International Evidence-based Guideline on the Assessment and Management of PCOS 2018:

PCOS 2018 Guideline Explained

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On behalf of the international PCOS network

This work is supported by the NHMRC funded Centre for Research Excellence in Polycystic Ovary Syndrome (project number APP1078444).
Sydney, Australia
Disclosure

• Virtus Health shares

• Past sponsorship by pharmaceutical companies to present at scientific meetings
International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

Authorship
This guideline was authored by Helena Teede, Marie Misso, Michael Costello, Anuja Dokras, Joop Laven, Lisa Moran, Terhi Piltonen and Robert Norman on behalf of the International PCOS Network in collaboration with funding partners and collaborating organisations, see Acknowledgments.

Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome

Helena J. Teede1,2,3, Marie L. Misso1,2,3, Michael F. Costello4, Anuja Dokras5, Joop Laven6, Lisa Moran1,2,3, Terhi Piltonen7, and Robert J. Norman1,2,8, on behalf of the International PCOS Network9.

Clinical Endocrinology. 2018;1-19.

Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome

Evidence-based guidelines

Large-Scale Evidence-Based Guideline Development Engaging the International PCOS Community

Misso Costello et al, Sem in Repro Med 2018

This work is supported by the NHMRC funded Centre for Research Excellence in Polycystic Ovary Syndrome (project number APP1078444).
International collaboration
3 Partners (Aust CRE-PCOS, ESHRE, ASRM)

5 guideline development groups comprising 63 international multidisciplinary experts & consumer members

37 leading international societies and consumer groups across 71 countries

60 evidence reviews (40 SRVs & 20 NRVs)
166 recommendations & practice points (31 EBRs, 59 CCRs, 76 CPPs)

3 years to complete

Approved by the Australian NHMRC
1 guideline (201 pages) & 1 guideline technical report (1803 pages)
International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

TECHNICAL REPORT FOR:
International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

For submission to NHMRC for consideration of approval under section 14A of the NHMRC Act 1992.

https://www.monash.edu/medicine/sphpm/mchri/pcos
5 Key Priority Areas

Prioritised clinical questions

Prioritisation of guideline clinical questions was informed by an International Delphi exercise and by the multidisciplinary GDGs, with final questions (detailed in the methods section) addressed across:

<table>
<thead>
<tr>
<th>GDG 1</th>
<th>Screening, diagnostic assessment, risk assessment and life-stage</th>
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</thead>
<tbody>
<tr>
<td>GDG 2</td>
<td>Prevalence, screening, diagnostic assessment and management of emotional wellbeing</td>
</tr>
<tr>
<td>GDG 3</td>
<td>Lifestyle management and models of care</td>
</tr>
<tr>
<td>GDG 4</td>
<td>Medical treatment</td>
</tr>
<tr>
<td>GDG 5</td>
<td>Screening, diagnostic assessment and management of infertility</td>
</tr>
</tbody>
</table>

> 3000 international health professionals & consumers involved in focus groups & surveys to formulate & rank topics
Interpreting the recommendations is key

• **Categories**
  - Evidence Based Rec (EBR)
  - Clinical Consensus Rec (CCR)
  - Clinical Practice Point (CPP)

• **Quality of Evidence**
  - High, moderate, low and very low

• **Grade (and strength) of Recommendation**
  - Strong
  - Conditional (weak)
## GRADE Approach: Strength of Recommendation from the perspective of the clinician

<table>
<thead>
<tr>
<th>Strong</th>
<th><strong>should just do it</strong> (or brief explanation of relative merits of alternatives)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>as <strong>most (all or almost all) informed patients</strong> would choose the recommended management</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weak (conditional)</th>
<th><strong>offer intervention</strong> with <strong>more discussion of alternatives (benefits/risks)</strong> considering the patient’s values &amp; preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>as <strong>most, but not all patients</strong> would follow the recommendation (dependent on their values and preferences)</td>
</tr>
</tbody>
</table>
Diagnostic criteria for PCOS

Use Rotterdam criteria for adults

Rotterdam diagnostic criteria requires two of:
1. Oligo- or anovulation
2. Clinical and/or biochemical hyperandrogenism
3. Polycystic ovaries
   and exclusion of other aetiologies

Use NIH criteria for adolescents (< 8yrs post menarche)

NIH diagnostic criteria requires:
1. Oligo- or anovulation; and
2. Clinical and/or biochemical hyperandrogenism;
   and exclusion of other aetiologies

Teede et al MJA 2011, Rotterdam HR 2003
Assessment of PCOM on Ultrasound

**CCR** Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for 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.

**CPP** If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.

**CPP** In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.
Lifestyle: Improving outcomes

First line therapy fertility, reproductive, metabolic

- **Healthy lifestyle** (healthy eating, regular physical activity) for excess weight gain prevention is important for all women with PCOS regardless of weight

- **Excess weight** (overweight or obese): aim for 5-10% weight loss (yields significant clinical improvements) over 6 months

- **Diet**: no specific diet, general energy deficit -30%

- **Exercise: prevention of weight gain**: moderate intensity \( \geq 150 \text{ min/week} \) or vigorous \( \geq 75 \text{ min/week} \)

- **Exercise: weight loss**: moderate intensity \( \geq 250 \text{ min/week} \) or vigorous \( \geq 150 \text{ min/week} \)

- **Behavioural strategies**: include goal-setting, self monitoring, slower eating etc
Combined oral contraceptive pill (COCP): Use

- The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles (EBR, strong rec, low QOE)

- The COCP alone should be considered in adolescents (either with a clear diagnosis of PCOS or deemed “at risk” but not yet diagnosed with PCOS) for management of clinical hyperandrogenism and/or irregular menstrual cycles (EBR, conditional, low QOE)
COCP: Type

- Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended in adults and adolescents with PCOS and practice should be informed by general population guidelines (EBR, conditional, low QOE)

- The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS as per general population guidelines, due to adverse effects including venous thromboembolic risks (CCR, conditional against, QOE not applicable)
COCP: consider adding …

• **Metformin** if
  • metabolic features (i.e. IGT, high risk for T2DM) if failed lifestyle changes (EBR, strong, low QOE)

• **Anti-androgen** if
  • ≥ 6 mths of COCP + cosmetic therapy failed to adequately improve hirsutism (EBR, conditional, low QOE)

  • treatment of androgen-related alopecia (CCR, conditional, QOE not applicable)
Other pharmacological treatments: consider

- **Metformin + lifestyle** if BMI ≥ 25kg/m^2 for management of weight and metabolic outcomes (EBR, conditional, low QOE)

- **Anti-obesity medications + lifestyle**, if failed lifestyle, for the management of obesity as per general population recommendations (CCR, conditional, QOE not applicable)

- **Anti-androgens** (with effective contraception) to treat hirsutism and androgen-related alopecia where COCPs are contraindicated or poorly tolerated (EBR, conditional, very low QOE)

- **Inositol** as an experimental therapy in PCOS with the need for further research (EBR, conditional against, very low QOE)
GDG 5: Assessment & management of infertility

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Costello (Chair)</td>
<td>Australia</td>
</tr>
<tr>
<td>Robert Norman (Deputy Chair)</td>
<td>Australia</td>
</tr>
<tr>
<td>Adam Balen</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Luigi Devoto</td>
<td>Chile</td>
</tr>
<tr>
<td>Roger Hart</td>
<td>Australia</td>
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<tr>
<td>Cailin Jordan</td>
<td>Australia</td>
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<tr>
<td>Richard Legro</td>
<td>USA</td>
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<tr>
<td>Edgar Mocanu</td>
<td>Ireland</td>
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<tr>
<td>Jie Qiao</td>
<td>China</td>
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<td>Raymond Rodgers</td>
<td>Australia</td>
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<td>Luk Rombauts</td>
<td>Australia</td>
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<tr>
<td>Shakila Thangaratinam</td>
<td>United Kingdom</td>
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<tr>
<td>Eszter Vanky</td>
<td>Norway</td>
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<tr>
<td>Louise Johnson</td>
<td>Australia</td>
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</tbody>
</table>

This work is supported by the NHMRC funded Centre for Research Excellence in Polycystic Ovary Syndrome (project number APP1078444).
Letrozole is 1<sup>st</sup> line pharmacological OI

**EBR**  Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.

**CPP**  Health professionals and women need to be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.
Letrozole evidence

Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis

Rui Wang,1,2 Bobae V Kim,1 Madelon van Wely,3 Neil P Johnson,1,4 Michael F Costello,5 Hanwang Zhang,2 Ernest Hung Yu Ng,6 Richard S Legro,7 Siladitya Bhattacharya,8 Robert J Norman,1,9,10 Ben Willem J Mol1,11

the bmj | BMJ 2017;356:j138 | doi: 10.1136/bmj.j138

This work is supported by the NHMRC funded Centre for Research Excellence in Polycystic Ovary Syndrome (project number APP1078444).
1st Systematic Review and network meta-analysis in OI

**Aim:** to identify the best 1st line OI treatment in WHO Group II including PCOS anovulation

**8 OI Rx’s:** placebo/no Rx, CC, LET, MET, CC+MET, TAM, Gn’s, LOD
Summary of main clinical findings

- All pharmacological OI Rx’s superior to placebo (PB)/no Rx (OR, PR)

- Letrozole can be recommended as 1\textsuperscript{st} line Rx
  1. LET superior to CC for all outcomes (OR, PR, LBR, MPR)
  2. LET only OI Rx superior to CC for LBR
  3. LET only OI Rx superior to CC in therapy naive women (PR)
  4. LET only OI Rx superior to CC in high quality RCTs (PR)

- Both MET (OR = 0.22) and LET (OR = 0.46) have a lower MPR compared to CC
Letrozole superior to CC for LBR

**Franik 2018**

### Figure 4. Forest plot of comparison: 2 Aromatase inhibitors compared to other ovulation induction agents, outcome: 2.1 Live birth rate.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Aromatase inhibitor</th>
<th>Other agents for OI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>2.1.1 Alro versus clomiphene citrate</td>
<td>Amar 2017 (1)</td>
<td>38</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Bayer 2006 (2)</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Bagum 2009 (3)</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Denhavi 2009 (4)</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Lepro 2014 (5)</td>
<td>103</td>
<td>374</td>
</tr>
<tr>
<td></td>
<td>Liu 2017 (6)</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Roy 2012 (7)</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Roy 2012 (8)</td>
<td>39</td>
<td>104</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>252</td>
<td>816</td>
<td>839</td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 2.63, df = 7 (P = 0.92), I² = 0%

Test for overall effect: Z = 5.01 (P = 0.00001)

**OR 1.79 (1.42-2.25)**
Algorithm 5: Assessment and treatment of infertility

1st line non-pharmacological management for infertility → Lifestyle interventions

1st line pharmacological management for infertility

- Letrozole (consider Letrozole as 1st line therapy)
- Clomiphene citrate
- Clomiphene citrate + metformin
- Metformin

Gonadotrophins

2nd line pharmacological/surgical management

- Gonadotrophins
- Laparoscopic ovarian surgery

3rd line management could be other appropriate interventions including IVF
Gonadotrophins could be 1st line pharmacological OI

EBR

Gonadotrophins could be considered as first 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.

Figure 7. Forest plot of comparison: 3 Antioestrogen versus gonadotropin, outcome: 3.1 Live birth/ongoing pregnancy.

CC V Gn’s in TN PCOS women

OR 0.64 (0.41-0.98)
Adding metformin to gonadotrophins in CCR PCOS could be used to improve reproductive outcome.
Gonadotrophins should be used in preference to clomiphene citrate combined with metformin for OI in CCR PCOS with to improve ovulation, pregnancy and live birth rates.

Table 1. Methods and results of the meta-analysis.

<table>
<thead>
<tr>
<th>Outcome/subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 NET+CC vs. LED</td>
<td>1</td>
<td>50</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.85 (95% CI 0.29-2.56)</td>
<td>0.76</td>
</tr>
<tr>
<td>3.2 NET+CC vs. gonadotrophins</td>
<td>2</td>
<td>170</td>
<td>OR (M-H, Fixed, 95% CI)</td>
<td>0.33 (95% CI 0.13-0.85)</td>
<td>0.02b</td>
</tr>
</tbody>
</table>

OR 0.33 (0.13 – 0.85)
Algorithm 5: Assessment and treatment of infertility

1st line non-pharmacological management for infertility
- Lifestyle interventions

1st line pharmacological management for infertility
- Letrozole* (consider Letrozole as 1st line therapy)
- Clomiphene citrate
- Clomiphene citrate + metformin
- Metformin*
- Gonadotrophins#

2nd line pharmacological/surgical management
- Gonadotrophins
- Laparoscopic ovarian surgery

3rd line management could be other appropriate interventions including IVF

CCR In the absence of an absolute indication for IVF ± intracytoplasmic sperm injection (ICSI), women with PCOS and anovulatory infertility could be offered IVF as third line therapy where first or second line ovulation induction therapies have failed.
**IVF + ICSI**

• **GnRH antagonist protocol** is preferred **GnRH agonist long protocol** to reduce the incidence of OHSS
  
  (EBR, conditional recommendation, low QOE)

• **urinary or recombinant FSH** can be used
  
  (CCR, conditional recommendation, QOE not applicable)

• **exogenous rec-LH should not be routinely used** with FSH
  
  (CCR, conditional recommendation, QOE not applicable)

• **Adjunct metformin therapy** could be used with a **GnRH agonist protocol** to improve the clinical pregnancy rate and reduce the risk of OHSS
  
  (EBR, conditional recommendation, low QOE)

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Algorithms

Clinical decision support tool

Series of 5 algorithms based on the PCOS guideline development areas

Promote best practice

Ensures consistent, standardised evidence-based care

Free digital access and downloadable
Consumer visual fact sheets

Aim to reach an international audience, low health literacy

Series of 5

Extensive testing by PCOS consumers

Visually engaging/low text

Free digital access and downloadable

PCOS, fertility and pregnancy

Most women with PCOS achieve their desired family size. For some of these women medical support may be needed.
PCOS guideline translation program – APP

ASKPCOS.Admin@monash.edu
PCOS App

First evidence-based PCOS App

Innovative design, self diagnosis function, question prompt list

Delivery of personalised information, able to store personal information

Variable pricing policy (low cost in developing countries)

Available iTunes 2018 in 5 languages – English, Mandarin, Vietnamese, Hindi, Spanish
Acknowledgement: International PCOS Network

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Authorship

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70 members of International PCOS Network who all contributed to the Guidelines

https://www.monash.edu/medicine/sphpm/mchri/pcos