.001
Infertility duration (years)	5 (3,7)	6 (3,9)	0.008
Body Mass Index (kg/m2)	22.80 (20.57,25.63)	24.57 (21.45,27.78)	0.017
Type of Infertility [n (%)]			
Primary	101 (84.20%)	99 (82.50%)	0.863
Secondary	19 (15.80%)	21 (17.50%)	
AFC	19 (16,23)	10 (6,12)	<0.001

Data are presented as median (q1, q3), and Mann-Whitney test is used. Data are presented as the number of subjects and percentage [n (%)], and Chi-square tests are used for the categorical variable.

As shown in Table 2, the findings of the investigation into the hormonal parameters and the profile of ovarian stimulation are presented. As can be seen in the table, the levels of adrenocorticotropic hormone (AMH) and basal luteinizing hormone (LH) were discovered to be significantly higher in the group that was diagnosed with polycystic ovarian syndrome (PCOS) in comparison to the group that served as the control. In particular, the levels of AMH were 6.77 (5.85,8.52) compared to 2.05 (1.03,3.11), and the p-value was shown to be positive. Upon comparing the levels of basal FSH in the PCOS group to those in the control group, it was seen that the PCOS group exhibited a significantly lower level (5.83 (5,6.81) against 7.86 (6.61,9.29); the statistical significance of this finding was determined to be less than 0.001). There was not a significant difference in the levels of basal estradiol and progesterone between the group with PCOS and the group that served as the control (P = 0.098 and P = 0.661, respectively). On the other hand, the PCOS group experienced a significantly lower beginning dose and total gonadotropin utilization during ovarian stimulation in comparison to the control group (225 (150,300) versus 300 (300,300), with a p-value of less than 0.001; 1800 (1500,2400) versus 2438 (2400,2700), with a p-value of less than 0.001 respectively). The levels of progesterone and estradiol on the trigger day were significantly higher in the group with polycystic ovary syndrome (PCOS) compared to the control group (5900 (3319,7825 vs. 2288 (1582,3113), P<0.001; 0.98 (0.72,1.4) vs. 0.53 (0.27,0.76), P<0.001 respectively). In contrast, the group that was diagnosed with polycystic ovary syndrome (PCOS) had a significantly higher concentration of estradiol compared to the group that was used as a control. Stimulation was given to both the group with PCOS and the control group for a period of nine days, which was comparable to the length of time that the trial was conducted.

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Table 2. Comparison of hormonal and stimulation profile in PCOS and the control group

Parameters	Study Group		P-Value
	PCOS	Control	
Basal LH (mIU/mL)	6.8 (5.00,9.33)	5.3 (4.2,6.8)	<0.001
Basal FSH (mIU/mL)	5.83 (5.00,6.81)	7.86 (6.61,9.29)	<0.001
AMH (ng/mL)	6.77 (5.85,8.52)	2.05 (1.03,3.11)	<0.001
Basal Estradiol (pg/mL)	34.1 (26.8,42.53)	36.41 (28.12,48.72)	0.098
Basal Progesterone (ng/mL)	0.18 (0.07,0.28)	0.15 (0.07,0.26)	0.661
Starting dose (IU)	225 (150,300)	300 (300,300)	<0.001
Stimulation duration (days)	9 (8,9)	9 (8,9)	0.899
Total Gonadotropin used (IU)	1800 (1500,2400)	2438 (2400,2700)	<0.001
Estradiol on trigger day (pg/mL)	5900 (3319,7825)	2288 (1582,3113)	<0.001
Progesterone on trigger day (ng/mL)	0.98 (0.72,1.40)	0.53 (0.27,0.76)	<0.001

Data are presented as median (q1,q3), and Mann-Whitney test is used. Data are presented as the number of subjects and percentage [n (%)], and Chi-square tests are used for the categorical variable.

In terms of laboratory outcomes, we found an interesting result in which the PCOS group had a significantly higher number of retrieved oocytes and number of mature oocytes as compared to the control group (18 (13,24) vs. 8 (5,12), P<0.001; 12 (9,18) vs. 6 (4,9), P<0.001). The number of fertilizations, the number of cleavages, the number of top-quality cleavages were also higher in the PCOS group than in the control group (10 (6,14) **vs.** 4 (2,7), P<0.001; 10 (6,14) vs. 4 (2,7), P<0.001; 4 (2,7) vs. 2 (1,3), P<0.001). At the blastocyst stage, the number of blastocyst and the number of top-quality blastocysts were significantly higher in the PCOS group compared to the control group (9 (6,12) **vs.** 4 (1,6), P<0.001); 4 (1,6) vs. 1 (0,3), P<0.01). The number of embryo transfers was comparable in both groups but the clinical pregnancy in the control group was significantly higher than in the PCOS group (20/18 (52.6%) vs. 2/10 (16.7%); P = 0.045).

Table 3. Comparison of laboratory outcome in PCOS and the control group

Laboratory Outcomes	Study Group		P-Value
	PCOS	Control	
Number of retrieved oocytes	18 (13,24)	8 (5,12)	<0.001
Number of mature oocytes	12 (9,18)	6 (4,9)	<0.001
Number of fertilizations	10 (6,14)	4 (2,7)	<0.001
Number of cleavages	10 (6,14)	4 (2,7)	<0.001
Number of top-quality cleavages	4 (2,7)	2 (1,3)	<0.001
Number of blastocysts	9 (6,12)	4 (1,6)	<0.001
Number of top-quality blastocysts	3 (2,6)	1 (0,3)	<0.001
Number of embryo transfer	2 (1,2)	2 (1,2)	0.442
Clinical Pregnancy (n=50)	2/10 (16.7%)	20/18 (52.6%)	0.045

Data are presented as median (q1, q3), and Mann-Whitney test is used. Data are presented as the number of subjects and percentage [n (%)], and Chi-square tests are used for the categorical variable

DISCUSSION

Our study demonstrated that the level of basal LH and AMH in PCOS subjects is significantly higher than in the control group. The level of basal FSH is significantly lower in the PCOS group whereas the level of basal estradiol and progesterone is comparable in all examined groups. In terms of laboratory outcome, PCOS subjects had a higher number of retrieved oocytes, mature oocytes,

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fertilization, cleavage, number of top-quality cleavages, number of blastocysts, and number of top-quality blastocysts. The number of embryo transfers was similar among the group but the control group had a significantly higher clinical pregnancy rate than the PCOS group. PCOS is a hormonal imbalance prevalent in women of reproductive age.[16] The mean age of PCOS subjects in our study was 33 years old with a BMI of 22.80. Our finding was in line with the previous study in which the average age of women with PCOS was reported younger than healthy women which suggested might be associated with normalized ovarian ultrasound features with increasing age due to follicular cohort physiological decline.[13,17]

In contrast to a previous study[18], PCOS women in our study were normoweight. Although patients with PCOS are likely obese, some patients have a normal body mass index (BMI; ≤25 kg/m^2).[19] Several data suggested that Asian PCOS patients had lower BMI compared to other populations which might attributed to differences in lifestyle.[10,20] In terms of hormonal profile, our finding agrees previous report by which Wiweko et al.[17] showed that the level of LH and AMH among PCOS patients were higher than in the control and the level of FSH was lower as compared to the control. The exaggerated GnRH pulse due to the neuroendocrine hallmark of PCOS promotes LH hypersecretion which leads to elevated LH levels over FSH levels. The insufficiency of FSH, whose role is to recruit and stimulate follicular growth, subsequently disrupts follicular selection and accumulates small and pre-antral follicles. AMH, which is produced by antral follicles, is consequently elevated[9] and therefore describes the finding of our study. AMH has been proposed as a diagnostic marker for PCOS given its circulating level in the blood is not affected by the menstrual cycle and hormone drug use.[21]

During IVF, PCOS women usually have a suboptimal cycle outcome as previously reported.[22,23] However, our study found that the number of retrieved oocytes, mature oocytes, and fertilization was higher in the PCOS group. This finding was consistent with a previous report as Ciepiela et al.[24] demonstrated that the total number of retrieved oocytes and mature oocytes was significantly higher in women with PCOS compared to the non-PCOS group and Su Liu et al.[25] found a higher fertilization rate among PCOS women than in control. PCOS women typically had elevated LH/FSH ratio due to excessive LH production. Wiser et al.[26] reported that women with an LH/FSH ratio >1.5 had a significantly higher number of retrieved oocytes and mature oocytes than those with a lower ratio. Moreover, Chung et al.[27] suggested that a higher BMI was associated with decreased insulin sensitivity and a decline in the number of mature oocytes from PCOS women was reported to be a part of insulin resistance.[22] We assumed that the higher number of recovered and mature oocytes in the PCOS group of the present study was probably attributed to the raised LH/FSH ratio and normal BMI. Recovering more oocytes and attaining higher mature oocytes then leads to a higher subsequent fertilization rate.

In terms of embryo development, it was suggested that PCOS does not affect early embryonic development.[28–30] Nevertheless, we depict that the number of cleavages, blastocysts, and top-quality blastocysts was significantly higher in the PCOS group. In accordance, a morphokinetic study demonstrated that embryos from PCOS women had faster growth until the 9-cell stage with the highest at t7, t8, and t9.[31] A time-lapse data of 459 zygotes further suggested that the blastocyst rate, expansion rate, and implantation rate of faster-cleaving embryos are higher than slower-cleaving embryos.[32] We hypothesized that the higher cleavage rate in the PCOS group of the present study might be associated with its faster development which in turn leads to a higher number of blastocysts and top-quality blastocysts. The premise seems to be consistent as a study done by Lemmen et al.[33] found that early cleavage was significantly correlated with remarkably better embryo development and implantation. However, a significant rise in LH level seems to

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have a detrimental effect on subsequent embryo development represented by the lowered clinical pregnancy rate of the PCOS group in this study. Huirne et al.[34] demonstrated that a significant rise or decrease in LH levels will reduce the clinical pregnancy rate.

CONCLUSION

Our study demonstrated that PCOS women in the Indonesian population presented elevated LH levels, increased AMH levels, and decreased FSH levels. Following the IVF cycle, the majority of the patients had a higher number of retrieved oocytes, number of mature oocytes, number of fertilizations, number of cleavages, number of top-quality cleavages, number of blastocysts, and number of top-quality blastocysts but lower clinical pregnancy rate.

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DECLARATIONS

Author Contribution. AMS: conceptualization, study design, manuscript preparation, and manuscript final draft. TAW: data collection, data analysis, statistical analysis. NMP: laboratory work, data analysis. AD: supervision, manuscript review. A: supervision, manuscript review. AB: supervision, funding. HF: supervision, manuscript review. AB: conceptualization, supervision, funding.

Conflict of interest. The authors declare no conflict of interest.

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