ORIGINAL ARTICLE

Phenotype Classification and Risk Factors of Polycystic Ovary Syndrome Among Infertility Patients Treated at Subfertility Clinic, National Population and Family Development Board Malaysia

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder with rising incidence in Malaysia. The phenotype of PCOS is based on patients' clinical and biochemical characteristics. Therefore, this study aimed to determine the phenotype classification and the main risk factor for PCOS in women attending infertility treatment at the Subfertility Clinic, National Population and Family Development Board (NPFDB). **Materials and methods:** This cross-sectional study was conducted among women undergoing infertility treatment at the Subfertility Clinic of NPFDB from January 2018 to December 2019. The women underwent physical examination, had their menstrual history recorded, and were diagnosed with PCOS based on Rotterdam criteria. Meanwhile, blood was taken for lipid, glucose and reproductive hormone analysis. **Results:** A total of 84 women who attended for infertility treatment were diagnosed with PCOS. The findings showed that the majority of PCOS women were diagnosed with PCOS phenotype D. PCOS women exhibited notable characteristics, including significantly increased body mass index (BMI), increased blood pressure, menstrual irregularities, polycystic ovaries and hirsutism. Elevated levels of luteinizing hormone (LH) and testosterone were observed in PCOS women, while follicle-stimulating hormone (FSH) and progesterone levels were significantly diminished. Moreover, PCOS women manifested lower levels of high-density lipoprotein (HDL) and increased 2-hour postprandial glucose levels compared to the control group. Interestingly, progesterone levels showed a statistically significant relationship with PCOS, whereby high progesterone levels decrease the risk of PCOS development (odds ratio [OR], 0.793; 95% confidence interval [CI], 0.638–0.987, $p<0.05$). **Conclusion:** PCOS women who came for infertility treatment in Subfertility Clinic, NPFDB were predominantly phenotype D, had low progesterone levels and presented anovulation problems with polycystic ovaries, and these characteristics are risk factors for PCOS.
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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women and the most common cause of anovulatory infertility, which affects 5 to 20% of women worldwide (1). A study conducted among female workers in Malaysia revealed that the prevalence of polycystic ovary syndrome (PCOS) was about 12.6% (2). Different sets of diagnostic criteria for PCOS have been developed, and the most applicable tool to diagnose PCOS worldwide is the Rotterdam Criteria (3). According to these criteria, PCOS is characterised when two out of clinical features are present: (i) oligo ovulation or anovulation, (ii) clinical and/or biochemical hyperandrogenism, and (iii) presence of polycystic ovaries on pelvic ultrasound (3).

About 80% to 85% of women experiencing hyperandrogenism are diagnosed with PCOS (4), which is mainly associated with fertility and metabolic problems (5). In women with PCOS, hyperandrogenism is clinically diagnosed through the presence of hirsutism, acne, and androgenic alopecia. Meanwhile, biochemically,

it is identified by increased levels of serum androgen (6). Approximately 30% of female infertility issues are due to ovulation problems, which are linked to abnormal menstrual cycles such as oligomenorrhea (7). Meanwhile, menstrual irregularity due to anovulation is a key feature of PCOS for many women (8). About 85–90% of females with oligomenorrhea, while 30–40% of females with amenorrhea suffered from PCOS (9).

On top of that, about 50 to 70% of women with PCOS are also characterised by insulin resistance accompanied by compensatory hyperinsulinemia (10); hence, women diagnosed with PCOS may show pre-diabetic features and may lead to the development of type 2 diabetes mellitus (11). There is increasing evidence suggesting that hyperinsulinemia plays an important role in the pathogenesis of PCOS, whereby hyperinsulinemia contributes to hyperandrogenism by stimulating ovarian androgen production (12). In addition, the prevalence of hyperglycemia increases with the increase in body mass index (BMI), being higher in obese PCOS women (11). It is estimated that between 50-80% of women with PCOS are classified as obese, with body mass index (BMI) higher than 30 kg/m2. Roughly 30-35% of these women experience impaired glucose tolerance, while 8-10% have either been diagnosed with diabetes or have a family history of diabetes (13).

PCOS is a complex disorder in which interactions between genetic, epigenetic, and environmental factors initiate and affect the pathogenesis and clinical manifestation of PCOS. Numerous studies demonstrated that ethnicity plays a role in the prevalence and clinical features of PCOS. Significant differences exist in the symptoms of PCOS shown across geographic locations and between different races or ethnic groups (14). In addition, ethnic variation is also a contributing factor that influences the clinical, hormonal, and metabolic characteristics of women with PCOS (15). For instance, Japanese women with PCOS are usually less obese and do not have hirsutism when compared to Euro-American women with PCOS. Although Japan has lower rates of obesity and hirsutism, Japanese women still have the same rates of androgen excess and insulin resistance as Caucasians (16). Over time, studies have shown that the manifestation of PCOS may differ across different regions, and ethnic variations and environmental factors may play significant roles in its development. Identifying the phenotype of PCOS is important for patient management especially in tackling the infertility issue (17). Following criteria proposed by the Androgen Excess and PCOS Society (AE-PCOS) who suggested that the diagnosis of PCOS should be based on clinical or biochemical hyperandrogenism in combination with oligoanovulation or polycystic ovaries, NIH consensus panel introduced the phenotype approach to classifying PCOS based on biochemical and clinical presentation (18).

Even though many studies have been done elsewhere, to the best of our knowledge, scarce data exist on PCOS patients in Malaysia. The National Population and Family Development Board (NPFDB) is one of the referral centres for infertility treatment in Malaysia. Therefore, this study aimed to provide information on the phenotype classification and main contributing risk factors of PCOS women seeking treatment at the Subfertility Clinic, NPFDB, Malaysia.

MATERIALS AND METHODS

Study design and research procedures

This cross-sectional study was conducted at the Subfertility Clinic, NPFDB, Malaysia from January 2018 to December 2019. Written informed consent was obtained from all participants and this study was approved by the Research and Ethics Committee, NPFDB (Bil. (8) NPFDB/SPK 10/2/3 Jld.4). The women were Malaysian citizens under 40 years old seeking infertility treatment and diagnosed with PCOS according to the Rotterdam criteria 2004 (3). The Rotterdam criteria specify that two of the following three parameters must be present for diagnosis: i) oligo- or anovulation detected by progesterone levels during the luteal phase, ii) clinical hyperandrogenism determined by hirsutism and biochemical hyperandrogenism measured by serum total testosterone, and iii) polycystic ovarian morphology observed through ultrasound examination (3). Any women who presented with thyroid, renal, or liver diseases, endocrine disorders such as hyperprolactinemia, or had taken medications or hormones within the past year were excluded from this study. Meanwhile, the control group consisted of women who sought treatment at the clinic due to male factor infertility and were not categorised as PCOS women.

The women were required to attend four appointments which were scheduled based on their menstrual cycle. The first appointment was set up during the follicular phase between the second and fifth days of the menstrual cycle for the purpose of determining follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels (19). During this appointment, the women were also inquired about their demographic background, menstrual history, determination of body mass index (BMI) and blood pressure by nurses. Menstrual history was categorised as regular menstrual cycles, oligomenorrhea and amenorrhea. Meanwhile, the presence of hirsutism was confirmed by a medical doctor. Modified Ferriman-Gallwey (mF-G) method was used to identify the presence or absence of hirsutism for each women. Hirsutism was defined as an mF-G score ≥8 (20).

During the second appointment, blood was drawn to determine the progesterone level during the luteal

phase of the menstrual cycle, with the aim of assessing ovulation status. Testosterone levels were also assessed during this period. On the third appointment, a trained doctor performed a transvaginal ultrasound to determine the number of follicles and the volume of the ovaries. The women were diagnosed with polycystic ovaries if they had 12 or more follicles with a diameter of 2-9 mm in each ovary and/or an increase in the volume of each ovary by at least 10 mL (3). Finally, on the fourth appointment, blood was taken for lipid profile determination and an oral glucose tolerance test (OGTT) was conducted on all women.

Hormonal and biochemical assay

Serum levels of FSH, LH, progesterone, and total testosterone were measured using an automated electrochemiluminescence immunoassay analyzer (ECLIA Analyzer, Cobas e411, Roche Diagnostic). Glucose, total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) levels were analysed by using a fully automated photometric chemistry analyser (Cobas c311, Roche Diagnostic).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0. Shapiro–Wilk test was applied to test the distribution normality of the continuous variables. Students' t-tests were used to compare the means of between the two groups, while categorical variables were compared using the Chi-square test. All continuous variables were shown as mean ± standard error of means. Logistic regression was used to identify the risk factors associated with women diagnosed with PCOS. The effects of variables in the logistic regression model were described by odd ratio (OR) and 95% confidence interval. The ratio of each parameter was defined, with OR > 1 being considered to be associated with an increased risk of developing PCOS (risk factor) and OR < 1 being associated with a reduced risk (protective factor). p-value less than 0.05 was considered to be statistically significant.

RESULTS

A comprehensive socio-demographic profile of all the women who participated in the study, comprising 84 women diagnosed with PCOS and 50 healthy controls, is presented in Table I. The mean age of PCOS women were 29.32 ± 3.0 years, and the mean age for controls were 34.06 ± 3.4 years. The majority of the PCOS women were Malay, which is 92.9%, whereas all control women were Malays. Most PCOS women had a marriage period between 2 to 5 years (81.0%), followed by 6 to 9 years (19.0%). On the other hand, 52% of the controls had a marriage period between 2 to 5 years, followed by 6 to 9 years (44.0%) and more than 10 years (4.0%).

Table I: Demographic profile of participants involved in the study

Variables	PCOS (n=84)	Control (n=50)
Age	29.32±3.0	34.06±3.4
Ethnic		
Malay	78 (92.9%)	50 (100.0%)
Non-Malay	6 (7.1%)	0 (0.0%)
Duration of marriage		
2- 5 year	68 (81%)	26 (52%)
6- 9 year	16 (19.0%)	22 (44.0%)
>10 year	0 (0.0%)	2 (4.0%)

Data were presented as mean ± standard deviation (SD) / frequency (%).

Table II presents the subjects' medical history. A total of 10.7% of the PCOS women were previously treated for PCOS prior to the present study. Meanwhile, 2.4% of them experience hypertension, 1.2% have diabetes mellitus, and 8.3% have other chronic diseases.

Table II: Medical history of participants involved in the study

Criteria	PCOS (n=84)	Control (n=50)
Healthy	65 (77.4%)	49 (98.0%)
PCOS	9 (10.7%)	0 (0.0%)
Hypertension	2 (2.4%)	0 (0.0%)
Diabetes mellitus	1(1.2%)	0 (0.0%)
Other chronic diseases	7 (8.3%)	1 (2.0%)

Data were presented as frequency (%).

In this study, PCOS women were divided into four main phenotypes, which are presented in Table III. The results showed that the majority of women (76 individuals, 90.48%) were diagnosed with PCOS phenotype D. PCOS phenotype C was observed in only 4.76% (4 individuals) of women, while another 4.76% (4 individuals) were diagnosed with PCOS phenotype B. No women were diagnosed with PCOS phenotype A.

Table III: Patients with polycystic ovary syndrome are categorized according to phenotypes based on the Rotterdam Criteria

Phenotypes	PCOS n=84(%)
Phenotypes A (Oligomenorrhea/anovulation, hyperandrogenism and polycystic ovaries)	0 (0%)
Phenotypes B (Oligomenorrhea/anovulation and hyperandrogenism)	4(4.76%)
Phenotypes C (hyperandrogenism and polycystic ovaries)	4(4.76%)
Phenotypes D (Oligomenorrhea/anovulation and polycystic ovaries)	76(90.48%)

Data were presented as frequency (%).

Table IV shows the women with PCOS and those in the control group underwent assessment for blood pressure, BMI, menstrual irregularities, polycystic ovaries, hirsutism, acne, and oily skin. The average for systolic and diastolic blood pressure as well as BMI were significantly higher in PCOS women compared to controls (p<0.05). In addition, a significantly higher number of PCOS women exhibited menstrual irregularities, polycystic ovaries, hirsutism, acne, and oily skin compared to the control group (p<0.05).

Table IV: Clinical characteristic in PCOS women and control

Variables	PCOS (n=84)	Control (n=50)	*P*-value
Systolic blood pressure (mmHg)[a]	124.98 ± 11.70	118.50 ± 10.11	<0.01*
Diastolic blood pressure (mmHg)[a]	80.44 ± 9.90	76.46 ± 11.12	<0.05*
BMI (kg/m2)[a]	28.57 ± 5.48	25.92 ± 4.73	<0.01*
Menstrual Irregularities[b]	29(34.5%)	0 (0.0%)	<0.001*
Polycystic Ovary[b]	79(94.0%)	0 (0.0%)	<0.001*
Hirsutism[b]	22 (26.2%)	0 (0.0%)	<0.001*
Acne[b]	28 (33.3%)	7 (14.0%)	<0.05*
Oily Skin[b]	27 (32.1%)	2 (4.0%)	<0.001*

p significant at <0.05; Data were presented as mean ± standard deviation (SD/ frequency (%). a: Independent t-test; b: Chi-square (χ^2)

Results for serum lipid, OGTT, progesterone, LH, FSH and testosterone are shown in Table V. The study found that women with PCOS had significantly lower HDL (1.17 ± 0.35 mmol/L) levels compared to the control group (1.62 ± 0.31 mmol/L) (p<0.05). On the contrary, PCOS women showed significantly higher (p<0.05) OGTT (2-hour postprandial glucose) levels (6.67 ± 2.92 mmol/L) compared to the control group (4.99 ± 1.23 mmol/L). However, there was no significant difference in TC, LDL, TG and OGTT (fasting) levels between these two groups. Additionally, PCOS women had significantly higher levels of LH (8.88 ± 5.68 mIU/ml) and testosterone (1.38 ± 0.76 nmol/L) but significantly lower levels of FSH (5.97 ± 1.76 mIU/ml) and progesterone (5.58 ± 9.93 nmol/L) compared to the control group (LH: 5.11 ± 1.91 mIU/ml, testosterone: 0.54 ± 0.29 nmol/L, FSH: 7.27 ± 1.47 mIU/ml, progesterone: 50.94 ± 16.41 nmol/L) (p<0.05).

Table V: Biochemical profile in PCOS women and control

Parameters and Normal Range	PCOS (Mean±SD)	Control (Mean±SD)	P value
Total Cholesterol (mmol/L)	5.12 ± 0.11	5.16 ± 0.92	0.795
LDL (mmol/L)	3.27 ± 0.89	3.27 ±0.85	0.963
HDL (mmol/L)	1.17 ± 0.35	1.62 ± 0.31	<0.001*
Triglyceride (mmol/L)	1.29 ± 0.99	1.01 ± 0.54	0.066
OGTT (Fasting)	5.14 ± 1.77	4.97 ± 0.53	0.510
OGTT (2 hours postprandial)	6.67 ± 2.92	4.99 ± 1.23	<0.001*
FSH (mIU/ml)	5.97 ± 1.76	7.27 ± 1.47	<0.001*
LH (mIU/ml)	8.88 ± 5.68	5.11 ± 1.91	<0.001*
Progesterone (nmol/L)	5.58 ± 9.93	50.94 ± 16.41	<0.001*
Testosterone (nmol/L)	1.38 ± 0.76	0.54 ± 0.29	<0.001*

p significant at <0.05. Data were presented as mean ± standard deviation (SD). Results were analysed using an independent t-test
Reference range (mmol/l): Total cholesterol: <5.2; Triglyceride: <1.7; HDL: >1.68; LDL: <2.6; OGTT: 7.8-11.0; FSH (follicular phase): 3.5-13. mIU/mL; LH (follicular phase): 2.4-12.6 mIU/mL; Progesterone (luteal phase): 5.3-86.0 nmol/L; Testosterone: 0.22-2.9 nmol/L

In addition, logistic regression analysis was performed to identify relationships between PCOS and risk factors (BMI, blood pressure (systolic or diastolic), hormones (FSH, LH, progesterone, or testosterone), HDL, and 2-hours postprandial glucose levels) after adjustment for the confounding factors (Table VI). The analysis found that only progesterone showed a statistically significant relationship with PCOS. This finding suggests that women with high progesterone levels may have a lower risk of developing PCOS (OR, 0.793; 95% CI, 0.638–0.987, p<0.05).

Table VI: Relationships between PCOS and risk factors after adjustment for the confounding factors

	P value	Odds ratio	95% C.I for odds ratio	
			lower	upper
Age	0.271	0.685	0.349	1.343
BMI	0.955	0.986	0.599	1.623
Systolic blood pressure	0.878	0.984	0.802	1.208
Diastolic blood pressure	0.826	1.013	0.905	1.133
FSH	0.260	0.546	0.191	1.566
LH	0.377	1.679	0.531	5.301
Progesterone	0.037*	0.793	0.638	0.987
Testosterone	0.682	4.161	0.005	3845.251
HDL	0.069	0.000	0.000	2.688
OGTT (2 hours postprandial)	0.275	4.340	0.310	60.673

p significant at <0.05, CI-confidence interval

DISCUSSION

The socio-demographic profile of the subjects is an essential aspect of identifying factors that can influence the study outcomes. The majority of the subjects who participated in this study were Malay ethnicity, aligning with the annual trend of patients at the Subfertility Clinic, NPFDB. Based on the yearly patient data at the NPFDB Subfertility Clinic, 80% of individuals receiving treatment belong to the Malay ethnic group, thus explaining the dominance of Malay ethnicity in the current study population. Additionally, it is widely

known that Malays constitute the largest ethnic group in Malaysia Peninsular (21).

The mean age of PCOS women was 29, while controls had a mean age of 34, revealing that the majority of individuals seeking fertility treatment were still within the reproductive age range. In addition, most women diagnosed with PCOS sought fertility treatment within 2 to 5 years of marriage. This finding is almost similar to a previous study conducted in Iran (22), reporting that the majority of women who come for treatment are 27.3 years old after 5.3 years of marriage. Fertility levels vary with age, and a woman in her early to mid-20s typically has a 25-30% chance of successfully conceiving in each menstrual cycle. The age range associated with the highest fertility rate in women is usually observed in their twenties. However, as women surpass the age of 35, fertility levels and the quality of the female egg tend to decline, where the fertility rate decreases by almost 60% by age 35. By the age of 40, the likelihood of getting pregnant in any given monthly menstrual cycle is approximately 5% (23). According to Deshpande and Gupta, for couples who have been married for less than five years, infertility is commonly attributed to PCOS and sexually transmitted infections (24). Conversely, for couples who have been married for more than five years, infertility is often associated with unexplained factors and an elevated incidence of male factor issues.

Menstrual irregularities often occur in PCOS women. An irregular menstrual cycle is often associated with anovulation, which can lead to oligomenorrhea. This condition is characterised by having fewer than nine menstrual cycles per year or menstruation lasting more than 35 to 40 days (25). This study found that 34.5% of PCOS women experienced menstrual irregularities. Approximately 30% of infertility issues are attributed to ovulation problems, which are linked to abnormal menstrual cycles (oligomenorrhea) or the absence of menstruation (amenorrhea) (26). The prevalence of polycystic ovaries has been suggested to be higher than 20% in both Asian and Western women and is the most frequently used criterion in PCOS diagnosis (27). Our results showed that 95.2% of PCOS women who were clinically diagnosed with PCOS based on the Rotterdam criteria had polycystic ovaries. This finding is supported by a study conducted on Taiwanese women, revealing that 91% of individuals diagnosed with PCOS based on the Rotterdam criteria exhibited the presence of polycystic ovaries (27).

Women with PCOS have an increased risk of individual components of metabolic syndrome, including dyslipidemia, increased fasting plasma glucose and increased blood pressure (28). Overweight or obesity in PCOS women have more severe reproductive and metabolic effects (29). In this study, PCOS women have higher BMI and blood pressure. This finding is in line with a previous study, reporting that the blood pressure of women with PCOS during reproductive age is significantly higher compared to the control group. PCOS women also have a higher risk of developing high blood pressure during their reproductive years (30). In addition, obese PCOS women tend to have higher systolic and diastolic blood pressure (31).

PCOS women are usually associated with type 2 diabetes mellitus. Even though the 2-hour postprandial glucose level of PCOS women was significantly higher than the control group, the glucose level was still in the normal range. The finding of this study supports a previous finding (32) whereby PCOS women who have chronic anovulation may not necessarily have insulin resistance. However, it was suggested that the transition rates from normal glucose tolerance to impaired glucose tolerance or type 2 diabetes mellitus were higher in women with PCOS compared to healthy women (33). Therefore, it is advisable for women with PCOS to undergo regular screening for the early detection of diabetes (34). On the other hand, the mean HDL level for PCOS women was significantly lower than controls, but no differences were seen in the LDL, TC and TG levels. In this study, the risk factors for metabolic syndrome, such as elevated blood pressure and obesity, were significant in the PCOS women, but not for dyslipidemia and glucose tolerance disorders.

Hyperandrogenism is the main characteristic of PCOS women, and the most clinically relevant hormone for this condition is testosterone. It can be also identified clinically through the presence of hirsutism. However, in clinical practice, not all women with PCOS exhibit hirsutism (35). This study revealed that PCOS women prominently presented with hirsutism compared to controls. On top of that, despite their mean testosterone levels being within the normal range, the values were significantly higher compared to controls. This finding demonstrates that although PCOS women may show clinical presentations of hyperandrogenism, their testosterone levels can still be within the normal range. A study by Rashidi et al. (36) reported a decrease of 20-50% in testosterone levels in PCOS patients, particularly after the age of 30. This fact shows that the biochemical marker of hyperandrogenism, used as a parameter to diagnose PCOS, becomes less reliable with age and may hamper the diagnosis of PCOS after 30 years of age (37). Therefore, this is probably why PCOS women in this study showed lower levels of testosterone despite exhibiting hyperandrogenism features.

A previous study revealed that the majority of women with PCOS exhibited elevated levels of LH and androgens along with reduced FSH levels (38). However, although our study showed that the mean levels of FSH, LH and progesterone of PCOS women were found to be within the normal range, both the progesterone and FSH levels were significantly lower compared to the controls. Interestingly, it is important to note that the progesterone

levels in PCOS women in this study were borderline low in the reference range. This result suggests that PCOS women may have ovulation issues, as indicated by low progesterone levels. The assessment of progesterone levels in PCOS women experiencing oligomenorrhea and amenorrhea is recommended to be conducted in the middle of the luteal phase of the menstrual cycle, usually around day 21 (39) This is because progesterone hormone levels above 30 nmol/L during the luteal phase indicate that a woman is ovulating, and hence, a low level of progesterone indicates anovulation (39). PCOS women who have low progesterone levels in the luteal phase will cause ovulation failure (39). In this study, low progesterone levels were observed in PCOS women (5.58 nmol/L), signifying ovulation issues.

Based on biochemical and clinical presentation PCOS has been classified into phenotype A, B, C and D approach. The phenotypes recognized are: Phenotype A (full-blown syndrome PCOS: includes hyperandrogenism (HA) (clinical or biochemical), ovulatory dysfunction (OD), and polycystic ovaries (PCO), phenotype B (non-polycystic ovaries (PCO) PCOS: HA + OD) phenotype C (ovulatory PCOS: HA+PCO), and phenotype D (non-hyperandrogenic PCOS: OD+PCO) (40). Identifying the phenotype of PCOS is important for patient management especially treating the infertility issue because different phenotypes have different characteristics. Over time, studies have shown that the manifestation of PCOS may differ across different regions, and ethnic variations and environmental factors may play significant roles in its development. In most of the previous study, irrespective of the patients' ethnicity, phenotype A emerged as the predominant phenotype, characterised by the presence of all three PCOS features (41). A study done in South India revealed that 49.7% of PCOS is classified as phenotype A (42). Meanwhile, PCOS patients in Kuwait were predominantly of phenotype A (40%), followed by phenotype C (35%) and B (25%) (43). Similarly, PCOS phenotype A was the most prevalent among infertile Iranian women, accounting for 46.3% of cases (44). In contrast, our study found that the majority of PCOS women (90.48%) were classified as phenotype D, followed by phenotype B or C (4.76%). Notably, in this study, the majority of the participants were of Malay ethnicity.

The predominant phenotype of this study is similar to the predominant phenotype for East Asian countries including Japan, China and South Korea, whereby phenotype D is most prevalent (17). In addition, a study from Sudan (45) also similarly identified phenotype D as the most prevalent among infertile Sudanese women. PCOS phenotype D is characterised by polycystic ovaries and experiencing anovulation as indicated by low progesterone levels, but without hyperandrogenism. A previous study (46) suggests that women with anovulatory polycystic ovaries but no hyperandrogenism are less likely to experience metabolic disturbances. This report aligns with our findings, where PCOS women are more significantly associated with issues of anovulation and obesity rather than insulin resistance or dyslipidemia, as the majority are diagnosed as PCOS phenotype D. Metabolic disturbances are more prevalent in the classic phenotypes A and B, followed by C (ovulatory), and less frequently D (non-hyperandrogenic) (47). Moreover, as the mildest and least severe PCOS phenotype, it was reported that PCOS patients of phenotype D responded best to infertility treatment compared to other phenotypes (48).

Women with PCOS require higher levels of progesterone to decrease the frequency of GnRH pulse secretion, leading to adequate plasma FSH synthesis and persistent plasma LH stimulation of ovarian androgens (49). Interestingly, the logistic regression analysis revealed that progesterone serves as a protective factor against developing PCOS, whereby a higher progesterone level correlates to a reduced risk of women developing PCOS. The negative association is closely linked to the fact that adequate levels of progesterone play a key role in facilitating normal ovulatory function, which in turn helps to reduce the risk of PCOS. This finding supports a previous study on cyclic progesterone therapy for androgenic PCOS patients, whereby progesterone therapy has been shown to improve symptoms of PCOS (50).

CONCLUSION

Based on the findings of this study, it is revealed that PCOS patients who came for infertility treatment at the Subfertility Clinic, NPFDB, were predominantly phenotype D, had low progesterone levels and presented anovulation problems with polycystic ovaries. Analysis showed that progesterone acts as a protective factor, whereby increased progesterone levels are associated with a decreased risk of women developing PCOS. This finding could assist medical professionals in selecting fertility treatments that are tailored to the specific needs of PCOS patients. However, this study only involved a single-centre study (Subfertility Clinic, NPFDB). Hence, the population may not accurately represent Malaysia's general population.

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