

REVIEW

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# Progress of the application clinical prediction model in polycystic ovary syndrome

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## Abstract

Clinical prediction models play an important role in the field of medicine. These can help predict the probability of an individual suffering from disease, complications, and treatment outcomes by applying specific methodologies. Polycystic ovary syndrome (PCOS) is a common disease with a high incidence rate, huge heterogeneity, short- and long-term complications, and complex treatments. In this systematic review study, we reviewed the progress of clinical prediction models in PCOS patients, including diagnosis and prediction models for PCOS complications and treatment outcomes. We aimed to provide ideas for medical researchers and clues for the management of PCOS. In the future, models with poor accuracy can be greatly improved by adding well-known parameters and validations, which will further expand our understanding of PCOS in terms of precision medicine. By developing a series of predictive models, we can make the definition of PCOS more accurate, which can improve the diagnosis of PCOS and reduce the likelihood of false positives and false negatives. It will also help discover complications earlier and treatment outcomes being known earlier, which can result in better outcomes for women with PCOS.

**Keywords** Clinical prediction model, Polycystic ovary syndrome, Application progress, Reproduction, Endocrine, Overweight PCOS

## Background

Clinical prediction models use specific methodologies to predict individual probabilities of illness, complications, treatment outcomes, and includes a diagnostic model and a prognostic model [1]. There are several basic steps

from model creation to model application. It includes the formulation of research questions, assessment design, data collection, establishment and evaluation of clinical prediction models, validation and application, and updating of models [2]. Researchers have created a tool called PROBAST to assess the risk of bias and applicability of a prediction model. It is also used in a specific population and has shown initial success [3–6]. Clinical prediction models use a small number of predictors to predict disease status and prognosis. These predictors can be easily collected and detected.

Recently, several emerging technologies have been used in clinical prediction models. For example, computer technology, interdisciplinary communication, application of big data, and many advanced methods such as machine learning and artificial intelligence were applied. Combining these new technologies with a clinical prediction model can ensure proper allocation of medical

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resources. Moreover, it can achieve the goals of the three levels of prevention.

Clinical prediction models have been widely used in the medical field, including prediction models for tumor diseases [7–9], non-tumor diseases [10–12], and obstetrics and gynecology diseases [13–15]. In recent years, clinical prediction models have been extensively used in the field of reproduction. For example, the application of clinical prediction models for polycystic ovary syndrome (PCOS) has been increasingly studied. PCOS is one of the most common reproductive disorders. It has attracted the most attention because of its high incidence, considerable heterogeneity, and complex treatments. Moreover, it can also cause short- and long-term complications that require long-term management [16]. Several studies have focused on PCOS by creating models from different perspectives.

In this study, we reviewed and interpreted the progress of clinical prediction models for PCOS from different perspectives. With the help of this study, we provided a comprehensive review of related research and a better guide for clinical management. Moreover, it can achieve more accurate treatment for individual patients with PCOS.

## Methods

We conducted a comprehensive literature systematic review up to April 2023, utilizing PubMed, Embase, and Web of Science databases. Our search terms encompassed “polycystic ovary syndrome” or “PCOS” along with “prediction model,” “nomogram,” or “model.” We limited our selection to research papers published in English and prioritized those published since 2020, excluding any lacking full manuscripts.

## Diagnosis standards and guidelines or recommendations of PCOS

PCOS is the most common endocrine disorder in women of reproductive age, affecting 6–10% of women of reproductive age [17]. There are many guidelines and diagnostic standards for PCOS, including the National Institutes of Health (NIH) standard in 1990 [18], Rotterdam Standard in 2003 [19], Androgen Excess Society (AES) standard in 2006 [20], PCOS Diagnosis and Treatment Guidelines issued by the Endocrine Society of America in 2012 [21], and recommendations from international evidence-based guidelines for the assessment and management of polycystic ovary syndrome in 2018 [22]. The most widely used standard for PCOS is the Rotterdam 2003 criteria. PCOS is defined as sporadic menstruation, sporadic ovulation or non-ovulation, blood biochemistry or clinical signs of hyperandrogenemia except from other

diseases, and ultrasound suggesting polycystic changes, conforming to two out of three contents [19].

## Application of clinical prediction model in PCOS

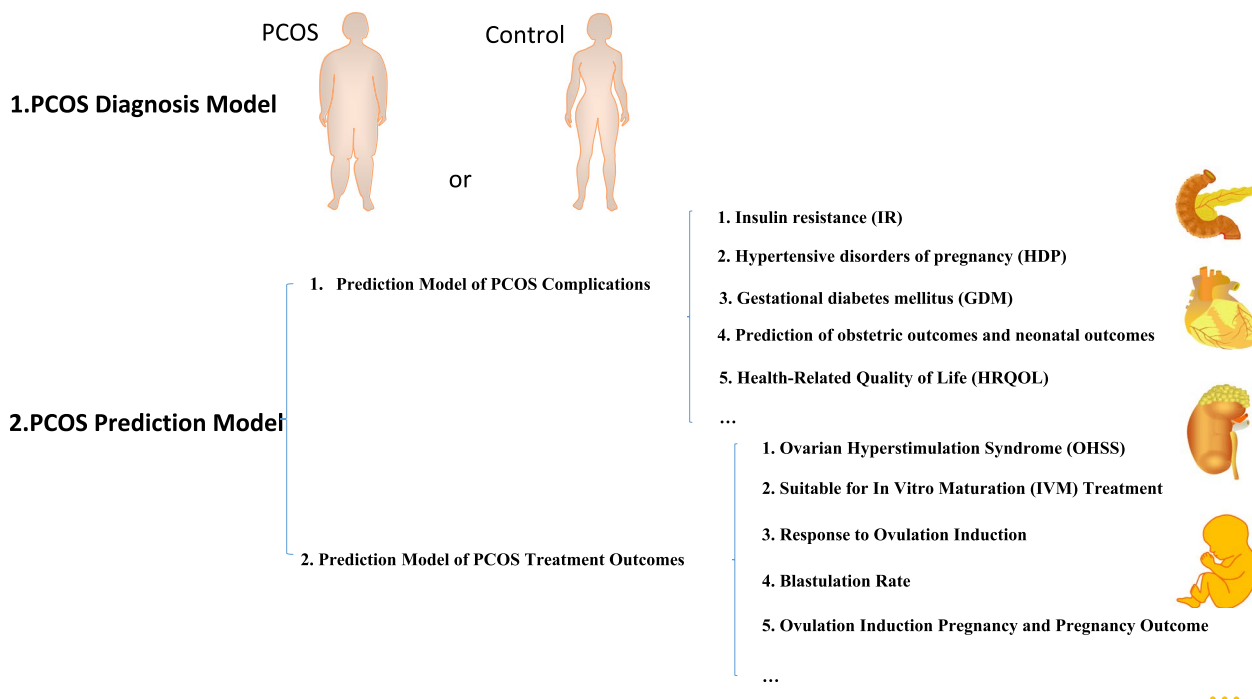
As shown in Fig. 1, we have primarily categorized the prediction models for PCOS into two types, encompassing diagnostic models for PCOS, prediction models for PCOS (mainly divided into two categories: Prediction Model of PCOS Complications and Prediction Model of PCOS Treatment Outcomes).

## PCOS diagnosis model

Studies have shown that up to 75% of PCOS cases have not been identified in clinical practice, which inevitably leads to missed diagnoses [23]. Identifying individuals at high risk of PCOS in precision medicine could help achieve early treatments.

In 2007, Pedersen et al. used questionnaires to diagnose PCOS based on demographic information, medical history, related disease diagnosis, menstrual history, reproductive history, and other relevant factors. It can be useful for screening women with menstrual irregularities, hirsutism, or other related findings consistent with PCOS. However, the questionnaire has not been validated in a family medicine setting. A score  $\geq 2$  was deemed as PCOS [24]. Zhang et al. used a supervised machine learning algorithm to predict PCOS genes by comparing 306 PCOS genes as positive samples and 306 negative samples from 13,681 genes. In total, 233 PCOS genes were identified in this study. This opens a new avenue for identifying patients at risk of PCOS [25]. Similarly, Deshmukh et al. identified four independent predictors of PCOS, including free androgen index (FAI), anti-Müllerian hormone (AMH), waist circumference (WC), and 17OHP (17 $\alpha$ -hydroxyprogesterone). However, there are certain limitations, including the lack of external validation and inability to evaluate the other three PCOS phenotypes [26]. Sun et al. found that several coagulation parameters (prothrombin time, thrombin time, and fibrin degradation products) were predictive of PCOS. These results highlighted the potential of anticoagulation therapies to lower the risk of adverse outcomes in PCOS patients [27].

Notably, by using polygenic risk prediction, Joo YY et al. identified phenome-wide comorbidity patterns characteristic of PCOS that improved diagnostic accuracy [23]. Two initial genome-wide association studies (GWAS) identified several new susceptibility loci for PCOS. Both GWAS were performed in Han Chinese populations [28, 29]. These new susceptibility loci were subsequently replicated in European cohorts [30–33]. A large-scale genome-wide meta-analysis of PCOS suggested a shared genetic architecture for the different



**Fig. 1** A summary of progress of the application clinical prediction model in polycystic ovary syndrome

diagnostic criteria [34]. The above studies have improved our ability to diagnose and treat PCOS.

Vagios et al. constructed an age-adjusted model that combined AMH and Body Mass Index (BMI) to predict oligo-anovulation diagnosis (mainly PCOS). This model served as a tool for patient counselling in the setting of anovulatory infertility [35]. Strowitzki et al. appraised this prediction model and pointed out that it can be used as a good tool, especially in patients with a minor clinical form of PCOS [36].

Importantly, the prevalence of PCOS in adolescents increases by up to 30% [37]. Li M et al. found that combining AMH and testosterone (TT) may be used in a multivariate predictive model to predict PCOS in adolescent girls [38].

With the COVID-19 global pandemic in mind, Zigarelli et al. developed two types of models using machine learning techniques. The models can help users acquire pre- or self-diagnosis and counsel for the risk of PCOS with or without lab tests and access the platform at home without delay [39]. The details of the above studies are provided in Supplement Material 1.

**PCOS prediction model**

**Prediction model of PCOS complications**

PCOS is always accompanied by obesity, metabolic dysfunction, short-term complications, and long-term

complications. It is associated with an increased risk of delivery complications during pregnancy [40, 41].

**Insulin resistance (IR)**

IR is an underlying feature of PCOS. Up to 75% of PCOS patients have IR [42]. It can be measured, but there is no tool to predict whether patients will develop IR. Hence, in 2020, Jiang et al. developed a prediction model to evaluate an individual PCOS patient’s risk of IR. The model includes five predictors: occupational category, disease duration (years), BMI, metformin use, and physical activity [43]. Previous studies have explored the factors influencing insulin sensitivity in PCOS patients and found that sex hormone-binding globulin (SHBG) and other indicators can predict IR. However, there are certain limitations, mainly including small sample size and lack of external verification [44, 45].

**Hypertensive disorders of pregnancy (HDP)**

In 2021, Khomami et al. [46] performed the Australian Longitudinal Study on Women’s Health and clarified the impact of PCOS on the incidence of HDP. The key control variables included in this study were age, BMI, country of birth, parity, multiple pregnancies, infertility treatment, gestational diabetes mellitus (GDM), family history of GDM, and socioeconomic status. Univariate analysis showed that PCOS positively correlated with the incidence of HDP. Further subgroup analysis

showed that PCOS was also positively associated with HDP incidence in nonobese women. A meta-analysis and population-based study on 9.1 million pregnancies proved that PCOS is an independent risk factor for HDP [47, 48].

**GDM** Pregnant women with PCOS have an increased likelihood of developing GDM compared with normal pregnant women [49]. A study involving 326 PCOS patients (148 PCOS patients without GDM and 41 PCOS patients with GDM) used certain factors to develop a clinically useful prediction model to predict the risk of GDM in PCOS patients [50]. Risk factors include type 2 diabetes in a first-degree relative, fasting glucose, fasting insulin, androstenedione, and SHBG. It is noteworthy that the model was not externally validated. Therefore, this model should be used with caution. In addition, Wang et al. developed a simple model to predict the risk of GDM in the first trimester without using blood examination indexes. Predictors including pre-pregnancy BMI, abdominal circumference in the first trimester, age, PCOS, gravidity, irregular menstruation, and family history of diabetes were easily obtained in the first trimester at the primary health care center. The model can be easily used and would facilitate intervention plans for maternal and infant healthcare to prevent the risk of GDM in early pregnancy [51].

**Prediction of obstetric outcomes and neonatal outcomes** Studies have shown that women with PCOS have worse obstetric and neonatal outcomes than normal females [52–54]. A review pointed out that PCOS patients had an increased risk of pregnancy complications and adverse child outcomes in that PCOS is associated with heterogeneous etiological factors and comorbidities [55]. In 2020, Christ et al. identified the association between baseline characteristics of PCOS patients and major obstetric and perinatal complications. The results suggested that the primary disease characteristics of PCOS, chiefly hyperandrogenism and changes in blood glucose regulation, are relevant in predicting obstetric complications among women with PCOS [56]. Therefore, pre-pregnancy intervention may be a good way to reduce the risk of adverse pregnancy outcomes in patients with PCOS.

**Health-related quality of life (HRQOL)** To explore the factors that contribute to HRQOL and improve or maintain HRQOL in PCOS patients, Bazarganipour et al. found that the most significant predictors of HRQOL in patients with PCOS include self-esteem, body image, and sexual function. They recommended that healthcare providers should be made aware of HRQOL impairment in

women with PCOS, which requires appropriate management and adequate treatment if available [57, 58].

Details of the above studies are provided in Supplement Material 2.

### **Prediction model of PCOS treatment outcomes**

**Ovarian Hyperstimulation syndrome (OHSS)** Controlled ovarian hyperstimulation (COH) may be one treatment option for some PCOS patients who are experiencing infertility and have difficulty ovulating, it is not a universal requirement for all PCOS patients. This process of COH is often difficult to control and can result in multiple follicle development, multiple pregnancies, and OHSS [59, 60]. OHSS is a common iatrogenic complication that occurs after ovulation hyperstimulation and is accompanied by pleural and abdominal effusions, dyspnea, blood hypercoagulability, and in severe cases, death [61].

Li et al. in 2021 investigated the risk factors of OHSS in PCOS patients after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). They developed an equation describing the probability of OHSS:

$$P = -3.47315 + 0.05521 \times \text{FSH} + 0.24700 \times \text{AMH} \\ + 0.00014 \times \text{total dosage of Gn used} + 0.00015 \\ \times \text{E2 value on the day of hCG injection} + 0.07249 \\ \times \text{follicle number on the day of hCG injection}$$

This is a simple, intuitive, practicable, and valuable method for clinical applications [62]. Another study in 2021 [63] explored the effect of seasonality on high-risk OHSS patients after oocyte retrieval. A total of 2030 patients with PCOS infertility underwent the follicular phase protocol. The risk of OHSS is seasonal and more serious during the summer and winter. Gn dosage, number of oocytes collected, E2 values, average diameter of both ovaries on hCG injection day, type of infertility, bilateral average ovarian diameter on hCG injection day, infertility type, and average temperature were independent risk factors. They found that the incidence of OHSS features important seasonal fluctuations; moreover, extreme weather conditions increase the risk of OHSS.

**Suitable for in vitro maturation (IVM) treatment** Currently, there is some controversy regarding whether PCOS patients should undergo IVF or IVM. A cohort study that included 124 PCOS patients who received continuous IVM treatment found that in this population, AMH and AFC are good predictor factors to guide the patient in choosing IVM treatment or obtain at least eight cumulus

oocyte complexes (COC) available for IVM culture [64]. The study addressing the indications for IVM will surely provide a relatively accurate screening standard.

**Response to ovulation induction** Some prediction models have been developed for this purpose in women with WHO type II anovulation, which encompasses a subgroup of PCOS patients [65–72]. The predictive variables identified in these studies were age, duration of infertility, BMI, measures of hyperandrogenism, and measures of insulin resistance because 91% of women with WHO type II anovulation are diagnosed with PCOS according to the Rotterdam criteria [73].

Importantly, Verit et al. found that total antioxidant capacity (TAC), ovarian volume (OV), and FAI could predict the response to ovulation induction to clomiphene citrate (CC) in nonobese PCOS patients. However, considering the small sample size and large heterogeneity of PCOS, these conclusions require further verification [74]. In addition, van Wely et al., by assessing the external validity of the model predicting the individual FSH response dose, found that it was inadequate in CC-resistant PCOS patients undergoing ovulation induction with recombinant FSH (rFSH) in a low-dose step-up regimen [75].

**Blastulation rate** Jin et al. developed a nomogram to predict the probability of extended culture to the blastocyst stage in women undergoing IVF for PCOS. The model exhibited fair performance and was well calibrated. If these predictive models are confirmed by external validation and the sample size is increased, they will represent convenient and practical tools to help guide the management of patients about extending culture to the blastocyst stage [76].

**Ovulation induction pregnancy and pregnancy outcome** PCOS patients often suffer from oligo-ovulation or anovulation. Therefore, a prediction model for ovulation induction and pregnancy-related outcomes is particularly important.

In 2015, Kuang et al. performed a secondary analysis of previously reported data from PCOS-I [70] and II trials [77]. The PCOS-I and PCOS-II trials included 626 and 750 patients, respectively. In the PCOS-I experiment, participants were randomly allocated to receive CC, metformin, or a combination of CC and metformin. In the PCOS-II experiment, participants were randomly allocated to receive either letrozole or CC. The investigators assessed the efficiency of the previous models and constructed a new predictive model based on the method of treatment, BMI, and other published variables. They

found that the predictive factors were similar between PCOS-I and PCOS-II. Age, FAI, insulin, time of conception, and SHBG level were important predictors of pregnancy outcomes. Moreover, they revealed that maternal smoking during pregnancy was associated with adverse pregnancy outcomes [78].

Based on clinical, ultrasonographic, and endocrinological parameters, van Wely et al. predicted ongoing pregnancy following ovulation induction with rFSH in women with PCOS. They also constructed a model that can be used in counselling of women with CC-resistant PCOS [69]. Gao et al. developed a nomogram and formula for live birth:

$$P = \frac{1}{[1 + \exp(2X)]}$$

Where X is:

$$X = 0.50654 - 0.57801 \times V1 - 0.20514 \times V2 - 0.08219 \times V3 + 0.43403 \times V4 + 0.90164 \times V5$$

V1 is the type of embryo transferred, V2 is total serum cholesterol (TC), V3 is basal FSH serum level, V4 is BMI, and V5 is age. It was developed to predict the live birth rate in PCOS patients [79]. Similarly, Jiang et al. predicted live births in PCOS patients who were undergoing frozen-thawed embryo transfer (FET) and constructed a nomogram model capable of predicting live birth outcomes [80]. Veltman-Verhulst et al. confirmed the overall good live birth prognosis of anovulatory women with PCOS who received conventional ovulation induction treatment according to age, infertility duration, and BMI. The clinical advantage of the identification of patients with poor prognosis allowed them to embark on alternative treatment options earlier [81]. Guan et al. predicted pregnancy after intrauterine insemination in women with PCOS and found that BMI plays a role in pregnancy outcomes, especially in obese women who require higher Gn doses and more days of COS to overcome the effects of weight [82]. The details of the above studies are provided in Supplement 3.

## Discussion

This review summarizes the current PCOS predictive models that have been reported, including the PCOS diagnosis model and predictive models (complications and treatment outcome models). PCOS is a heterogeneous disease that can be influenced by a variety of factors including genetic factors, environmental factors, and endocrine status [83]. The definition of PCOS evolved as knowledge of the disease continued to deepen. Overall, the definition of PCOS has become clearer [84, 85]. Hence, based on this review, we propose future research

directions for PCOS predictive models. We live in an era of precision medicine in which PCOS incidence differs among different races, so it is necessary to make related prediction models based on different racial groups [86]. We can optimize the past prediction models and take advantage of the specificity and sensitivity to distinguish PCOS and other related diseases. There have been a handful of studies reporting that PCOS may frequently be concurrent with nonalcoholic fatty liver disease (NAFLD) [87, 88], obstructive sleep apnea syndrome [89, 90], diabetes [91, 92] and the like. Thus, we can also develop models predicting the occurrence of other related diseases in PCOS patients. Additionally, many studies on the relationship between gene polymorphism and PCOS have been reported [93–95]. We can predict PCOS by adding a genetic related predictor. Following up on the offspring of women with PCOS can help predict how to maximize the benefits in PCOS patients from the perspective of the offspring [96–98]. It has been reported that PCOS patients are prone to endometrial hyperplasia and endometrial cancer (EC) [99]. Moreover, PCOS may impair endometrial receptivity, which can increase adverse pregnancy outcomes [100, 101]. We can predict PCOS pregnancy outcomes by adding endometrial lesions predictor. By developing a series of predictive models, we can make the definition of PCOS more accurate, which can improve the diagnosis of PCOS and reduce the likelihood of false positives and false negatives. It will also help discover complications earlier and treatment outcomes being known earlier, which can result in better outcomes for women with PCOS.

## Conclusion

This study is the first review to summarize the PCOS prediction model, aiming to make more people aware of its wide application. It may enable doctors to counsel patients regarding the most effective and patient-tailored treatment strategy before treatment initiation. Notably, even if the models currently have poor prediction performance by internal and external validation, this does not mean that they are worthless [102]. As we all know, a model that performs well in an internal validation always produce poor predictions in other patients [103]. Hence, in the future, models with poor accuracy can be improved by adding well-known parameters and validations, which will further expand our understanding of this disease in terms of precision medicine.

## Abbreviations

PCOS	polycystic ovary syndrome
NIH	National Institutes of Health
AES	Androgen Excess Society
AMH	anti-Müllerian hormone

ICSI	intracytoplasmic sperm injection
FET	frozen-thawed embryo transfer
NAFLD	nonalcoholic fatty liver disease
OV	ovarian volume
CC	clomiphene citrate
EC	endometrial cancer
TC	total serum cholesterol
SHBG	sex hormone-binding globulin
rFSH	recombinant FSH
FAI	free androgen index
WC	waist circumference
TAC	total antioxidant capacity
17OHP	17 $\alpha$ -hydroxyprogesterone
GWAS	genome-wide association studies
TT	testosterone
IVF	in vitro fertilization
IVM	in vitro maturation
COC	cumulus oocyte complexes
BMI	Body Mass Index
IR	Insulin resistance
HDP	Hypertensive disorders of pregnancy
GDM	gestational diabetes mellitus
HRQOL	Health-Related Quality of Life
OHSS	Ovarian Hyperstimulation Syndrome
COH	controlled ovarian hyperstimulation

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13048-023-01310-2>.

**Additional file 1: Supplement Material 1.** PCOS diagnosis model.

**Additional file 2: Supplement Material 2.** Prediction model of PCOS complications.

**Additional file 3: Supplement Material 3.** Prediction model of PCOS treatment outcomes.

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## Authors' contributions

Guan Guixue and Pu Yifu conceived and wrote the manuscript; Yang Wen provided funding and revised manuscripts. Gao Yuan, Liu Xialei, Shi Fan, Sun Qian, Xu Jinjin, Zhang Linna, Zhang Xiaozuo, and Feng Wen searched the relevant literature and revised the manuscript. All Authors approved the submitted version.

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## Availability of data and materials

All data generated or analysed during this study are included in this article.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

**Competing interests**

The authors declare no competing interests.

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