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Clinical practice guidelines on the diagnosis and management of polycystic ovary syndrome: A systematic review and quality assessment study

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Abstract:	Context: Clinical practice guidelines (CPGs) are key instruments to implement the practice of evidence-based medicine. We aimed to evaluate the methodological quality and variations in CPGs recommendations on the diagnosis and management of polycystic ovary syndrome (PCOS). Evidence Acquisition : We searched MEDLINE, EMBASE, and CENTRAL until December 2020 for all evidence-based CPGs and consensus statements on PCOS. We extracted data in duplicate to map clinical recommendations across pre-specified disease domains and assessed CPGs methodological quality of using the AGREE II tool. Evidence Synthesis : We included thirteen PCOS CPGs were published between 2007-2018. CPGs recommendations were mostly focused on screening for and managing metabolic disease (12/13, 92%), followed by cardiovascular risk assessment (10/13, 77%). Mental health (8/13, 62%) and diagnosis in adolescents (7/13, 54%) were the least reported domains. Most CPGs had a high quality for scope and purpose description (12/13, 92%) while stakeholder's involvement and applicability of recommendations to clinical practice were appropriate in only two CPGs (2/13, 15%). We identified inconsistency in recommendations on PCOS diagnosis in adolescents, optimal lifestyle interventions, hirsutism and acne treatments, interventions to reduce the risk of ovarian hyperstimulation syndrome, the frequency and screening criteria for metabolic and cardiovascular disease, and on optimal screening tools for mental health illness in women with PCOS. Conclusion: Current CPGs on the diagnosis and management of PCOS vary in their scope and methodological quality which may hinder evidence translation into clinical practice. We identified disease domains with existing evidence gap to guide future research and guideline updates.
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Clinical practice guidelines on the diagnosis and management of polycystic ovary syndrome: A systematic review and quality assessment study

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Abstract:

Context: Clinical practice guidelines (CPGs) are key instruments to implement the practice of evidence-based medicine. We aimed to evaluate the methodological quality and variations in CPGs recommendations on the diagnosis and management of polycystic ovary syndrome (PCOS).

Evidence Acquisition: We searched MEDLINE, EMBASE, and CENTRAL until December 2020 for all evidence-based CPGs and consensus statements on PCOS. We extracted data in duplicate to map clinical recommendations across pre-specified disease domains and assessed CPGs methodological quality of using the AGREE II tool.

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We identified inconsistency in recommendations on PCOS diagnosis in adolescents, optimal lifestyle interventions, hirsutism and acne treatments, interventions to reduce the risk of ovarian hyperstimulation syndrome, the frequency and screening criteria for metabolic and cardiovascular disease, and on optimal screening tools for mental health illness in women with PCOS.

Conclusion: Current CPGs on the diagnosis and management of PCOS vary in their scope and methodological quality which may hinder evidence translation into clinical practice. We

identified disease domains with existing evidence gap to guide future research and guideline updates.

Introduction:

Polycystic ovary syndrome (PCOS) is the commonest endocrine condition affecting women of reproductive age worldwide[1]. It significantly impacts women's wellbeing and quality of life often increasing the risk of longterm health complications such as subfertility, type 2 diabetes, metabolic syndrome and endometrial cancer[2].

Adopting the principles of evidence-based medicine (EBM) has stimulated research conduct and evidence synthesis on the diagnosis and management of PCOS over the past few decades[3]. Still, PCOS research remained largely segregated within different specialist disciplines caring for affected women such as primary care, endocrinology, gynaecology etc.. leading to poor integration of evidence and undesired heterogeneity in research conduct[4].

Clinical practice CPGs (CPG) and consensus statements are now primary tools to enable the practice of EBM and facilitate the implementation of evidence in everyday clinical practice[5]. Traditionally, CPGs were developed within professional societies and speciality health regulators. This, however, led to concerns about the CPG inclusiveness, scope, and applicability to address patients' needs in real life[6]. Specifically, engaging lay consumers in the process of guideline production could help to focus the scope of CPGs on patients' health needs and optimise the adoption of CPG recommendations into clinical practice[7]. Several quality standards and development frameworks were established to optimise CPG implementation in clinical practice, increase their relevance, and promote inclusiveness of key stakeholders in the process[8–10]. Adopting these principles into PCOS CPGs could be particularly challenging given the varied presentation of PCOS, its lifelong impact on affected women, and the numerous disciplines involved in PCOS care provision[3]. We aimed to systematically review all available CPGs on the management of PCOS and assess their quality using the AGREE II tool[9].

Methods:

We undertook a systematic review using a prospectively registered protocol (CRD42018116809) and reported in line with the PRISMA CPGs[11].

Literature search

We searched MEDLINE, EMBASE, and Cochrane CENTRAL databases using the following search terms to identify eligible CPGs on PCOS from inception until December 2020: Clinical, CPGs, consensus statement, position statement, recommendation?, polycystic ovary, polycystic ovary syndrome, hyperandrogen*, anovulation, *menorrhea, wom?n, female, pregnan*. Complementary searches was conducted in Google Scholar, Tripdatabase and Scopus. We searched the websites of established regulatory bodies on the topic of care for women with PCOS to identify relevant CPGs. We did not apply any search filters or language limitations.

Guideline selection and inclusion process

Two independent reviewers (BHA and MF) completed the study selection and inclusion process in two stages. Discrepancies were resolved in consensus with a third reviewer (LB). We included all purpose-developed evidence-based clinical CPGs and consensus statements addressing the diagnosis and/or management of PCOS across different clinical disciplines and populations. We excluded position or opinion statements that did not make direct recommendations linked to specific evidence and systematic reviews from scientific

societies. All other designs of primary or secondary studies evaluating a particular scientific question were excluded.

Data collection

Two independent reviewers (LB and MF) extracted data in duplicate into an electronic Excel sheet which was piloted for its face validity. Data integrity was double-checked by a third reviewer (BHA). We extracted data on the following guideline characteristics: producing authority, named authors, country of origin, year of publication, consensus method, stakeholders involved, disease domain addressed in the CPG, description of the search strategy to identify evidence, inclusion/exclusion criteria of evidence, quality assessment instruments used, grading system used. We mapped out the clinical recommendations in each guideline and tabulated them into the following pre-specified domains: diagnosis in adolescents and adults; lifestyle interventions; management of menstrual irregularity, hirsutism, acne, and infertility; risk assessment for metabolic disease, cardiovascular disease, mental health, and cancer.

Assessment of methodological quality

We used the Appraisal of CPGs for Research & Evaluation II (AGREE II) instrument[9] to assess the methodological quality of each guideline in six domains (scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, editorial independence) and 23 items. Each item was scored using a seven-point Likert scale anchored between 1 (strongly disagree) and 7 (strongly agree). We generated a total quality score using a prescribed formula[9]. We categorised scores to offer a summative quality

measure for each domain with scores from 10-7 showing high quality, 7-4 medium quality and scores below 4 showing low quality of guideline development.

Statistical analysis

We calculated a total guideline quality score by adding the scores of the various quality domains and standardising scores using a prescribed equation[9]. We reported on descriptive data using normal frequencies, median and ranges. We assessed correlation coefficients using Pearson correlation test. All statistical analyses were conducted using Microsoft Excel (Excel 2017, Microsoft, Redmond, Washington).

Results

Our electronic search identified 575 titles and abstracts of which we screened 26 articles in full against our inclusion criteria, and included a total of five national and eight international PCOS CPGs (n=13) (Figure 1).

The majority of included CPGs were published within the last ten years (range 2007-2018) and all but one[12] were reported as peer-reviewed. Most CPGs used simple panel discussions to reach consensus among co-authors, and only two (2/13, 15%) used an established consensus methodology (e.g. Delphi method)[13,14]. Seven CPGs used a clear evidence grading system when making recommendations (7/13, 54%) and only two (2/13, 15%) provided clear implementation tools for evidence into clinical practice[13,14] (Table 1).

The median number of recommendations made per guideline was 26 (range 6-90). Screening for and managing metabolic disease was the most commonly covered disease domain in twelve CPGs (12/13, 92%) followed by recommendations on cardiovascular risk assessment (10/13, 77%). Contrastly, management of mental health (8/13, 62%) and diagnosis in

adolescents (7/13, 54%) were the least commonly addressed disease domains across the included CPGs (Table 2).

Guideline quality

Our evaluation of CPGs' quality using the AGREE II tool showed variations across the assessed domains with most CPGs offering high-quality scope and purpose description (12/13, 92%) as well as clarity in presentation (9/13, 69%). Stakeholder involvement and applicability of recommendation to clinical practice were poorly addressed by most CPGs with only two showing good quality for each (2/13, 15%) (Figure 2). There was a poor correlation between guideline quality and year of publication (r=-0.02).

Summary of recommendations

Majority of CPGs focused on the different treatments of PCOS (10/13, 77%), risk assessment (10/13, 77%) and only nine made recommendations on the diagnosis of PCOS (9/13, 69%).

Diagnosis of PCOS

For the diagnosis of PCOS in adults, seven CPGs supported the use of the Rotterdam criteria[15] or its modification[16] though only one provided a clear definition for of polycystic ovarian morphology (PCOM) in adults[13]. Only four CPGs recommended systematic examination and assessment of clinical hyperandrogenism with only one guideline recommending the use of specific standardised assessment tools (Ferriman Gallwey score and The Ludwig visual score) for hirsutism and acne in adults[13]. All relevant CPGs supported the use of Testosterone (total or free) or the Free Androgen Index to diagnose hyperandrogenaemia, though there were variations on the value of Androstenedione and

Dehydroepiandrosterone Sulphate as routine blood tests to diagnose PCOS. Anti-Müllerian hormone was recommended as useful for diagnosing PCOS in one guideline[17] while the International PCOS guideline did not recommend its use[13].

Two CPGs were particularly focused on the diagnosis and management of PCOS in adolescents[18,19], and five generated recommendations on both adolescent and adult women with PCOS[13,14,17,20,21]. All relevant CPGs recommended against the use of PCOM as an independent ultrasonic diagnostic feature in adolescents emphasising the limited value of ultrasound scanning in this population. Only two CPGs made clear recommendations on the definitions for oligo and amenorrhea in adolescents as part of the PCOS diagnostic criteria[13,19]. There were variations in the recommendations made on the value of different biochemical tests to diagnose hyperandrogenaemia though all included CPGs recommended against the use of Anti-Müllerian hormone.

Lifestyle interventions

Nine CPGs recommended lifestyle treatments (LST) as 1st line intervention in adolescents and adult women with PCOS [12–14,18,20–25]. The majority of these CPGs recommended a mixture of calorie-restricted diet, exercise and behavioural interventions as the main features of LSTs. Four CPGs recommended a weight loss target between 5-10% with LSTs [14,18,20,22]. There were no clear recommendations on the type of diet to offer women with PCOS with varied recommendations for hypocaloric diet (deficit between 500 and 700 kcal/day) and a focus on low glycaemic index food intake [13,22]. Similarly, there was no clear consensus on the optimal duration or type of physical exercise to recommend. Three CPGs recommended 150 min/week [13,14,20] and 90 of aerobic moderate-high intensity exercise for weight maintenance. Three CPGs recommended combining LSTs with pharmacological treatments such as

metformin to optimise weight loss after 6 months [13,20,25] and three recommended bariatric surgery in obese women with PCOS if LST alone failed to achieve sufficient weight loss[13,14,23].

Management of menstrual irregularity

Six CPGs recommended the use of hormonal contraceptives as 1st line of treatment for managing menstrual irregularity in adult women with PCOS [12–14,18,20,21] and five recommended their use in adolescents with suspected/confirmed PCOS diagnosis [13,14,18,20,21]. The use of metformin, cyproterone acetate and drospirenone was recommended as 2nd line treatment for menstrual irregularity, hirsutism and acne in three CPGs[13,20,21]. Most of these CPGs recommended using the same screening criteria as for safe use of hormonal contraceptive in the general population. The use of progesterone to induce regular withdrawal bleeds in amenorrheic women with PCOS was recommended in three CPGs[13,20,25].

Management of hirsutism and acne

Only five CPGs made direct recommendations on treatments for hirsutism and acne with three CPGs recommending photoepilation and topical eflornithine as 1st line of treatment [12,18,20]. By contrast, the Endocrine Society guideline recommended using hormonal contraceptives as 1st line treatment in adolescents with suspected PCOS to treat acne, hirsutism and anovulatory symptoms. Anti-androgen medications alone or combined with hormonal contraceptives were recommended as 2nd line treatments in four CPGs [13,17,18,20].

Management of Infertility

Overall LSTs were considered the optimal 1st line treatment for anovulation in women with PCOS and infertility for 3-6 months[13,14,22]. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists guideline considered pharmacological ovulation induction a contraindication in obese women (body mass index >35 kg/m^2) with PCOS[23]. Three CPGs recommended the use of letrozole as the primary method of pharmacological ovulation induction[12,13,21]. This represented a shift in evidence compared to older CPGs such as the Australian NHMRC guideline considered it optional [14] and the Thessaloniki ESHRE/ASRM guideline recommended clomiphene citrate as first-line treatment[22]. Most CPGs recommended ovulation induction with gonadotropins or laparoscopic ovarian drilling as 2nd line. The Thessaloniki ESHRE/ASRM guideline recommended a gonadotropins starting dose of 37.5-50 IU/day with adherence to a 14-day stimulation period with close ovulation monitoring and a maximum of six stimulation cycles[22]. *In-Vitro* fertilisation was suggested as last option with a preference for gonadotropin-releasing hormone antagonist protocols and metformin to reduce the risk of ovarian hyper-stimulation syndrome[13,21], though there were limited recommendations on the best *In-Vitro* fertilisation protocols in women with PCOS.

Risk assessment and management of metabolic disease

Most of the included CPGs supported using Metformin alone or in combination with other treatments (e.g. hormonal contraceptives) in overweight/obese women to optimise weight management, reduce insulin resistance and minimise hyperandrogenism[12–14,17,18,20–22,26,27]. There was no advice regarding the point of commencement or duration of treatment. There was uncertainty on the safety of Metformin in pregnancy especially in those who received it during ovulation induction. Two CPGs suggested stopping it once pregnancy is

confirmed[13,20]. Similarly, there were no clear criteria for its use in adolescents with suspected PCOS across included CPGs.

An oral glucose tolerance test was considered the gold standard to screen for impaired glucose intolerance and type 2 diabetes though there were variations on the recommended frequency of screening (Table 3). More frequent screening was suggested in women with risk factors for type 2 diabetes including body mass index > 25kg/m2 or in Asians >23kg/m2, central adiposity, substantial weight gain, increased waist circumference, symptoms of diabetes, family history of impaired glucose intolerance, type 2 diabetes, chronic hypertension or high-risk ethnicity, age > 40 years, personal history of gestational diabetes or high blood glucose level, use of antihypertensive medications, smoking, physical inactivity [13,14,21,26,27]. HbA1C was recommended as a substitute screening/diagnostic test when oral glucose tolerance test is not feasible[13,20,21].

Two CPGs recommended screening for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in women with insulin resistance and metabolic syndrome suggesting vitamin E as preferred treatment with specialist multi-disciplinary team input[20,21].

Mental health

Routine assessment for mental health and quality of life was supported in seven CPGs [13,14,20,21,23,26,27] though only the International PCOS guideline recommended the use of specific screening and assessment tools[13]. Referral for appropriate mental health counselling and management was recommended though no specific referral pathways were suggested[13,14,20,21,23,27].

Cardiovascular disease

Assessment of cardiovascular risk factors in women with PCOS was recommended in eight CPGs using an array of risk factors including obesity especially increased abdominal adiposity, smoking, hypertension, dyslipidaemia, subclinical vascular disease, impaired glucose tolerance, family history of premature cardiovascular disease, lack of physical activity, metabolic syndrome and type 2 diabetes, obstructive sleep apnoea, high levels of CRP and homocysteine[12–14,20,21,23,26,27] One guideline[20] supported the use of serum homocysteine as a test for hyperhomocysteinemia-mediated repeated pregnancy losses in women with previous miscarriage although the quality of associated evidence was poor.

Five CPGs recommended routine screening for obstructive sleep apnoea in women with PCOS by checking associated symptoms such as snoring, waking unrefreshed from sleep, daytime sleepiness. All these CPGs considered a polysomnography test as the gold standard diagnostic test for obstructive sleep apnoea[13,20,21,23,27] and only the International PCOS guideline supported the use of the Berlin tool for screening in symptomatic women[13].

Cancer

Routine screening for endometrial cancer was not recommended in women with PCOS in three CPGs [13,20,21]. Two CPGs recommended performing a transvaginal ultrasound scan to evaluate the endometrium in case of abnormal uterine bleeding, spotting and prolonged amenorrhea (>90 days)[13,21]. Three CPGs recommended inducing a withdrawal bleeding using progesterone in women with prolonged amenorrhea every 3-4 months and offering an endometrial biopsy and/or hysteroscopy to assess thickened endometrium or an endometrial polyp[13,27] The Royal College of Obstetricians and Gynaecologists guideline considered

hyperplasia to be unlikely in women with PCOS and an endometrial thickness <7 mm and also recommended no additional surveillance for breast or ovarian cancer[25].

Discussion:

Summary of main findings

We captured a high number of evidence-based CPGs produced over the last decade covering varied disease domains with a consistently increasing number of recommendations. Guideline quality was varied with poor stakeholders involvement and a substantial lack of clear implementation pathways.

Reassuringly, most of the included CPGs recommended the use of homogenous PCOS diagnostic criteria. Still, there were variations in the recommended reference ranges for diagnosing biochemical hyperandrogenism and on the diagnostic value of Anti-Müllerian hormone in adolescents with PCOS.

Most CPGs recommended routine screening for cardiovascular and metabolic diseases in affected women, however, the recommended frequency of screening, measurement tools, and associated risk factors varied substantially (Table 3). Mental health was particularly underrepresented in most of the included CPGs with much uncertainty on the most effective screening and treatment pathways for women with PCOS.

Most of the included CPGs emphasised the importance of LST as 1st line treatment strategy for PCOS, although details on specific dietary regimes were lacking. Similarly, the role of anti-obesity medications and insulin sensitizers was varied across included CPGs. Few CPGs recommended particular treatments for hyperandrogenism which could be linked to the limitations of available evidence on this domain. Lastly, with a growing body of evidence on

fertility treatments for women with PCOS, there were consistent recommendations on treatment pathways for anovulation and subfertility. Variations existed on the role of Letrozole as the primary ovulation induction agent; however, this is unsurprising giving the evolution of evidence on its effectiveness and safety over the last decade. There was limited guidance about the optimal ovarian stimulation protocols and adjuvant treatments to reduce the risk of ovarian hyper-stimulation syndrome in women with PCOS.

Strength and limitations

To our knowledge, our review is the first to evaluate the quality of all available evidence-based CPGs and consensus statements regarding the diagnosis and management of PCOS. We followed an established methodology to systematically review the literature and applied the AGREE II tool to assess guideline quality. Lastly, we mapped out CPGs recommendations to identify underrepresented disease domains and topics of uncertainty to aid future research conduct.

Our analysis has a few limitations. The use of the AGREE II tool is relatively recent and older CPGs may not have adopted recently developed standards which may skew our findings; specifically, the practice of involving stakeholders, including lay consumers in CPGs development as well as active guideline implementation in clinical practice are relatively new. Therefore, these features may be absent in older CPGs. We aimed to provide a systematic assessment of current literature to illustrate the improvement in guideline quality over time. Interestingly, we did not detect a correlation between guideline quality and year of publication.

We were unable to assess the quality and confidence in linked evidence to guideline recommendations as different evidence grading systems were used. This limited our ability to

provide an in-depth analysis of the current evidence gap. The poor quality of available primary studies on PCOS is often reported as a source of heterogeneity and imprecision in published CPGs[13]. Recognizing this evidence gap is helpful to specify future research need and priorities[3].

Implications for clinical practice and future research

PCOS is uniquely expressed as a multi-systemic condition often with varied phenotypes across affected women[28]. To address the complexity of diagnosing and managing the different aspects of PCOS, care provision could be optimised within multi-disciplinary teams shared across primary and secondary care[29]. This vision, however, has not prevailed in most of the evaluated CPGs, many of which were produced by specialist professional societies focused on particular disease domains. Consequently, several important health aspects were infrequently present such as PCOS diagnosis in adolescents and screening for mental health issues. Going forward, future guideline updates should adopt the multi-disciplinary approach to PCOS care provision to minimise fragmentation in health services and optimise women's access to treatments[3]. Specifically, involving lay consumers in future CPGs development could help the process of evidence implementation into clinical practice with a focus on addressing real patients' health needs[30]. For example, qualitative evidence suggested a common theme of women's frustration on the delay in diagnosing PCOS [31]. Acknowledging this need helped to focus research and policymaking efforts on developing clear diagnostic criteria for PCOS including specific diagnostic tools such as PCOM [13]. Our findings suggest that more work is needed to investigate the role of promising diagnostic tests such as Anti-Müllerian hormone and other biomarkers.

As more treatment options become available to address the different aspects of PCOS, there is a need to continuously update available CPGs as well as efficient data collection to enable large scale evidence synthesis and optimise the practice of EBM. This was particularly evident in this review with the limited scope of recommendations made on certain treatments such as the use of different contraceptive for management of hirsutism and acne in PCOS (Supplementary Table 2). Similarly, several new pharmacological agents are now used as fertility treatments for women with PCOS, yet comprehensive and high-quality evidence to support their effectiveness remains limited (Supplementary Table 2). Addressing this evidence gap using randomised trials might be slow and inefficient given the varied phenotypes in women with PCOS. As such, investing in prospective large cohorts and big data research infrastructure may offer a valuable alternative to aid comprehensive evaluation of the effectiveness and safety of newly developed treatments[32].

Conclusion: Current CPGs on the diagnosis and management of PCOS vary in their scope and methodological quality which may hinder evidence translation into clinical practice. We identified disease domains with existing evidence gap to guide future research and guideline updates.

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Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Contribution to authorship: BHA conceived the idea, wrote the protocol, performed the primary analysis and drafted the 1st manuscript. LB and MF extracted data and helped with

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Table (1): Characteristics of included evidence-based clinical guidelines on polycystic ovarian syndrome.

Producing authority	Publication year	Peer reviewed	Consensus methodology	Search strategy	Inclusion/exclusion criteria	Evidence grading system	Implementation tools	Number of recommendations
ICPE[18]	2017	Yes	Panel discussion	N/A	N/A	N/A	No	26
AE-PCOS[26]	2010	Yes	Panel discussion	Systematic review of published peer-reviewed medical literature by 3 investigators.	Inclusion: CVD risk factors for women with and without PCOS. Exclusion: other hyperandrogenic disorders were not excluded, PCOS diagnosis uncertain, controls not described	N/A	No	13
NHMRC[14]	2011	Yes	Consensus voting technique	An internet search strategy for evidence-based guidelines and systematic reviews using the Google 'Advanced Search' function	Included guidelines < 4 years old, pass the AGREE benchmark criteria (Systematic methods used to search for evidence with an explicit link between the recommendations and the supporting evidence)	NHMRC	Yes	66
ES[21]	2013	Yes	Panel discussion	Systematic review of published literature	N/A	GRADE system	No	27
IFS[20]	2018	Yes	Panel discussion	Systematic review of existing guidelines, meta-analyses, systematic reviews, key cited articles	N/A	GRADE system	No	59
CREPCOS[13]	2018	Yes	Delphi and nominal group techniques	Systematic review	N/A	GRADE system	Yes	90+76 clinical practice points

AES[25]	2007	Yes	Panel discussion	Systematic review on MEDLINE	Excluded unpublished data or data published only in abstract for were not included	N/A	No	6
RANZCOG[23]	2017	Yes	N/A	Systematic review on MEDLINE	N/A	N/A	No	9
RCOG[32]	2014	Yes	Committee consensus	Systematic review	Inclusion: 'PCOS', 'metabolic', 'diabetes', 'cardiovascular', 'cancer', English language, limited to humans.	Green-top Grading	No	19
PES[19]	2015	Yes	Committee consensus	Systematic review	N/A	AGREE criteria	No	27
AACE[17]	2015	Yes	Committee consensus	Systematic review	N/A	N/A	No	11
ACOG[12]	2018	No	N/A	Systematic review MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents	N/A	US preventive services task force	No	13
ESHRE/ASRM[22]	2008	Yes	Panel discussion	N/A	N/A	N/A	No	55

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Table (2): Summary of disease domains covered by recommendations in evidence-based clinical guidelines on polycystic ovary syndrome.

Guideline	Diagnosis in adolescents	Diagnosis in adults	Lifestyle	Menstrual irregularity	Hirsutism and acne	Infertility	Metabolic disease	Mental health	Cardiovascul disease
ICPE[18]	✓	x	✓	✓	✓	x	✓	✓	✓
AE-PCOS[26]	x	x	x	x	x	x	✓	✓	✓
NHMRC[14]	✓	✓	✓	✓	✓	✓	✓	✓	✓
ES[21]	✓	✓	✓	✓	✓	✓	✓	✓	✓
IFS[20]	✓	✓	✓	✓	✓	x	✓	✓	✓
CREPCOS[13]	✓	✓	✓	✓	✓	✓	✓	✓	✓
AES[25]	x	x	x	x	x	x	✓	x	✓
RANZCOG[23]	x	✓	✓	x	x	✓	✓	✓	✓
RCOG[32]	x	✓	✓	✓	✓	x	✓	✓	✓
PES[19]	✓	x	x	x	x	✓	x	x	x
AACE[17]	✓	✓	x	x	✓	x	✓	x	x
ACOG[12]	x	x	✓	✓	✓	✓	✓	x	✓
ESHRE/ASRM[22]	x	x	✓	x	x	✓	✓	x	x

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Table (3): Summary of suggested screening tools and risk assessment for women with polycystic ovary syndrome in evidence-based clinical practice guidelines.

Disease domain	Screening tool	Suggested screening frequency
Impaired glucose tolerance and type 2 diabetes mellitus	Oral glucose tolerance test or HbA1c	No specific frequency, ranging from annually to once every 5 years, sooner if any of the following risk factors:
Cardiovascular disease	Screen for risk factors	No specific frequency.
Weight including waist circumference and body mass index	Direct measurement	Each visit with a minimum suggested period between 6 and 12 months
Blood pressure	Direct measurement	Each visit with a minimum suggested period between 6 and 12 months
Lipids	Serum blood tests	Every 2 years
Gestational diabetes	Oral glucose tolerance test	Between 24 and 28 weeks gestation.
Obstructive sleep apnea	Clinical assessment of associated symptoms	Only in symptomatic women
Mental illness	PCOS quality of life tool (PCOSQ)	No specific frequency
Endometrial cancer	Transvaginal ultrasound scan to assess endometrial thickness	Only in women with unexpected uterine bleeding or spotting.

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Clinical CPGs for polycystic ovary syndrome: A systematic review and quality assessment study

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Supplementary materials

Abbreviations list:

17-OH P4	17-Hydroxyprogesterone
AA	Anti-androgen medications
AMH	Anti-Müllerian hormone
BMI	Body mass index
BP	Blood pressure
CAH	Congenital adrenal hyperplasia
CC	Clomiphene citrate
CVD	Cardiovascular disease
ET	Endometrial thickness
FSH	Follicular stimulating hormone
GDM	Gestational diabetes mellitus
GnRH	Gonadotropin-releasing hormone
GT	Gonadotrophin
HCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HIT	High intensity training
HTN	Chronic hypertension
ICSI	Intracytoplasmic Sperm Injection
IGT	Impaired glucose intolerance

IR	Insulin resistance
IUI	Intra-uterine insemination
IVF	In-vitro fertilisation
IVM	In-vitro maturation
LDL	Low-density lipoprotein
LET	Letrozole
LH	Luteinizing hormone
LOD	Laparoscopic ovarian drilling
LST	Lifestyle intervention treatment
MBS	Metabolic syndrome
MDT	Multi-disciplinary team
MIT	Moderate intensity training
MTF	Metformin
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
OCP	Oral contraceptive pill
OGTT	Oral glucose tolerance test
OHSS	Ovarian hyperstimulation syndrome
OI	Ovulation induction
OSA	Obstructive sleep apnoea

PCOM	Polycystic ovarian morphology
PET	Pre-eclampsia
PGZ	Pioglitazone
PTL	Preterm labour
QOL	Quality of life
SNL	Spironolactone
T2DM	Type 2 diabetes mellitus
TT/FT	Total Testosterone/Free Testosterone
TVUS	Transvaginal ultrasound scan
VTE	Venous thromboembolism

Supplementary Table (1): Summary of guidelines' recommendations for the diagnosis of polycystic ovary syndrome in adolescents and adults.

Guideline	Diagnosis in adolescents	Diagnosis in adults
ICPE[18]	-PCOM alone is not diagnostic of PCOS. -Measurement of ovarian volume, follicle number and size and uterine dimensions is useful but not essential to diagnose PCOS in girls with amenorrhoea. -Diagnose clinical hyperandrogenmia as moderate to severe hirsutism +/- inflammatory acne and biochemical hyperandrogenism with TT/FT based on the methodology used, as no clear cut-off exists for adolescents. - Do not use AMH, T/DHT ratios, proteins microRNA, insulin resistance, compensatory hyperinsulinemia, or obesity for diagnosis. -Mild hirsutism may be a sign of androgen excess when associated with menstrual irregularities. -Moderate or severe inflammatory acne unresponsive to topical therapy may require investigation of androgen excess, but Isolated acne and/or alopecia should not be considered diagnostic criteria for PCOS in adolescence. -Persistent menstrual disturbance >2 years after menarche or primary may suggest androgen excess.	-Not reported
AE-PCOS[26]	-Not reported	-Not reported
NHMRC[14]	-USS is not recommended as first-line diagnostic test and TVUSS is not appropriate in non-sexually active adolescents. -Consider PCOS in adolescents with >2 years history of irregular periods post menarche as a diagnosis of exclusion.	-Check biochemical hyperandrogenism using TT, FT or FAI as first-line investigation, the addition of Androstenedione and DHEAS could be second-line investigation. If androgen levels are markedly above laboratory reference ranges, secondary causes need to be excluded including CAH. -Assessment of biochemical hyperandrogenism should be performed after 3 months' withdrawal of OCPs.
ES[21]	-Anovulatory symptoms and PCO morphology are not sufficient for diagnosis.	-Diagnostic criteria with 2/3 of androgen excess, ovulatory dysfunction, or polycystic ovaries (PCO) after excluding other causes.

	-Consider PCOS in adolescents with oligomenorrhea and clinical/biochemical hyperandrogenism after excluding other causes.	-Physical examination should document cutaneous manifestations of PCOS: terminal hair growth, acne, alopecia, acanthosis nigricans, and skin tag. -Presumptive diagnosis of PCOS with long-term history of oligomenorrhea and hyperandrogenism in perimenopausal and menopausal women.
IFS[20]	-Diagnosis in adolescents should include 5 tests: Total T (>60 ng/dL), OGTT, 17– OH P4, TSH, and prolactin. - Serum LH, follicle stimulating hormone(FSH) and cortisol should be assessed. -Do not use AMH for diagnosis. -Oligomenorrhea or amenorrhea >2 years after menarche is early clinical sign of PCOS.	-Consider PCOS in Indian women showing at least one biochemical characteristic (overweight/obesity, markers of insulin resistance (aconthosis nigricans), family history of DM or PCOS, dyslipidaemia) in conjunction with one clinical symptom (pubertal deviations, menstrual irregularity, PCOM, early, persistent severe or frequently replapsing acne or hirsutism for more than two years). Women at risk should be screened by an appropriate healthcare provider and all clinical and biochemical risk factors documented in the case history. - Diagnosis as per the Rotterdam criteria. -Cutaneous manifestations such as hirsutism, acne and androgenic alopecia, Indian specific grading should be performed. - Acanthosis nigricans with or without obesity is an additional diagnostic criterion. - Mild prolactinaemia and subclinical hypothyroidism are common in PCOS. -In peri-menopausal and menopausal women with a clinical history of prolonged periods of androgen excess and oligomenorrhea during the reproductive years, additional evidence of PCO morphology, log ovarian volume, follicle number, and testosterone should be considered to diagnosis PCOS.
CREPCOS[13]	-For adolescents who have features of PCOS but do not meet diagnostic criteria, an " increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before OCP commencement, those with persisting features and those with significant weight gain in adolescence. -PCOM should not be used in the diagnosis of PCOS in girls < 8 years after menarche. -TVUS is preferred if sexually active and acceptable.	-PCOM should be on either ovary, a follicle number per ovary of > 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present. -PCOM should be considered to diagnose PCOS in peri-menopausal and menopausal women with a clinical history of prolonged periods, oligomenorrhea and androgen excess -Completed history and physical examination for symptoms and signs of clinical hyperandrogenism, (acne, alopecia, hirsutism) using Standardised visual scales

		(Ferriman Gallwey score and The Ludwig visual score). There are no universally accepted visual assessments for evaluating acne. -Assess biochemical hyperandrogenism using high quality assay free or bioavailable T and FAI and other causes of biochemical hyperandrogenism need to be considered. -Androstenedione and DHEAS could be considered if TT or FT are not elevated. -Interpret androgen levels using the reference ranges of the laboratory used as different methods and laboratories vary widely and normal values should be based on levels from a well phenotyped healthy control population. -Do not use AMH for diagnosis. -Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured. -Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception. -In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis. -Consider PCOS in menopausal women if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years. New-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis
AES[25]	-Not reported	-Not reported
RANZCOG[23]	-Not reported	-Diagnosis of PCOS should be made using current international criteria such as the Rotterdam Criteria
RCOG[32]	-Not reported	-PCOS should be diagnosed according to the Rotterdam consensus criteria. -TVUS should be considered in women with PCOS and no withdrawal bleeds or with abnormal uterine bleeding. -In PCOS, an endometrial thickness of less than 7 mm is unlikely to be hyperplasia.

		-A thickened endometrium or an endometrial polyp should prompt consideration of endometrial biopsy and/or hysteroscopy.
PES[19]	-There is no compelling criteria to define PCOM in adolescents. -An ovarian volume >12cm can be considered enlarged. -Follicle counts should not be used to define PCOM in adolescents. -Multifollicular pattern (the presence of large follicles distributed throughout the ovary) with no hyperandrogenism, is more common in adolescents and is not a pathological finding. -Abdominal USS in adolescents particularly obese girls may yield inadequate information. -Ovarian imaging can be deferred during the diagnostic evaluation for PCOS. -AMH concentrations should not be used to characterise PCOM. -Isolated mild hirsutism should not be considered clinical evidence of hyperandrogenism in the early post-menarche. -Biochemical evidence of hyperandrogenism (persistently high TT or FT) should be used to diagnose hyperandrogenism in an adolescent girl with symptoms of PCOS after excluding other causes of androgen excess using a thorough medical history, physical examination and appropriate laboratory assessment. -A single androgen level >2SD above the mean is not evidence of hyperandrogenism in asymptomatic adolescents. -Insulin resistance and hyperisulinaemia are not diagnostic of PCOSI in adolescents, but can be considered as indications to investigate and treat potential comorbidities. -In healthy girls with regular menstrual cycles and without hyperandrogenism, PCOM does not indicate a diagnosis of PCOS. -Menstrual intervals persistently <20 days or >45 days two years after menarche are evidence of oligo-anovulation.	-Not reported

	-Menstrual intervals >90 days are rare and require further investigation regardless of years after menarche. -Amenorrhea by 15 years or >2-3 years after thelarche warrant consideration of PCOS. - PCOS diagnosis should not be confirmed if oligomenorrhoea has not persisted for >2 years in adolescents with clinical and biochemical hyperandrogenism. -No validated diagnostic criteria with robust clinical and hormonal findings exist to avoid over-diagnosis and unnecessary treatment in otherwise healthy normal girls without hyperandrogenism.	
AACE[17]	-Ultrasound in not the first line investigation in girls <17 years. -Persistent oligomenorrhoea (>40 days) 2-3 years after menarche predicts ongoing menstrual irregularities. -Ovarian dysfunction in adolescents should be based on oligomenorrhoea and/or biochemical evidence of oligo/anovulation.	-Diagnose PCOS based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological) and polycystic ovaries after careful clinical assessment of women's history, physical examination, and laboratory evaluation, emphasizing the accuracy and validity of the methodology used for both biochemical measurements and ovarian imaging. -New ultrasound machines allow diagnosis of PCOM in patients having at least 25 small follicles and ovarian size >10mL. - FT are more sensitive than the measurement of TT. - 17OH-P4 and AMH are useful for diagnosis of PCOS. -Midluteal P4 is the best way to assess ovulation (>7ng/mL). -Cycle length >35 days suggests chronic anovulation, but cycle length slightly longer than normal (32 to 35 days) or slightly irregular (32 to 35-36 days) needs assessment for ovulatory dysfunction.
ACOG[12]	-Not reported	-Not reported
ESHRE/ASRM[2] [2]	-Not reported	-Not reported

Supplementary Table (2): Summary of guidelines' recommendations for the management of polycystic ovary syndrome in adolescents and adults

Guideline	Lifestyle	Menstrual irregularity	Hirsutism and acne	Infertility
ICPE[18]	-LST should include calorie-restricted diets exercise, and behavioural as 1st line therapy in overweight women aiming for 5-10% weight loss with longterm goals of maintaining 10-20% weight reduction. -Extremely obese adolescents respond poorly to LST. Offer combined weight loss and physical exercise as 1st line therapy aimed to decrease hepato-visceral adiposity, enhance central fat loss, and attenuate pre-gestational oligo anovulation gestational complications such as GDM, PET, PTL. -In normal weight adolescents, increased physical activity is effective in reducing MBS, but exclusive weight loss is not supported.	-No specific OCP is recommended over another in adolescent with PCOS. -In some adolescents with or at risk for PCOS, normal ovulatory function may exist or emerge with time and present as ovulatory adolescent PCOS.	-AA are superior to MTF alone and should only be used when contraceptive measures are guaranteed. -Offer photoepilation as 1st line for localised hirsutism, topical Eflornithine as an adjuvant therapy for laser-resistant facial hirsutism in adolescents >16 years or as monotherapy in those where photoepilation is not indicated. -Diode and Alexandrite lasers are preferred for treatment of hirsutism. -Alexandrite laser is superior to IPL methods in facial hirsutism. -Topical Finasteride is not recommended.	-Not reported.
AE-PCOS[26]	-Not reported.	-Not reported.	-Not reported.	-Not reported.
NHMRC[14]	-Recommend 5-10% weight loss in overweight women as beneficial and feasible initial target. -Single or combined LST (diet, exercise, behavioural) should be 1st line therapy targeting weight loss if BMI ≥25kg/m^2 and prevention if BMI ≤25kg/m2 -Promote weight loss by reducing dietary caloric intake and prevention of weight gain by monitoring caloric intake with healthy food choices irrespective of diet composition.	-Consider OCP in adolescents after 12 months of irregular cycles (>35 or <21 days) from menarche. -OCP should be withdrawn for 3 months in non- sexually girls to assess biochemical hyperandrogenism for the diagnosis of PCOS.	-Not reported.	-LST (diet and exercise) should be used to optimise health generally and to alleviate PCOS clinical severity including infertility. -Use 3 to 6 months intensive LST alone or pharmacological agent as 1st line therapy for OI in women with BMI ≥30kg/m2. -Consider pharmacological OI as 2nd line if LST fails. -Pharmacological OI should not be recommended as 1st line therapy in morbidly obese women until after appropriate weight

	-Provide Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support to overweight women with MTD input from all health professionals caring for women with PCOS. -Recommend 150 min/week exercise of this, 90 min/week should be aerobic activity at moderate-high intensity. -LST alone without pharmacological therapy should be first-line therapy for 3-6 months for ovulation induction in women with BMI ≥30kg/m2. -Discuss the following issues before bariatric surgery: -A structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health should continue post-operatively. -Inform of the risk of pre-and post-operative nutritional deficiencies with MDT input including a bariatric surgeon, a dietitian and other team members. -Psychological factors should be considered and managed in infertile women to optimise engagement and adherence with LST. -Bariatric surgery should not be conducted in pregnancy.			loss through diet, exercise, bariatric surgery, or other means. -Morbid obesity increases pregnancy risks and should be regarded as a relative contraindication to assisted fertility. -Offer CC as 1st line pharmacological therapy for OI with monitoring to reduce the risk of multiple pregnancy. -MTF could be used alone to improve ovulation and pregnancy rate in anovulatory, overweight, or women with unexplained infertility. -Combine CC and MTF for OI in obese women with no other infertility factors. -Offer GT as 2nd line pharmacological OI when CC has failed, it could be considerd as 1st line therapy in anovulatory infertile women with no other infertility factors. -LET could be offered as 1st line treatment for OI with caution after explaining its off label use. -Offer LOD only as 2nd line therapy when CC has failed, or as 1st line if laparoscopy is indicated for other causes. -Offer bariatric surgery as 2nd line therapy to improve fertility outcomes in anovulatory, women (BMI ≥35kg/m^2) with failed LST and/or drug interventions for >6 months.

	-Pregnancy should be avoided during periods of rapid weight loss and for at least 12-18months after bariatric surgery. -Contraception should be discussed prior to surgery. -If pregnancy occurs, discuss pre- and post-operative nutritional deficiencies with MDT input including an obstetrician, bariatric surgeon a dietitian and other team members. -Fetal growth should be monitored during pregnancy.			
ES[21]	-Consider exercise therapy for overweight and obesity women. -Consider calorie-restricted diets as weight loss strategies but no evidence that one type of diet is superior for overweight or obese adolescents and adults. -Offer LST (calorie-restricted diet and exercise) with the objective of weight loss as 1st line treatment for overweight/obesity.	-Recommend hormonal contraceptives (OCP, patch, or vaginal ring) as 1st line management for the menstrual abnormalities, hirsutism, acne after screening for contraindications, no one hormonal contraceptive formulation is preferred over another. -Consider MTF as 2nd line therapy for menstrual irregularity if OCP are contraindicated.	-Offer contraceptives as 1st line treatment in adolescents with suspected PCOS to treat acne, hirsutism, or anovulatory symptoms, or to prevent pregnancy. -Consider contraceptives in premenarchal girls with advanced pubertal development for clinical and biochemical hyperandrogenism.	-Exclude other causes of infertility, beyond anovulation, in couples with subfertility. -Screen ovulatory status using menstrual history. Women with eumenorrheic menstrual history may still experience anovulation and a midluteal serum P4 may be used as a screening test. -Offer preconceptual assessment of BMI, BP, and OGTT to reduce the risk of pregnancy complications (GDM, PTL, PET). -Offer preconceptional counselling on lifestyle, weight reduction and exercise in overweight women, smoking cessation and alcohol consumption reduction before fertility treatments. -Offer CC as 1st line treatment of anovulatory infertility. -Consider MTF as an adjuvant therapy for infertility to prevent OHSS in women with PCOS undergoing IVF.

				-Explain OI is highly effective with a cumulative singleton live birth rate of 72%. Patient-tailored approaches should be developed based on women characteristics which may result in deviation from the suggested ovulation strategies in well-defined subsets of women. -Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. -Consider LET as 1st line pharmacological treatment for OI in women with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates. -CC could be used alone with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates. -MTF could be used alone with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -CC is preferred to MTF for OI in obese women (BMI ≥ 30 kg/m^2) with anovulatory infertility and no other infertility factors. -CC and MTF could be combined for OI in obese women (BMI ≥ 30 kg/m^2) with anovulatory infertility and no other infertility factors.to improve ovulation, pregnancy and live birth rates, rather than persisting with CC alone. -GT could be considered as 1st line treatment, in the presence of ultrasound monitoring, following counselling on cost

				and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors. -GT, where available and affordable, should be used in preference to CC+MTF, in women with CC-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -GT could be combined with MTF in women with CC-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -Offer GT or LOD an individual basis if CC failed to result in pregnancy. Explain the risk of multiple pregnancy and intense monitoring of ovarian response with GT. Explain LOD is usually effective in 50% of women and additional ovulation induction may be required. -Either GT or LOD could be used in women with CC-resistance and no other infertility factors, following counselling on benefits and risks of each therapy. -With GT OI, only trigger ovulation if <3 mature follicles and advise to avoid unprotected intercourse. -LOD could be offered as 1st line treatment if laparoscopy is indicated for another reason. -Offer IVF as 3rd line treatment if OI has failed. -GNRH antagonist protocol is preferred for IVF ± ICSI cycle to reduce the stimulation duration, total GT dose and risk of OHSS.

				-MTF (1-2.5g daily) could be used as adjunct before and/or during ovarian stimulation in IVF ± ICSI therapy with a GnRH agonist protocol to improve the clinical pregnancy rate and reduce the risk of OHSS. Stop MTF at the time of the pregnancy test or menses unless otherwise indicated, and explain potential side-effects.
IFS[20]	-Recommend daily strict physical activity sessions for at least 30mins/day or 150mins/week. -Recommend LST (healthy, balanced diet consisting of regular, calorie-restricted meals) in obese adolescents and adults. -Recommend calorie restricted diet (low carbohydrate and fat, high protein) in consultation with dietician and lifestyle modification as 1st line therapy for at least 6 months, then add MTF as 2nd line therapy. -In adolescents/children with hyperandrogenism, obesity and signs of insulin resistance offer LST as 1st line therapy and only offer MTF as 2nd line therapy 2 years post-menarche.	-Recommend P4 withdrawal bleeds as 1st line therapy till menopause to avoid the risk of endometrial proliferative disorders. -Recommend OCP (drospirenone and desogestrel as progestin component) for menstrual irregularity and contraception. Drospirenone has been shown to be more beneficial than desogestrel in Indian conditions. -MTF is not recommended as 1st line therapy for the management of menstrual irregularity. -SNL is not recommended for menstrual irregularity. -Use low-dose OCP (with or without drospirenone and desogestrel) for the management of menstrual irregularity between 12-16 years of age, for short period (up to 7 days). After 16 years, low-dose OCP to be used for longer periods. -Reduce VTE risk with OCP by identifying susceptible patients and/or pausing for 3 months after 1 year treatment.	Use of direct hair removal methods as 1st line therapy along with OCP. -Alternative (acupuncture) and complementary therapeutic options (e.g. myoinositol, omega-3 fatty acids) are not recommended for hyperandrogenism. -Use topical medication along with pharmacological interventions for acne as early as possible, in consultation with dermatologist. -Use OCP (cyproterone acetate, drospirenone, or desogestrel as progestin component) as 1st line therapy for management of all types of acne lesions. Cyproterone acetate has been shown to be more beneficial than other progestins in Indian conditions. -If OCP are not helpful or tolerated, offer SNL or FS but stop 6 months before a planned pregnancy. -Use OCP and androgen blockers are recommended as 1st line therapy for alopecia. -The ideal time to stop hormonal therapy for hyperandrogenism cannot be established.	-Not reported.

CREPCOS[13]	-Recommend multicomponent LST including diet, exercise and behavioural strategies for reductions in weight, central obesity and insulin resistance. -Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months using SMART (Specific Measurable, Achievable, Realistic and Timely), goal setting and self-monitoring can enable achievement of realistic lifestyle goals. -Consider psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, to optimise engagement and adherence to LST. -Consider using adolescent and ethnic-specific BMI and waist circumference categories. -Comprehensive health behavioural or cognitive behavioural interventions could increase support, engagement, retention, adherence and maintenance of LST. -Consider a diet with an energy deficit of 30% or 500 -750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women with excess weight to achieve weight loss. There is no or limited evidence that any specific energy equivalent diet type is better than another. -Recommend regular exercise for weight gain prevention: >150 min/week MIT or >75 min/week of HIT for adults,	-Recommend OCP alone in adult women and consider it in adolescents with a clear diagnosis of PCOS for management of hyperandrogenism and/or irregular menstrual cycles. -Consider OCP in adolescents deemed “at risk” but not yet diagnosed with PCOS. - Cannot recommend specific types or dose of progestins, estrogens or combinations of OCP and practice should be informed by general population guidelines. -Do not offer 35 mcg ethinyloestradiol +cyproterone acetate as 1st line therapy due to adverse effects including VTE risks. -Consider MTF+OCP for management of metabolic features if OCP+LST failed and in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	-Consider OCP+AA to treat hirsutism, if OCP and cosmetic therapy have failed after >6 months. -Consider OCP+AA for the treatment of androgen-related alopecia. -Consider AA alone to treat hirsutism and androgen-related alopecia if OCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception.	-Infertile women with anovulation alone and normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis. -Consider tubal patency testing prior to ovulation induction in women with PCOS with suspected tubal infertility. -Offer LET as 1st line pharmacological treatment for OI in women with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates. -CC could be used alone with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates. -MTF could be used alone with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -CC is preferred to MTF for OI in obese women (BMI ≥ 30 kg/m^2) with anovulatory infertility and no other infertility factors. -CC and MTF could be combined for OI in obese women (BMI ≥ 30 kg/m^2) with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates, rather than persisting with CC alone. -GT could be used as 2nd line pharmacological agents if 1st line oral ovulation induction therapy failed. It could be considered as 1st line treatment, in the presence of USS monitoring, following counselling on cost and potential risk of

	>60 minutes of MIT/HIT >3 times weekly For adolescents. -Recommend regular exercise for weight loss: >250 min/week MIT or >150 min/week of HIT + minimised sedentary, screen or sitting time. -Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote LST and minimise sedentary behaviours. -Consider MTF+LST in adult obese women for the treatment of weight, hormonal and metabolic outcomes and offer it to non-obese adults. -Consider Anti-obesity medications + LST for the management of obesity in adults as per general population recommendations if LST alone failed.			multiple pregnancy, in women with anovulatory infertility and no other infertility factors. -GT, where available and affordable, should be used in preference to CC+MTF, in women with CC-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -GT could be combined with MTF in women with CC-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. -Either GT or LOD could be used in women with CC-resistance and no other infertility factors, following counselling on benefits and risks of each therapy. -With GT OI, only trigger ovulation if <3 mature follicles and advise to avoid unprotected intercourse. -LOD could be offered as 1st line treatment if laparoscopy is indicated for another reason. -Pharmacological anti-obesity agents should be considered an experimental therapy for the purpose of improving fertility. -Offer IVF as 3rd line treatment if OI has failed. Only offer ICSI if indicated for other infertility causes, Urinary or recombinant FSH can be used. Exogenous recombinant LH should not be routinely used. -GNRH antagonist protocol is preferred for IVF ± ICSI cycle to reduce the stimulation duration, total GT dose and risk of OHSS.

				-Use lowest HCG dose to trigger final oocyte maturation and reduce OHSS incidence. GNRH agonist trigger could also be considered to reduce OHSS as well as elective freezing of all suitable embryos. -MTF (1-2.5g daily) could be used as adjunct before and/or during ovarian stimulation in IVF ± ICSI therapy with a GnRH agonist protocol to improve the clinical pregnancy rate and reduce the risk of OHSS. -Stop MTF at the time of the pregnancy test or menses unless otherwise indicated, and explain potential side-effects. -IVM could be offered to achieve pregnancy and livebirth rates approaching those of standard IVF without the risk of OHSS. -Bariatric surgery should be considered an experimental as fertility therapy.
AES[25]	-Not reported.	-Not reported.	-Not reported.	-Not reported.
RANZCOG[23]	- Offer LST including healthy diet and exercise. -Management of HTN and dyslipidaemia should be undertaken as indicated. - Use of bariatric surgery should be considered where obesity is not controlled by lifestyle modifications	-Not reported.	-Not reported.	-OI is contraindicated in women with a BMI >35 Kg/m^2 due to the increased risks of pregnancy.
RCOG[32]	-Recommend LST including diet, exercise and weight loss as 1st line therapy before or with pharmacological treatments. -Consider bariatric surgery for morbidly obese women (BMI of 40 kg/m^2) or those with BMI >35kg/m^2 and high-risk obesity-	- Recommend treatment with gestogens to induce a withdrawal bleed at least every 3-4 months to reduce the risk of endometrial hyperplasia and later carcinoma in women with oligo- or amenorrhoea.	-Weight reduction drugs may be helpful in reducing hyperandrogenaemia.	-Not reported.

	related conditions if standard weight loss strategies have failed.			
PES[19]	-Not reported.	-Not reported.	-Not reported.	-Consider treatment options to alleviate current symptoms and decrease the risk of subsequent comorbidities in adolescents with no definitive PCOS diagnosis.
AACE[17]	-Not reported.	-Not reported.	-Hirsutism develops gradually and intensifies with weight gain. -In the neoplastic virilising states, hirsutism is of rapid onset, usually associated with clitoromegaly and oligomenorrhea. -Girls with severe acne or acne resistant to oral and topical agents, including isotretinoin (Accutane), may have a 40% likelihood of developing PCOS. -Hair loss patterns are variable in women with hyperandrogenemia, typically the vertex, crown or diffuse pattern, whereas women with more severe hyperandrogenemia may see bitemporal hair loss and loss of the frontal hairline. -OCPs can effectively lower androgens and block the effect of androgens via suppression of ovarian androgen production and by increasing sex hormone–binding globulin. -OCP can effectively lower androgens and block the effect of androgen production. -Physiologic doses of dexamethasone or prednisone can directly lower adrenal androgen output.	-Not reported.

			- OCPs as monotherapy are not very effective in arresting mild to moderate hirsutism and are preferably combine with AA. -SNL is relatively effective to treat hirsutism. -Consider 5aR inhibition therapy for severe hirsutism if OCP and SNL are ineffective. -Consider AA side effect on bone mass in adolescents.	
ACOG[12]	-Recommend weight loss to improve pregnancy rates, decreased hirsutism, lipid levels, and improve glucose tolerance. -An increase in exercise combined with dietary change has consistently been shown to reduce diabetes risk comparable to or better than medication.	-Consider OCP for long-term management of menstrual disorders.	- There is no clear primary treatment for hirsutism. -Consider combining eflornithine and laser treatment for hirsutism.	-Recommend LET as 1st line treatment for OI. -Consider adding MTF to CC for OI to pregnancy rates. -Consider GT or LOD for 2nd line treatment OI if CC or LET fails. -Recommend a low-dose GT regimen for OI.
ESHRE/ASRM[22]	-Recommend LST as 1st with hypocaloric diet (500Kcal/day deficit) and reduced glycaemic load to achieve a 5% weight loss and physical activity while considering the possible orthopaedic and cardiovascular limitations.	-Not reported.	-Not reported.	-Offer preconceptinal counselling to identify risk factors for reproductive failure and correct them prior to fertility treatment. -Recommend Folate supplementation and smoking cessation. -Recommend weight loss as 1st line therapy in obese women seeking pregnancy to improve ovulation rates aiming for at least a 5% of body weight loss. -Caution about conceiving while on hypocaloric diets, excessive physical exertion, pharmacological intervention or during the period of rapid weight loss after bariatric surgery.

				-CC remains the treatment of first choice for OI with a starting dose of 50mg/day (for 5 days) and maximum dose of 150mg/day. -Monitoring of OI with CC by ultrasound or progesterone is not mandatory to ensure good outcome. -Further studies should demonstrate efficacy and safety of aromatase inhibitors. -MTF is less effective than CC in OI, but could be added to CC in a Step-up regimens. -2nd line intervention should CC fail to result in pregnancy is either GTor LOS. -If follicle development is not observed on USS after one week of starting GT for OI the dose can be increased. Once follicle growth is observed, the same GT dose should be maintained until follicular selection is achieved to reduce the risk of OHSS. -Adherence to a 14 day starting period at least for the first cycle with a recommended starting dose of GT is 37.5-50IU/day is less likely to cause OHSS. -The duration of GT generally should not exceed six ovulatory cycles. -Low-dose GT protocols are effective for OI. -Intense ovarian response monitoring in OI is required in order to reduce complications and secure efficiency. -Routine use of GnRH agonists is not recommended.

				-LOD can achieve unifollicular ovulation with no risk of OHSS or high-order multiples. Does not require intensive follicular development monitoring. Should not be offered no non-fertility indications. -IVF is a reasonable 3rd option for OI in combination with IUI is indicated in women with an associated male factor

Supplementary Table (3): Summary of guidelines' recommendations for the risk assessment and longterm follow up of adolescents and adult women with polycystic ovary syndrome.

Guideline\Domain	Metabolic disease	Mental health	Cardiovascular	Cancer
ICPE[18]	-MTF is helpful in overweight/obese adolescents. -MTF improves ovulation and testosterone levels in non-obese adolescents. -Where available, triple low-dose combinations of MTF, SNL and PGZ is favourable than OCP aimed to reduce hepato-visceral adiposity, central fat, pregestational oligo-anovulation.	-Not reported	-Not reported	-Not reported
AE-PCOS[26]	-Offer MTF only if no improvement in IGT after LST or in women with IGT and normal weight. -Combine pharmacotherapy with LST for persistent HTN. -Anti-obesity agents are not recommended. -Check OGTT in women with BMI >30, or if older >40yrs, history of GDM or Family history of T2DM) to detect IGT or T2DM and repeat every 2 years or sooner if additional risk identified.	-Assess for depression, anxiety and QOL routinely.	-Categorise CVD risk as at risk in those with obesity, smoking, HTN, dyslipidaemia, subclinical vascular disease, IGT, FHx of premature CVD. At high risk in those with MBS, T2DM or overt vascular or renal disease. -Record WC and BMI at every visit. -Check lipids every 2 years or sooner if weight gain occurs. -If no CVD risk factors aim for LDL-C <130mg/dl, if high risk for CVD aim for LDL-C<70-100mg/dl (CPP). -Check BP at each visit aiming for ideal BP ≤120/80.	-Not reported
NHMRC[14]	-Test for IGT and/or T2DM in all women with PCOS and OGTT should be performed every two years in women with no risk factors and annually in those with risk factors for T2DM. -Assess the risk of developing T2DM by screening for the following risk factors: age, gender, ethnicity, parental history of diabetes, History of high blood glucose level, use of antihypertensive medications, smoking, physical inactivity, waist circumference.	-Screen routinely for depression, anxiety, negative body image, Psychosexual dysfunction, disordered eating and offer appropriate management if detected.	-Assess individual CVD risk factors (obesity, smoking, dyslipidemia, HTN, IGT, lack of physical activity, MBS and T2DM) -Check weight gain at every visit using age and gender appropriate BMI. -Check lipids every two years or annually in those with abnormal lipid profiles and/or excess weight. -Check BP annually with BMI ≤25kg/m^2 and at every visit with BMI ≥ 25kg/m^2.	-Not reported

			-Offer interdisciplinary care, with multiple health professionals involved where appropriate based on the chronic and complex nature of the disease.	
ES[21]	-Do not use MTF as a 1st line treatment for cutaneous manifestations or prevention of pregnancy complications. -MTF can be used as 2nd line for the treatment of obesity, for T2DM or IGT who fail LST. -Do not use insulin sensitisers, such as inositols (due to lack of benefit) or thiazolidinediones (given safety concerns), for the treatment of PCOS. -Do not use statins as treatment for hyperandrogenism and anovulation in PCOS and only used in women who meet indications for statin therapy. -Use OGTT to screen for IGT and T2DM every 3–5 years, or more frequently if clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop. -HbA1c test may be considered if a patient is unable or unwilling to complete an OGTT. -Routine screening for NAFLD and NASH is not recommended but raised awareness is supported.	-Screen women and adolescents for depression and anxiety by history and, if identified, providing appropriate referral and/or treatment.	-Screen women and adolescents for risk of adiposity using BMI and waist circumference. -Screen overweight/obese adolescents and women for symptoms of OSA, seek a definitive diagnosis using polysomnography, a refer affected women to specialised treatment centres. -Screen for CVD using the following risk factors: family history of early CVD, smoking, IGT/T2DM, HTN, dyslipidemia, OSA, and obesity especially increased abdominal adiposity.	-Routine ultrasound screening for endometrial thickness in women with PCOS is not recommended.
IFS[20]	-In women with risk factor of T2DM, screening at a clinically feasible periodicity is suggested. -Screen for IGT and T2DM using a OGTT; an HbA1c test should only be used when an OGTT is not feasible. -Early referral to specialist diabetological care is recommended for timely management of T2DM.	-Routinely screen for depression and anxiety with appropriate psychological instruments and offer counselling by an appropriate professional. -In women with psychosocial dysfunction, a more detailed clinical interview and appropriate treatment for	-Routinely screen for BMI and WC as an index for increasing adiposity and development of hyperandrogenism. -Screen for CVD using the following risk factors: family history of early CVD, smoking, IGT/T2DM, HTN, dyslipidemia, OSA, and obesity especially increased abdominal adiposity, vascular disease, high sensitivity CRP, homocysteine. -High CVD risk factors include metabolic syndrome, T2DM, overt vascular or renal disease.	-Without abnormal uterine bleeding, routine screening using TVUS is not recommended. -Assess ET using TVUS in women with unexpected uterine bleeding and spotting.

	-Use MTF only in adolescents with hyperandrogenism and IGT confirmed using OGTT. -Use MTF alone or in combination with OCP in women with IGT or T2DM. -MTF in pregnancy is not recommended. -Screen for NAFLD and NASH in women IS and MBS. -In patients with NASH, treatment with vitamin E is preferred with specialist MDT input and MTF is not suggested for reduction of MBS.	improvement of QOL is suggested.	-Assess obesity (BMI and WC), lipid profile, OGTT and BP in adult women at baseline and repeat lipid profile and OGTT at 6 months for borderline risk and annually for normal profiles. -Preconception screening for markers of obesity, HTN and IR is advised to reduce the risk of pregnancy related complications. -Assess serum homocysteine levels for identification and treatment of hyperhomocysteinemia mediated repeated pregnancy losses in women with previous miscarriage. -Routinely screen for OSA and insomnolence in symptomatic women using polysomnography and refer to appropriate institution for further therapy.	-Induce a withdrawal bleed using progestogens every 3-4 months in women at risk of endometrial Cancer. -Regular oncological referrals for screening at a clinically feasible periodicity are recommended for timely detection of endometrial cancer.
CREPCOS[13]	-Assess glycaemic status using OGTT, FPG, or HbA1c at baselines and then every one to three years based on diabetes risk factors (BMI > 25kg/m2 or in Asians >23kg/m2, family history of IGT, T2DM, HTN or high-risk ethnicity). -Perform OGTT in women planning pregnancy or seeking fertility treatment. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation. -Use a combination of MTF and OCP in adolescents and adults with BMI ≥ 25kg/m2 where OCP and LST alone were not helpful to achieve desired goals. -Combination of MTF and OCP may be most beneficial in high metabolic risk groups including those with diabetes risk factors, IGT or high-risk ethnicity. -Offer MTF+LST in adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made.	-Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. -Use the PCOS quality of life tool (PCOSQ), or the modified PCOSQ, to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns. -The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgment, considering risk factors, comorbidities and life events. -If positive, further assessment and/or referral for assessment and treatment should be	-Routinely monitor weight changes and excess weight and ideally waist circumference at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the woman. -Screen for CVD risk factors including obesity, smoking, dyslipidemia, HTN, IGT and lack of physical activity. -Optimise preconception factors including blood glucose, weight, BP, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health to improve reproductive and obstetric outcomes, aligned with recommendations in the general population. -Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (cholesterol, LDL, HDL and triglyceride level at diagnosis and regularly checked based on hyperlipidemia and global CVD risk. -Check BP annually, or more frequently based on global CVD risk. -Screen for OSA only in women with related symptoms, such as snoring, waking unrefreshed from sleep, daytime	-In women with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight, evaluation with TVUS and/or endometrial biopsy is recommended to rule out endometrial cancer. -Routine US screening is not recommended and optimal prevention is not known. A pragmatic approach could include OCP or progestin therapy in those with cycles >90 days.

	-Consider AOM plus LST in obsess women as per general population recommendations. -Inositol (in any form) should currently be considered an experimental therapy in PCOS. -Stop MTF once pregnancy is confirmed.	completed by suitably qualified health professionals, informed by regional guidelines. -Consider factors that could exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing including obesity, infertility, hirsutism.	sleepiness, and the potential for fatigue to contribute to mood disorders using a simple screening questionnaire, preferably the Berlin tool, and if positive, referral to a specialist considered. -Ethnic groups with PCOS who are at high cardiometabolic risk	
AES[25]	-Offer intensive LST and weight loss in obese patients as the mainstay of treatment for all patients with PCOS and IGT. -Screen for IGT in all women regardless of BMI using OGTT, and if normal re screen every two years or earlier if additional risk factors are identified. -Screen women with IGT annually for T2DM. -Screen adolescents for IGT using OGTT every two years, and if positive offer intensive LST +/- MTF. -Consider Insulin-sensitising agents in women with IGT.	-Not reported	Not reported	Not reported
RANZCOG[23]	-Routine use of insulin sensitising agents is not recommended -Screen for metabolic dysfunction with OGTT and repeat screening based on key predictors such as BMI and Family history. -Measurement of insulin levels is not recommended.	-Screen routinely for depression and anxiety and if positive offer management appropriately.	-Screening for CVD using BMI, fating lipids and lipoprotein levels and MBS risk factors. -Screen for OSA using formal symptom questionnaires and arrange further investigation and management as indicated.	-Not reported
RCOG[32]	-Screen for T2DM annually in overweight women with IGT or other risk factors (age > 40 years, personal history of GDM or family history of T2DM) using OGTT. -Insulin-sensitising agents are not licensed for use in women without diabetes in the UK.	-Consider psychological issues and routinely screen for depression and/or anxiety. If positive, further assessment and appropriate counselling and intervention should be offered by a qualified professional.	-Inform women of the possible long term implications risks to health at diagnosis. -Screen for OSA with symptoms questionnaires about snoring and daytime fatigue/somnolence, and offer investigation and treatment when necessary.	-Offer treatment with P4 to induce a withdrawal bleed every 3-4 months in women with oligo- or amenorrhoea to reduce the risk of endometrial

	-Offer screening for GDM at 24–28 weeks of gestation to overweight women and those with additional risk factors (age > 40, history of GDM or family history of T2DM) using an OGTT, with referral to a specialist obstetric diabetic service if abnormalities are detected.		-Conventional CVD calculators have not been validated in women with PCOS. -Screen for CVD risk factors (obesity, lack of physical activity, smoking, personal or family history of T2DM, dyslipidaemia, HTN, IGT) at time of initial diagnosis. -Offer HTN treatment, however, lipid-lowering treatment is not recommended routinely and should only be prescribed by a specialist.	hyperplasia and carcinoma. -Offer TVUS to assess endometrial thickness and assess abnormal uterine bleeding. Hyperplasia is unlikely with an endometrial thickness <7 mm. -Consider an endometrial biopsy and/or hysteroscopy to assess thickened endometrium or an endometrial polyp. -No additional surveillance is required for breast or ovarian cancer.
PES[19]	-Not reported	-Not reported	-Not reported	-Not reported
AACE[17]	-Use MTF as first-line monotherapy or in combination with OCP and anti-androgen medications in adolescents. A low dose (850mg daily) may be effective in lean adolescents and a higher dose (1.5 to 2.5g daily) could be offered in overweight and obese adolescents.	-Not reported	-Not reported	-Not reported
ACOG[12]	-Improving insulin sensitivity with insulin-sensitizing agents is associated with decrease in circulating androgen levels, improved ovulation rate and improved glucose tolerance. -Screened for T2DM and IGT with OGTT.	-Not reported	-Screened for CVD risk factors including BMI, fasting lipid and lipoprotein levels, and MBS risk factors. -Screen for CAH using 17-OH P4.	-Not reported
ESHRE/ASRM[22]	-Use MTF only in women with IGT. -Consider bariatric surgery and pharmacological weight loss for the treatment of obesity in PCOS.	-Not reported	-Not reported	-Not reported

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Figure (1): Selection and inclusion process for the systematic review on the quality of evidence-based clinical guidelines on polycystic ovarian syndrome

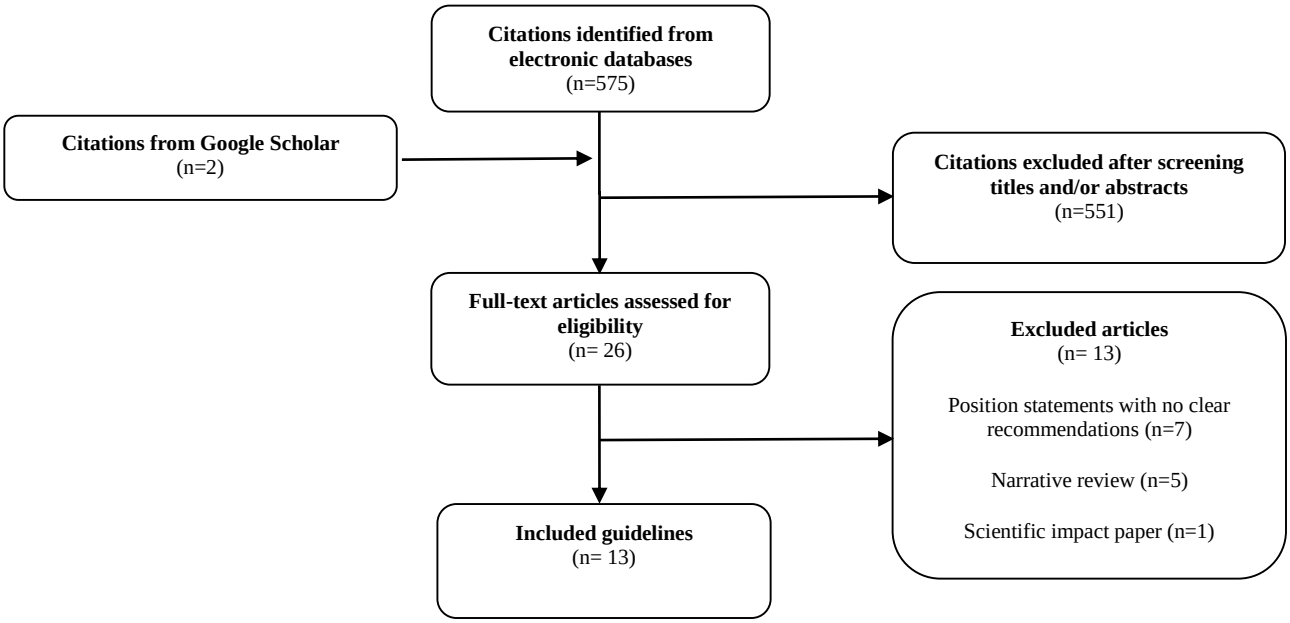

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Figure (2): Quality of included evidence-based clinical guidelines on polycystic ovarian syndrome using the AGREE II tool.