

Clinical practice guidelines on polycystic ovary syndrome: a systematic review and comparative meta-analysis

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Summary

Objective: This study used a systematic review to evaluate the clinical guidelines for polycystic ovary syndrome (PCOS) to guide clinical applications. **Materials and Methods:** PCOS guidelines were electronically retrieved from Medline, EMBASE, the Cochrane Library, CBM, CNKI, and VIP. The time span for the search extended until December 2016. Two researchers searched the literature according to the inclusion and exclusion criteria, and applied appraisal of guidelines research and evaluation II (AGREE II) to evaluate the quality of the guidelines. In the case of disagreement the results were discussed with experts in obstetrics and gynecology. **Results:** Sixteen clinical guidelines were included in this study. The study years ranged from 2004-2016. Average scores from five domains were 65.62%, 62.15%, 46.55%, 91.15%, and 41.01%. The data distribution in the sixth domain was abnormal. One guideline included "strongly recommended," 13 guidelines included "revise and improve the recommendation," and 2 guidelines included "not recommended." Sixteen guidelines involved diagnoses of infertility, metabolic and cardiovascular diseases, health problems, and long-term complications. **Conclusion:** It has been suggested that an evidence-based medical approach be used to develop clinical guidelines. The quality of guidelines from China should help to develop and improve high-quality care and shorten the gap in the international development.

Key words: Polycystic ovary syndrome; Guideline; Systematic review; AGREE II; Meta-analysis.

Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine and metabolic disorder that affects puberty, child-bearing age, and persists lifelong. The clinical manifestations of PCOS include hirsutism, acne, abnormal menstruation, infertility, hyperandrogenism, and polycystic ovary manifestations. At the same time, the following metabolic abnormalities can appear: (1) obesity; (2) insulin resistance; and (3) dyslipidemia. The etiology of PCOS has not been fully defined. It is a multifactorial disorder characterized by genetic, metabolic, endocrine, and environmental abnormalities [1]. A retrospective analysis of the diagnosis and management of PCOS showed that the treatment of patients with PCOS vary, treatment reflects the consensus view [2]. Some countries are constantly improving PCOS treatment guidelines and management [3]. Over the past 30 years, some international organizations and countries have formulated clinical guidelines to provide guidance to clinicians who diagnose and manage patients with PCOS.

Vlayen *et al.* [4] searched the clinical guidelines evaluation tool and identified 24 evaluation tools in the Medline, Embase, and Cinahl databases in which AGREE was the only validated assessment method. The AGREE Next Steps Society released AGREEII in 2009. AGREEII consists of 6 areas with 23 specific and 2 overall evaluation items. The recommended assessment guidelines should be

reviewed by at least 2, but preferably 4 people. Each item has a score of 1-7. The first point represents that the guideline does not conform to the item completely. The seventh point represents a guideline that is in full compliance with the item; points 2-6 represent various levels of conformity/compliance with the stated item. AGREEII is the most comprehensive evaluation tool that has been validated [5].

In this study AGREEII was used to appraise the formulation and reporting quality of PCOS guidelines at home and abroad and to provide references for PCOS clinical diagnosis and guideline development.

Materials and Methods

To have PCOS treatment guidelines published at home and abroad in Chinese and English, the following types of articles were excluded: (1) guidelines for assisted reproduction; (2) comprehensive guideline referring to PCOS; and (3) articles in which old guidelines have been replaced/updated.

Guidelines were electronically retrieved from databases, including Medline, EMBASE, Cochrane Library, CBM, CNKI, and VIP; the retrieval time span extended to December 2016. The retrieval keywords, polycystic ovary syndrome, guidelines, consensus, recommendations, and statements, were used.

Table 1. — *The main characteristics of the included 16 guidelines.*

Number	Published time	Organization	Country or region	No. of authors	No. of references	Pages
1	2004	Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group [6]	Europe / U.S.A	33	95	7
2	2005	American Association of Clinical Endocrinologists (AACE) [7]	U.S.A.	8	64	9
3	2006	The Androgen Excess and PCOS Society (AE-PCOS) [8]	U.S.A.	11	97	9
4	2007	The Androgen Excess and PCOS Society (AE-PCOS)[9]	U.S.A.	6	78	11
5	2007	The Chinese Medical Association Branch of Obstetrics and Gynecology [10]	China	1	11	3
6	2008	European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ ASRM) [11]	Europe / U.S.A	31	166	16
7	2009	The Androgen Excess and PCOS Society (AE-PCOS) [12]	U.S.A.	11	303	33
8	2010	Society of Obstetricians and Gynaecologists of Canada (SOGC) [13]	Canada	11	69	8
9	2010	The Androgen Excess and PCOS Society (AE-PCOS) [14]	U.S.A.	10	139	12
10	2011	Polycystic Ovary Syndrome Association of Australia (POSAA) [15]	Australia	111	331	126
11	2011	The Androgen Excess and PCOS Society (AE-PCOS) [16]	U.S.A.	11	204	25
12	2012	European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ ASRM) [17]	Europe / U.S.A	14	301	11
13	2013	The Endocrine Society (TES) [18]	U.S.A.	7	296	29
14	2014	Royal College of Obstetricians and Gynaecologists (RCOG) [19]	United Kingdom	19	94	15
15	2014	European Society of Endocrinology (ESE) [20]	Europe	11	285	29
16	2016	Reproductive Endocrinology Group, Chinese Maternal & Child Health Industry Association, National Association of Health Industry & Enterprise Management [21]	China	13	14	4

AGREEII was used to evaluate the quality of the guidelines. All of the guidelines were independently evaluated by two researchers (Jingjing Dun and Jinbang Xu), discussed, and in the case of disagreement, decided upon by an obstetrics and gynecology specialist (Xiaoyun Wang). The two researchers read the user's manual carefully and consulted the AGREE website to complete online training. The AGREEII evaluation tool is divided into 6 domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence) and consists of 23 items. Each AGREEII item and two overall evaluation items are divided according to a score from 1-7, in which 1 represents strongly disagree and 7 represents strongly agree. Two researchers scored each item and an expert calculated each domain score sum and standard for the highest percentage score using the following equation: $\text{score} = (\text{actual score} - \text{minimum possible score}) / (\text{maximum possible score} - \text{minimum possible score}) \times 100\%$. The guidelines are divided into 3 levels: (1) "Strongly recommend for use in practice" in which 6 domain scores are $\geq 60\%$; (2) "Recommended for use with some modification," in which the number $\geq 30\%$ is ≥ 3 , but has the domain $< 60\%$; or (3) "Not recommended for use in practice," in which the number $< 30\%$ is ≥ 3 .

Results

A total of 1297 articles were screened according to the search strategy by reading the title, abstract, and full text; 1281 were removed and 16 were included in our PCOS clinical guidelines. Additional details are shown in Figure 1. In 16 guidelines, the European Society of Human

Reproduction and Embryology and the American Society for Reproductive Medicine that developed the Rotterdam standard, had formulated two guidelines on women's health and infertility. The Androgen Excess Society (AES) developed the AES standard that formulated three guidelines for glucose intolerance, cardiovascular disease risk, and hirsutism. The American Association of Clinical Endocrinologists, The Endocrine Society, the European Society of the Endocrinology Royal College of Obstetricians and Gynaecologists, the Society of Obstetricians and Gynaecologists of Canada, and the Polycystic Ovary Syndrome Association of Australia (POSAA) each developed one guideline, and the other two guidelines were formulated by the Chinese. The span of the search ranged from 2004-2016. Seven guidelines were from the United States (US), one was from Britain, one was from Australia, one was from Canada, two were from China, one was from Europe, and three were from Europe and America. The number of authors ranged from 1-112, and the number of references ranged from 11-331. The number of pages ranged from 3-126, and there were 9 evidence-based guidelines. Evidence-based guidelines included 3, 4, 7, 8, 9, 10, 11, 13, and 14. Additional details are shown in Table 1.

The scores of 16 guidelines are shown in Table 3, and the distribution of the data of the sixth domain was abnormal. The top 3 domains and the average score $\geq 60\%$ included clarity of presentation, scope and purpose, and stakeholder involvement. Additional details are shown in Table 2.

One guideline had 6 domains $\geq 60\%$ that included "strongly recommended" (from Australia). The scores of the domains of 13 guidelines that were concentrated around

Table 2. — Scores of 16 guidelines in six domains.

Number	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence
1	47.22	66.67	37.5	100	62.5	0
2	47.22	63.89	23.96	91.67	33.33	0
3	77.78	58.33	59.37	91.67	29.17	0
4	77.78	58.33	58.33	100	29.17	0
5	38.89	27.78	21.87	80.56	20.83	0
6	44.44	66.67	32.29	91.67	47.92	0
7	77.78	66.67	63.54	94.44	47.92	0
8	88.89	66.67	59.37	97.22	54.17	0
9	77.78	66.67	59.37	88.89	29.17	0
10	100	94.44	88.54	94.44	75	83.33
11	55.55	63.89	51.04	91.67	56.25	0
12	47.22	63.89	30.21	91.67	27.08	0
13	72.22	66.67	45.83	100	43.75	0
14	72.22	66.67	52.08	86.11	20.83	0
15	77.77	63.89	33.33	80.56	50	41.67
16	47.22	33.33	28.12	77.78	29.16	0
Total	65.62 ± 18.56	62.15 ± 14.69	46.55 ± 18.11	91.15 ± 6.97	41.01 ± 15.99	0 (0,83.33)

30% ~ 60% included “revise and improve the recommendation” with 7 from the US, 3 from Europe and America, 1 from the UK, 1 from Europe, and 1 from Canada. The scores of most domains in the 2 guidelines that were < 30% were not recommended (from China). Additional scores are shown in Table 3.

The average score was 65.62% and included 3 items. The guideline of number 10 achieved 100%, which fully covered the above 3 items. This guideline also used relevant evidence-based parameters and had invited guidance specialists who used the AGREEII evaluation tool, which scored 100% in this domain and was consistent with the scores of our researchers. Other guidelines on the three items were not comprehensive.

The average score was 62.15% and included 3 items. The highest score among the guidelines was number 10, which received a 94.44% and their own score was 91.67%. There were 112 participants (including 37 people from membership of the PCOS Australia Alliance and 74 people from membership of guideline development committees and other related fields). Patient and audience views were collected, and the target users of the guideline were explained. The average scores of other guidelines were around 60% with a range of authors from 6-33. Points were lost on the collection of the views of the patients and audience, while guideline 5 listed one author with the lowest score.

The average score was 46.55% and included 8 items. Guidelines 3, 4, 7, 8, 9, 10, 11, 13, and 14 used the systematic methods to retrieve evidence, while most guidelines used the Rotterdam, NIH, and/or the AES standards or referred to the Rotterdam and NIH standards. Guidelines 2, 12, and 16 did not use explicit criteria. Guidelines 4 and 10 were reviewed by external experts prior to release. Only guideline 10 showed the steps for updating the guidelines,

and none of the other guidelines had been sent to an external reviewer and did not mention updating steps.

The average score was 91.15% with an average score of the highest in the 6 areas and included 3 items. The recommendations of each guideline that were specific and listed different options were considered primary and secondary.

The average score was 41.01% and included 4 items. Guideline 7 provided the definition tool and the final appendix of guideline 10 included a questionnaire and evidence-based guideline development pathways. Guidelines 11 and 15 provided flow charts, whereas other guidelines lacked the application tools. Guidelines 1, 6, 8, 10, 11, 13, and 15 explained the cost of expenditure that other guidelines did not specify. All guidelines provided criteria for evaluation.

The distributions of the data of the domain were abnormal, with 14 guidelines scoring 0; 2 items were included in this field. Guideline 10 pointed out the independence of the guideline editors, which was not mentioned in other guidelines. Guidelines 10 and 15 described no conflicts of interest among members, while other guidelines were not mentioned.

Guideline 10, which was developed by POSAA, had the highest score. Each domain $\geq 60\%$ was noted as “strongly recommended.” Relevant evidence-based parameters and guidance specialists using the AGREEII evaluation tool were included. The score of each domain was similar to the present evaluation, but this guideline did not have much clinical application, and this study recommended clinical applications. Scores $\leq 30\%$ in 13 guidelines were ≤ 2 and consisted of “revise and improve the recommendation”. Two domains with low scores included applicability and editorial independence. Most guidelines lacked the application of tools for supporting the guidelines and did not explain the independence of the guidelines editors. Three

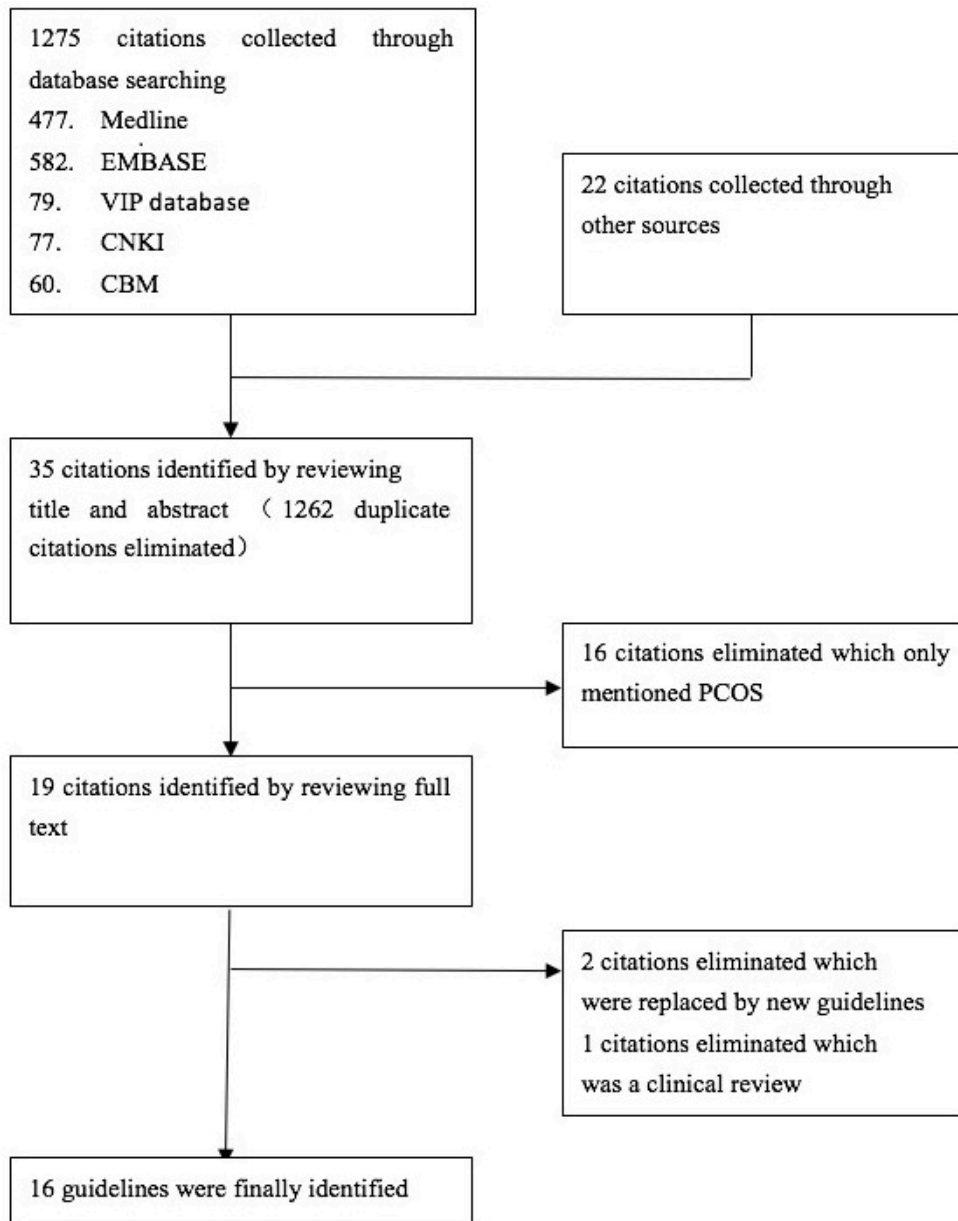


Figure 1. — The flow chart of literature retrieval.

or four domains of the second guideline were < 30% and included “not recommended” (from Chinese reviewers). Guideline 5 only had 1 author and received a low score in domains 3, 5, and 6.

The guidelines for the diagnosis were 1, 3, 5, 7, 11, 13, and 16. Guideline 1 was based on the Rotterdam diagnostic criteria, which consisted of several extensively used parameters: (1) rare ovulation or anovulation; (2) the clinical manifestations of hyperandrogenism, and/or hyperandrogenemia; (3) polycystic ovaries; and (4) two of three items can be diagnosed. Guidelines 3 and 7 followed AES standards. Based on the Rotterdam diagnostic criteria, AES standards emphasized the importance of hyperandrogenism. Guidelines 5 and 13 referred to the

Rotterdam diagnostic criteria. The diagnosis of PCOS of guideline 11 included hirsutism and/or elevated free testosterone and rare ovulation and/or polycystic ovarian changes and excluded atypical congenital adrenal hyperplasia (NC-CAH). The contents mainly involved infertility, metabolic diseases, cardiovascular diseases, youth PCOS, pregnancy outcomes, psychological problems, cancer, and long-term complications.

In the treatment of infertility, guideline 6 recommended clomiphene citrate for first-line intervention, exogenous gonadotropin or laparoscopic ovarian surgery for second-line intervention, and *in vitro* fertilization for third-line intervention. Guideline 8 presents the following recommendations for ovulation induction: (1) diet, exercise, and

Table 3. — Numbers of score $\geq 60\%$, $\leq 30\%$, and overall assessments.

Number	score $\geq 60\%$	score $\leq 30\%$	Overall assessments
	Numbers of domain	Numbers of domain	
1	3	1	Recommend with modification
2	2	2	Recommend with modification
3	2	2	Recommend with modification
4	2	2	Recommend with modification
5	1	4	Not recommend
6	2	1	Recommend with modification
7	4	1	Recommend with modification
8	3	1	Recommend with modification
9	3	2	Recommend with modification
10	6	0	Strongly recommend
11	2	1	Recommend with modification
12	2	2	Recommend with modification
13	3	1	Recommend with modification
14	3	2	Recommend with modification
15	3	0	Recommend with modification
16	1	3	Not recommend

lifestyle adjustments were first choices for obese PCOS patients who had recovered ovulation and were able to become pregnant; (2) clomiphene citrate was the first-line treatment for ovulation induction; (3) metformin combined with clomiphene could improve the ovulation and pregnancy rates, but could not improve the live birth rate; (4) gonadotropin was the second-line treatment for anovulation; (5) laparoscopic surgery could be applied to PCOS patients who demonstrated clomiphene citrate resistance; and (6) if gonadal hormone therapy was ineffective, *in vitro* fertilization was indicated if available. Guideline 14 recommended ovarian electrocautery as an approach to ovulation induction.

With respect to metabolism, diabetes, and cardiovascular disease, guideline 2 indicated that PCOS was an important risk factor for diabetes. PCOS patients > 30 years of age required diabetes screening. PCOS patients were more likely to have cardiovascular risk factors, such as hyperlipidemia, hypertension, atherosclerosis, and endothelial dysfunction. On the basis of glucose tolerance testing, guideline 4 recommended that PCOS patients should have a glucose tolerance screening test, and patients with normal glucose tolerance should be reviewed at least once every 2 years; if it was found that the risk factors increased, the frequency of follow-ups for patients with abnormal glucose tolerance should be reviewed annually. Guideline 9 proposed obesity, smoking, dyslipidemia, hypertension, impaired glucose tolerance, and subclinical vascular disease as risk factors for cardiovascular disease, and metabolic syndrome and/or type 2 diabetes were high risk factors for cardiovascular disease. For the prevention of PCOS in women, body mass index (BMI), waist circumference, blood lipids, and glucose levels should be monitored, and obese patients with PCOS should have a glucose tolerance test. With respect to women's health, guideline 12 described irregular

menstruation, increased metabolic risk, and menstrual disorder as more serious with a more obvious PCOS phenotype; not all PCOS phenotypes have metabolic risk. The metabolic risk of hyperandrogenism and oligomenorrhea was the highest. PCOS was the main risk for impaired glucose tolerance and type 2 diabetes. Obesity could aggravate the development of diabetes. Dyslipidemia, abnormal glucose tolerance, and type 2 diabetes were more common in PCOS patients; the risk of cardiovascular disease increased at any age in patients with PCOS. PCOS was prevalent in patients with elevated triglycerides, and high levels of low- and high-density lipoprotein changes. The risk of cardiovascular disease increased the risks for depression and anxiety. Endothelial dysfunction was related to abdominal obesity and insulin resistance. Guideline 14 proposed PCOS patients who were overweight and > 40 years or had a family history of diabetes or had gestational diabetes should be screened for type 2 diabetes. PCOS patients with snoring and daytime fatigue and/or sleepiness were at risk for sleep apnea. All PCOS patients should be evaluated for cardiovascular risk. For treatment, guidelines 2, 4, 9, and 14 recommended lifestyle changes, which included diet, exercise, and weight loss as the first type of treatment intervention for PCOS. Insulin sensitizers were used as glucose intolerance and diabetes drug treatments. Hypertension needed routine treatment, and dyslipidemia was treated with lipid-lowering therapies. Guideline 14 recommended that the body mass index should be ≤ 35 kg/m². It was recommended that patients ≥ 40 kg/m² and at high risk for obesity should undergo bariatric surgery.

Guideline 12 proposed that a diagnosis of adolescent PCOS should be different from women of reproductive age, and clinicians should identify obesity, hirsutism, menstrual irregularities, and other risks to avoid overdiagnosis. Adolescent PCOS characterized by obesity, hirsutism, and men-

strual irregularities should be treated. Guideline 13 proposed clinical or biochemical hyperandrogenism (excluding other diseases) in the continued existence of oligomenorrhea as the basis for young PCOS diagnosis. Ovarian anovulation or polycystic change was not enough for the diagnosis of PCOS as ovulation may return to normal in the reproductive stage. Oral contraceptives were first-line treatment for adolescent PCOS. Lifestyle adjustments were the first-line treatment for overweight and obese patients. Metformin was recommended for patients with impaired glucose tolerance or metabolic syndrome.

Guideline 12 proposed that there was an increase in adverse pregnancy outcomes in PCOS patients. These risks increased in obesity and insulin resistance, and the risk of hypertension and diabetes increased during pregnancy. There was no evidence that taking metformin before or during pregnancy increased the birth rate or reduced pregnancy complications. Guideline 13 maintained that risk of pregnancy complications, including gestational diabetes, preterm delivery, and preeclampsia, increase and recommended by assessment of BMI and blood pressure, and a glucose tolerance test. Guideline 14 suggested that PCOS patients should be screened for diabetes at 24–28 weeks of pregnancy.

Guideline 12 stated that there was an increase in psychological problems in PCOS patients. Guideline 14 suggested that PCOS should be considered in patients with psychological problems and that anxiety and/or depression should be used as a routine screening tool. Guideline 15 pointed out that PCOS should be considered in patients with psychological problems and quality of life as assessed by the HADS questionnaire, Rosenberg's Self-Esteem Scale, and the Beck Anxiety Inventory. The Beck Depression, Inventory and Symptom Checklist 90 were chosen and used for assessments according to recommendations by experts in different areas of research.

Guideline 12 presented some data that confirmed that PC patients are 2.7 times more likely to develop endometrial cancer. Limited data do not support an increased risk of PCOS ovarian and breast cancers. Guideline 14 considered that the risk of endometrial hyperplasia and endometrial cancer in patients with oligomenorrhea or amenorrhea was increased and should be treated with withdrawal bleeding every 3–4 months.

Discussion

Clinical guidelines were widely used and were of far-reaching significance for clinical practice. They were used to guide clinicians in diagnosis and treatment and standardized medical activities. This study included 16 clinical PCOS guidelines of PCOS that were mainly from the US, Britain, Europe, Canada, Australia, and China and have been published in the last 10 years. One guideline included “strongly recommended,” 13 guidelines included “revise and improve the recommendation,” and 2 guidelines included “not recommended.” The POSAA guidelines for

evidence-based guidelines have high scores in all areas that were highly recommended. The guidelines had been evaluated with AGREEII and were consistent with the scores in this study, but there was less clinical application. The Rotterdam diagnostic and AES standard were more applied in clinical settings with emphasis on the Rotterdam diagnostic standards, but the scoring was not the highest in all areas. The two guidelines from China, which included “not recommended,” scored low in the domains of rigor of development, applicability, and editorial independence. In the domain of editorial independence, and with the exception of two guidelines, none of the other guidelines mentioned these parameters and received 0 points in this field.

PCOS patients in China are increasing. China's PCOS guidelines need to improve quality, learn from international experience, and establish relevant professional organizations to develop high-quality, evidence-based guidelines based on foreign and domestic clinical guidelines. This will help breach the gap with the international development in which to conduct clinical diagnosis and treatment activities.

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Conflict of Interest

The authors declare no conflict of interest.

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