INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting up to 20% of reproductive-aged women. There are three available diagnostic criteria for PCOS: the National Institute of Health (NIH), ESHRE/ASRM Rotterdam consensus criteria and the androgen excess and PCOS society (AES). Biochemical hyperandrogenism is a common component of each of these diagnostic criteria. In this study, we developed a simple phenotypic algorithm that can capture the underlying clinical and hormonal abnormalities to help in the diagnosis and risk stratification of polycystic ovary syndrome (PCOS).

METHODS: The study consisted of 111 women with PCOS fulfilling the Rotterdam diagnostic criteria and 67 women without PCOS. A Firth's penalized logistic regression model was used for independent variable selection. Model optimism, discrimination, and calibration were assessed using bootstrapping, area under the curve (AUC) and Hosmer-Lemeshow statistics, respectively. The prognostic index (PI) and risk score for developing PCOS were calculated using independent variables from the regression model.

RESULTS: Firth penalized logistic regression model with backward selection identified four independent predictors of PCOS namely free androgen index ($\beta = 0.30$ (0.12), $P = 0.008$), 17-OHP ($\beta = 0.20$ (0.01), $P = 0.026$), anti-mullerian hormone (AMH; $\beta = 0.04$ (0.01) $P < 0.0001$) and waist circumference ($\beta = 0.08$ (0.02), $P < 0.0001$). The model estimates indicated high internal validity (minimal optimism on 1000-fold bootstrapping), good discrimination ability (bias corrected c-statistic = 0.90) and good calibration (Hosmer-Lemeshow $\chi^2 = 3.7865$). PCOS women with a high-risk score ($q_1 + q_2 + q_3$ vs $q_4$) presented with a worse metabolic profile characterized by a higher 2-hour glucose ($P = 0.01$), insulin ($P = 0.0003$), triglycerides ($P = 0.0005$), C-reactive protein ($P < 0.0001$) and low HDL-cholesterol ($P = 0.02$) as compared to those with lower risk score for PCOS.

CONCLUSIONS: We propose a simple four-variable model, which captures the underlying clinical and hormonal abnormalities in PCOS and can be used for diagnosis and metabolic risk stratification in women with PCOS.

KEYWORDS
17-OHP, AMH, FAI, PCOS, risk score
three criteria and can be assessed by using a variety of assays to test for relevant biomarkers in serum and/or saliva including serum levels of total testosterone (TT), free T, androstenedione and dehydroepiandrosterone sulphate (DHEAS) or by calculating available indices such as free androgen index. This plethora of available androgen biomarkers and indices in combination with the current little guidance on cut-offs indicative of androgen excess in the PCOS guidelines contribute to diagnosis- and risk stratification-related uncertainties. FAI is commonly used to define hyperandrogenaemia in the diagnosis of PCOS. However, recent data show that FAI is not a reliable indicator of free T when sex hormone-binding globulin (SHBG) concentration is low and hence can misclassify women who are being investigated for PCOS. Clinical hyperandrogenaemia, characterized by the presence of hirsutism, is recommended as a substitute of biochemical hyperandrogenaemia in the current guidelines but this can often be unreliable due to wide interobserver variation and ethnic variations. While the focus has been placed upon biochemical and clinical hyperandrogenaemia for the diagnosis of PCOS, recent data by our group and others have shown that elevated levels of anti-mullerian hormone (AMH), a surrogate measure of follicle count on ultrasound, can be an important supplement to the hormonal parameters used in the diagnosis of PCOS. While PCOS is a diagnosis of exclusion, the diagnosis can often be challenging, given the presentation of this syndrome as a spectrum of clinical features and metabolic abnormalities in the affected patients, rather than the presence of a single unified entity, PCOS. The aim of this study was to use relevant biochemical markers and quantifiable clinical features to derive a risk score that can capture the entire PCOS disease spectrum. This simple risk score has the potential to assist in diagnosis, severity prediction of the disease risk stratification of PCOS women.

2 | METHODS

2.1 | Study population

This was a cross-sectional study involving 111 well-characterized women with PCOS and 67 women without PCOS who presented sequentially and prospectively at the Department of Academic Diabetes, Endocrinology and Metabolism. All patients gave written informed consent. This study was approved by the Newcastle & North Tyneside Ethics committee (ISRCTN70196169) and was conducted in accordance to the Declaration of Helsinki and local regulations. The diagnosis of PCOS was based on at least two out of three of the diagnostic criteria of the Rotterdam consensus, namely clinical and biochemical evidence of hyperandrogenism (Ferriman-Gallwey score >8; free androgen index >4, total testosterone >1.5 nmol/L; oligomenorrhea or amenorrhea and polycystic ovaries on transvaginal ultrasound. Nonclassical 21-hydroxylase deficiency, hyperprolactinemia, Cushing’s disease and androgen-secreting tumours were excluded by appropriate tests. The study and study measurements are described in detail in our previous publication. In summary, we measured body mass index (BMI) (kg/m²), waist circumference (cm), hip circumference (cm), AMH (pmol/L), salivary testosterone (pmol/L), total testosterone (nmol/L), salivary androstenedione (pmol/L), serum androstenedione (nmol/L), SHBG (nmol/L), FAI (%), follicle-stimulating hormone (FSH) (IU/L), luteinizing hormone (LH) (IU/L), fasting glucose (mmol/L), 2-hour glucose (mmol/L), insulin (μU/mL) according to established protocols in women with PCOS and controls. We also ascertained oral contraceptive use and history of menstrual irregularity/amenorrhoea. All of the control women had regular periods, no clinical or biochemical hyperandrogenism, no polycystic ovaries on ultrasound, no significant background medical history and none of them were on any medications including oral contraceptive pills or over the counter medications.

2.2 | Study measurements

Blood samples were centrifuged within 5 minutes of collection and were stored frozen at ~80°C pending analysis. All study measurements and analysis were performed in accordance with the relevant guidelines and regulations. Serum T and A were measured by LC/MS/MS on an Acuity UPLC system coupled to a Quattro Premier XE mass spectrometer (Waters, Manchester, UK). Sex hormone-binding globulin (SHBG) was measured by an immunometric assay with fluorescence detection on the DPC Immulite 2000 analyzer using the manufacturer’s recommended protocol (upper limit of the reference range 2.0 nmol/L). The free androgen index (FAI) was calculated as the total testosterone × 100/SHBG. Serum insulin was assayed using a competitive chemiluminescent immunoassay performed on the manufacturer’s DPC Immulite 2000 analyzer (Euro/DPC, Lanberis, UK). The analytical sensitivity of the insulin assay was 2 μU/mL, the coefficient of variation was 6%, and there was no stated cross-reactivity with proinsulin. Plasma glucose was measured using a Synchron LX 20 analyzer (Beckman Coulter, Wycombe, UK), using the manufacturer’s recommended protocol. The coefficient of variation for the assay was 1.2% at a mean glucose value of 5.3 mmol/L. The insulin resistance was calculated using the HOMA method [HOMA-IR = (insulin × glucose)/22.5]. Anti-Müllerian hormone was measured using a Beckman Coulter Access automated immunoassay. A number of AMH immunoassays have been developed: we used the Beckman Coulter Access automated immunoassay from Beckman Coulter, as studies have shown good correlation between the Gen II, Elecsys assays and the new Access AMH assay.10 17-OHP was measured in the early morning sample and if on the higher side of the nomogram, congenital adrenal hyperplasia was excluded with ACTH stimulation test. The free androgen index (FAI) was calculated as the total testosterone × 100/SHBG.

2.3 | Collection and handling of saliva samples

This has been detailed previously for the saliva collection and for the salivary androgen measurement methodology. In brief, participants were asked to spit or drool directly into a 4 mL sealable polystyrene tube and to provide at least 3 mL of saliva. Unstimulated saliva samples were used to avoid any assay interference. The “passive drool” technique was used for the collection of saliva rather than
the “salivette” method. Salivary testosterone and salivary androstenedione were measured by LC-MS/MS analysis performed using a Waters Acquity UPLC system coupled to a Waters Xevo TQS mass spectrometer, giving a lower limit of quantification of 5 pmol/L for salT and 6.25 pmol/L for salA with an inter- and intra-assay precision coefficient of variation of <4% and <7.5%, respectively.

2.4 Statistical analysis

All the study variables were log transformed if they were not normally distributed. After the log transformation, we imputed the missing values using an iterative imputation method missForest.11 missForest is an implementation of random forest algorithm. It is a nonparametric imputation method, which builds a random forest model for each variable and subsequently uses the model to predict missing values in the variable with the help of observed values. To evaluate androgen levels between PCOS cases and controls, univariate Mann-Whitney tests on the imputed data sets. Means (standard deviations) or medians (interquartile range) were used to summarize continuous variables as appropriate, while proportions and frequencies were used to summarize categorical variables.

2.5 Risk prediction

In logistic regression models, if the sample size is small or if a predictor is strongly associated with one of the possible outcomes the estimated coefficients may be biased. To overcome this issue, we used logistic regression model with Firth’s bias-adjusted estimates. The basic idea of the Firth’s logistic regression (Firth 1993) is to introduce a more effective score function by adding a term that counteracts the first-order term from the asymptotic expansion of the bias of the maximum likelihood estimation—and the term will go to zero as the sample size increases.12 Model selection with Firth’s bias adjustments was done using R package “logistf”.12 Firstly, we included all the relevant variables in a model such as age, BMI, waist circumference, menstrual irregularity (yes/no), use of oral contraceptives (yes/no), serum testosterone, salivary testosterone, serum androstenedione, salivary androstenedione, oestradiol, SHBG, DHEAS, LH, FSH, Prolactin, 17-OHP, FAI and AMH levels. We did not include menstrual disturbances in the model as it is extremely difficult to quantify the extent duration and severity of menstrual disturbances and simply entering a yes/no variable can lead to model overfitting. Next, we used backward in logistf in R to identify best model from a set of candidate predictor variables by entering predictors based on P value cut-off of 0.05. The variable selection in logistf is simply performed by repeatedly calling add one or drop one methods for logistf and is based on penalized likelihood ratio test. In order to assess the stability of the model thus obtained compared this step-wise model based on P-values to a model using forward selection. As the apparent predictive performance (performance in the development cohort) usually overestimates the performance in other patients, owing to overfitting and peculiarities in the development cohort,13 we internally validated the model through bootstrapping using package boot in R. A bootstrap analysis with 1000 simulations was performed to compare the measures of effect obtained from the original model with the bootstrapped model.

We assessed model discrimination using area under the receiver operator curve (AUC) in a logistic regression model. Values >0.7 indicate good predictive performance, and values >0.8 indicate excellent predictive performance of the model. Goodness-of-fit were assessed using calibration plot and Hosmer-Lemeshow statistics.

In order to calculate an individual patient’s risk of having PCOS, we first calculated their prognostic index14 (PI). To achieve this, the estimated coefficients were multiplied by the values of the predictor variables of the patient and the sum of these multiplications were added to the intercept of the model. Using the PI, we then calculated the risk of PCOS as exp (PI)/(1 + exp (PI)).

For ease of interpretation, we back-transformed the significant variables retained in the model and presented the effect estimates and P-values associated with these. We did a sensitivity analysis using (a) untransformed raw variables with missing values and (b) untransformed raw variables with imputed values to assess model stability.

3 RESULTS

The anthropometric and hormonal characteristics of women with PCOS and controls from the Hull UK PCOS biobank are shown in Table 1. Women with PCOS were younger (P = 0.01) had higher BMI (P < 0.0001), waist circumference (P < 0.0001) and, overall, greater levels of all markers indicating hyperandrogenaemia compared to controls. Women with PCOS also had significantly higher levels of 17-OHP (P = 0.03) and AMH (P < 0.0001).

The logistic regression with backward selection model revealed four variables independently associated with PCOS namely, FAI \([\beta = 0.30 (0.12), P = 0.008], 17\text{-OHP} \[\beta = 0.20 (0.01), P = 0.026], \text{AMH} \[\beta = 0.04 (0.01), P < 0.0001]\) and waist circumference \([\beta = 0.08 (0.02), P < 0.0001] \) (Table 2). Relaxation and restriction of the removal criterion for backward selection to \(P < 0.20\) and \(P < 0.10\), respectively, did not change the final model. Similar results were also seen in a model with forward selection. A bootstrap analysis with 1000 simulations indicated minimal bias and model optimism in estimated effect sizes (Table S1). Bootstrap estimates of several discrimination indices to quantify the model are presented in Table S2. The optimism corrected estimate of the Somers’ D was 0.81 (Table S2) with a corresponding bias corrected c-statistic of \((1 + 0.8193)/2 = 0.90\).

The model with the four predictor variables had a high discrimination ability with a c-statistics of AUC = 0.91 (0.88-0.95). The AUCs for FAI, AMH, 17-OHP and WC were 0.81 (0.75-0.87), 0.75 (0.68-0.82), 0.59 (0.51-0.67) and 0.91 (0.88-0.95), respectively (Figure 1A-E). Model calibration was assessed using the Hosmer-Lemeshow statistics and a calibration plot (Figure 2). The model shows good calibration with Hosmer-Lemeshow chi-squared of 3.7865 and a P-value of 0.87.
Based on the penalized regression coefficient, we calculated a prognostic index (PI) for each of the PCOS cases using the formula 
\[-9.77 + (0.07\times WC) + (0.04\times AMH) + (0.3\times FAI) + (0.01\times 17OHP)\]
and calculated a risk score for each case of PCOS with formula exp (PI)/ (1 + exp (PI))*100. The metabolic profile of women with PCOS in the top three quartiles (q1-q3) of this risk score (classified as low-risk score) was compared with the metabolic profile of PCOS women in the bottom quartile (q4) of the risk score (classified as high-risk score). PCOS women with a high-risk score had a worse metabolic profile with significantly higher 2-hour glucose (P = 0.01), baseline insulin (P = 0.0003), TG (P = 0.0005) and CRP (<0.0001) levels and lower HDL-C levels (P = 0.02), as compared to those with a low-risk score (Table 3). We have constructed a mobile phone application for easy usage of this risk score in clinical settings. (Figure S1).

**TABLE 1** Baseline characteristics and hormonal parameters of women with and without PCOS in the Hull UK PCOS biobank

|                      | PCOS (n = 67) | Control (n = 111) | P-value |
|----------------------|--------------|-------------------|---------|
|                      | Median (IQR) | Median (IQR)      |         |
| Age                  | 27.68 (11)   | 29.92 (11)        | 0.01    |
| BMI                  | 34.15 (9.9)  | 26.86 (6.2)       | <0.0001 |
| Waist circumference (cm) | 101 (21.2)  | 78 (14.5)         | <0.0001 |
| Testosterone (nmol/L)| 1.30 (0.85)  | 0.94 (0.45)       | <0.0001 |
| Salivary androstenedione (pmol/L)| 146.4 (88.65) | 185.8 (112.4) | 0.0002 |
| Oestradiol (pmol/L)  | 190 (295)    | 180 (165)         | 0.43    |
| SHBG (nmol/L)        | 27 (18)      | 47 (31)           | <0.0001 |
| TSH (mU/L)           | 1.9 (1.2)    | 1.5 (1.1)         | 0.03    |
| DHEAS (µmol/L)       | 5.2 (3.8)    | 4.6 (4)           | 0.04    |
| Androstenedione (nmol/L)| 9.5 (5.8)   | 7.3 (4.4)         | <0.0001 |
| Prolactin            | 6.2 (5.6)    | 4.1 (4.3)         | 0.003   |
| LH                   | 4.9 (2.7)    | 5.5 (3.2)         | 0.09    |
| FSH                  | 4.5 (4.8)    | 1.98 (1.4)        | <0.0001 |
| 17-OHP (nmol/L)      | 4.4 (3)      | 3.9 (2)           | 0.03    |
| AMH                  | 37 (41)      | 18.1 (24.5)       | <0.0001 |

17-OHP, 17α-hydroxyprogesterone; AMH, anti-mullerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone, FAI, free androgen index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone.

**TABLE 2** Independent predictors of PCOS from penalized logistic regression model

|                      | GLM based logistic regression estimates | Firth’s penalized logistic regression estimates |
|----------------------|----------------------------------------|-----------------------------------------------|
|                      | Beta | SE    | P-value | Beta  | SE    | P-value |
| FAI                  | 0.32 | 0.12  | 0.008   | 0.30  | 0.12  | 0.008   |
| 17-OHP               | 0.21 | 0.09  | 0.026   | 0.20  | 0.09  | 0.026   |
| AMH                  | 0.04 | 0.01  | <0.0001 | 0.04  | 0.01  | <0.0001 |
| Waist circumference  | 0.08 | 0.01  | <0.0001 | 0.07  | 0.02  | <0.0001 |

17-OHP, 17α-hydroxyprogesterone; AMH, anti-mullerian hormone; FAI, free androgen index.

**DISCUSSION**

The diagnosis of PCOS is often challenging given the wide range of hormonal markers and derived indices used to measure hyperandrogenism and variations in clinical presentations. We developed and internally validated a simple four-variable model (ie, FAI, 17-OHP, AMH and waist circumference) for predicting the risk of having PCOS in clinical settings. This model showed good discrimination ability and good calibration. Each of the 4 variables reported in our model has been previously associated with PCOS. We have constructed a mobile phone application for easy usage of this risk score in clinical settings. (Figure S1).

In line with differential diagnoses of conditions causing hyperandrogenism in females, in this we measured 17-OHP levels to rule out a potential diagnosis of nonclassical congenital adrenal hyperplasia (NCCAH), which is another disorder of hyperandrogenism.
The normal levels of 17-OHP in females are well defined and the baseline mean level of 17-OHP in those with NCCAH is around 20 ng/mL (60 nmol/L). In this study, the PCOS women had mean baseline 17-OHP levels of 1.6 ng/mL (5 nmol/L) safely ruling out NCCAH. A baseline 17-OHP cut-off of 2 ng/mL is suggested for the screening NCCAH; however, it is not unusual for patients with PCOS to have levels of 17-OHP higher than this cut-off. A study by Pall et al. comparing the 17-OHP levels in PCOS and NCCAH showed that 25% of lean patients with PCOS, 21% of obese patients with PCOS and 7% of controls had basal 17-OHP levels above the cut-off level 2 ng/mL. Patients with PCOS have also been showed to have higher 17-OHP levels as compared to those without PCOS.

FIGURE 1 Graphs showing area under the curve (AUC) for anti-mullerian hormone (AMH); free androgen index (FAI); 17α-Hydroxyprogesterone (17-OHP) and waist circumference (WC) individually and combined. The c-statistics for the complete model was 0.91 (0.88-0.95) [Colour figure can be viewed at wileyonlinelibrary.com]
controls, with the levels being highest in those with severe phenotype of PCOS. Interestingly, a subgroup of PCOS patients with exaggerated 17-OHP response to GnRH agonist presented with severe hyperandrogenaemia, glucose-stimulated β-cell insulin secretion, and worse insulin resistance. The excess 17-OHP in patients with PCOS is thought to be the result of excess stimulation of theca interna cells by luteinizing hormone (LH). In this study, for the first time, we showed that 17-OHP is independently associated with PCOS, after adjustments of FAI, AMH and waist circumference. However, the discriminatory capacity of 17-OHP to detect PCOS was small and if not readily available, can be excluded from the model.

We also show that AMH was independently associated with PCOS diagnosis after adjustments for FAI, WC and 17-OHP. AMH is produced in the granulosa cells by the preantral and small antral follicles and it appears to inhibit the action of FSH on aromatase, and therefore, it contributes to the development of a single follicle for ovulation. AMH is elevated in PCOS due to the increased count of small antral follicle and increased secretion of AMH per follicle.

We have recently shown that those with raised AMH have up to 4-fold increased risk of having PCOS. It has also been suggested that serum AMH reflects ovarian size in PCOS patients and can be used as surrogate for transvaginal ultrasound in the diagnosis of PCOS.

The associations of FAI and waist circumference with PCOS are well-documented in the literature. Waist circumference, a measure of central adiposity, is a marker of severity of PCOS and has been suggested to be a better surrogate of glucose and lipid metabolism in PCOS than the disease status per se. Menstrual dysfunction is a common symptom in PCOS and is a consequence of anovulation. Ovulatory dysfunction can also be seen in women who have regular menstrual cycle and as a result menstrual history alone is insufficient in defining PCOS. The prevalence of nonspecific menstrual dysfunction is high in women, especially in adolescent population where it can be as high as 30%, 1-year post-menarche. It is difficult to identify real anovulation-related menstrual dysfunction and many of the women are already on oral contraceptive pills which makes it difficult to ascertain the history of menstrual dysfunction. Hence, we decided not to include this variable in our model.

In this study, we showed that those with a high-risk score derived from a model, which included waist circumference, FAI, AMH and 17-OHP, had a poor metabolic profile, as evidenced by a higher 2-hour glucose, raised TG levels, basal insulin, CRP and lower HDL-cholesterol. Thus, this risk score can not only identify patients who are at high risk of PCOS, but it can also risk stratify patients and identify those who are more likely to experience adverse PCOS-related metabolic outcomes. Collectively, the four variables in our model capture the full spectrum of PCOS, wherein, FAI reflects androgens excess, AMH grasps the ovarian size and/or follicle count.

**TABLE 3** Metabolic profile of PCOS patients with low- (Q1-Q3) and high-risk (Q4) score based on penalized regression model

|                        | PCOS cases with low-risk score (Q1-Q3) (n = 84) | PCOS cases with high-risk score (Q4) (n = 27) | P-value* |
|------------------------|-----------------------------------------------|---------------------------------------------|----------|
| Baseline glucose       | Mean (SD)                                     | Mean (SD)                                  | P-value* |
| 5.73 (0.49)            | 4.73 (0.48)                                   | 5.19 (1.91)                                | 0.41     |
| 2-hour glucose         | 5.51 (1.30)                                   | 7.73 (3.39)                                | 0.01     |
| Insulin                | 13.01 (8.27)                                  | 27.25 (21.98)                              | 0.0003   |
| LDL-c                  | 2.88 (0.90)                                   | 2.99 (0.73)                                | 0.94     |
| HDL-c                  | 1.26 (0.32)                                   | 1.10 (0.18)                                | 0.02     |
| TG                     | 1.26 (0.62)                                   | 2.46 (2.22)                                | 0.0005   |
| TC                     | 4.72 (0.98)                                   | 4.95 (0.95)                                | 0.19     |
| CRP                    | 3.64 (3.73)                                   | 8.45 (6.61)                                | <0.0001  |

CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

*P-values based on Mann-Whitney U test.
17-OHP represents the alteration in LH-FSH ratio and WC indicates the presence of metabolic abnormalities in PCOS. FAI, free testosterone and SHBG are routinely measured as a part of the diagnostic workup for PCOS, while 17-OHP is measured as per the endocrine society guidelines to rule out congenital adrenal hyperplasia. AMH measurement is routinely done in these patients as a part of their fertility workup; hence, no additional testing is required when this model is used. On the other hand, using this model, may eliminate the need for testing additional androgen markers such as salivary testosterone and androstenedione, and hence, it can reduce the cost associated with these tests.

Given the high prevalence of metabolic syndrome in PCOS, guidelines issued by the American College of Obstetricians and Gynaecologists and the Endocrine Society recommend that all women with PCOS should undergo screening for impaired glucose tolerance and dyslipidaemia with a 2 hour 75 g oral glucose tolerance test and fasting lipid profile upon diagnosis, with repeat screening of each test every 2-5 years.27 However, there is no guidance on how to identify women who are at high risk for developing metabolic syndrome and not all women with PCOS get metabolic syndrome screening in primary or secondary care. The advantage of this scoring system is that it may assist in the diagnosis of PCOS and highlights those women who are at high risk of developing metabolic syndrome to help prevent future metabolic complications.

Our study has several limitations. Our four variable risk model for PCOS is not externally validated. We have attempted to overcome this problem by bootstrapping, and the effects size of our model indicates very little optimism and good calibration. However, further external validation of this model in an ethnically diverse population is warranted. Secondly, although the mean levels of 17-OHP in our study are significantly lower than those seen in patients with CAH and NCCH, it is possible to have NCCH with a normal 17-OHP level. The sample size of our study was modest with 111 PCOS and 67 controls. However, this is a very well-characterized cohort of PCOS and control women which measures all the androgen and related markers (including salivary markers) and unique in the sense that all the participants had classical PCOS whereby all the three criteria for diagnosis of PCOS namely oligomenorrhea, hyperandrogenism and PCO morphology on ultrasound were met. Nonetheless, this model will need further validation in large prospective cohorts from different ethnicities for its validation. Another limitation of our study is that all the patients in our study had classical PCOS oligomenorrhea, hyperandrogenism and PCO as designated in the Rotterdam criteria. The other sub-phenotypes include ovulatory PCOS (hyperandrogenism, PCO and regular menstrual cycles), non-PCO PCOS (oligomenorrhea, hyperandrogenism and normal ovaries) and mild PCOS (oligomenorrhea, PCO and normal androgens). Hence, we were not able to evaluate our model for the other 3 phenotypes. However, the classical PCOS phenotype represents the largest subgroup of patients with PCOS, with an estimated prevalence of up to 80% amongst the PCOS population26 and this model can be generalized to the largest subgroup of the PCOS population. The strength of the study on the other hand is that it provides a simple four variable model and calculator which can predict the risk of PCOS in clinical settings and identify those with unfavourable PCOS-related metabolic consequences. Furthermore, this study consisted of a homogenous group of Caucasian women who fulfilled Rotterdam diagnostic criteria of PCOS, thus providing a robust database for model development.

5 | CONCLUSIONS

In summary, we have developed a simple model consisting of FAI, 17-OHP, AMH and waist circumference for risk prediction and risk stratification in PCOS, with these variables previously associated with PCOS. This model will have to be externally validated in populations across different ethnicities before a widespread clinical application.

CONFLICT OF INTEREST

Nothing to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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