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Update on PCOS: Consequences, Challenges and Guiding Treatment
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<p>SPECIAL REQUESTS:</p> <p>In place of a cover letter, enter specific comments or requests to the editors here</p>	<p>Dear Editors,</p> <p>Thank you very much for the opportunity to provide this mini-review on the topic of PCOS entitled “ Update on PCOS: Consequences, Challenges and Guiding Treatment”. PCOS remains a challenging condition that despite its prevalence remains under diagnosed and treated. We have jointly summarized and updated the recommendations of the International evidence-based guideline for the assessment and management of PCOS published in 2018 . We have reviewed relevant</p>

	<p>publications, clinical trials and meta-analyses published since 2018 and highlight areas of controversy in the diagnosis and management of the condition to aid future investigators and clinicians dealing with PCOS.</p> <p>We hope that this mini-review offers novel and practical information on PCOS origins, complications and treatments and translates recommended guidelines to general clinicians and investigators alike.</p> <p>We look forward to your review of this work and welcome any recommendations.</p> <p>Sincerely, Kathleen Hoeger Anuja Dokras Terhi Piltonen</p>
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1 Update on PCOS: Consequences, Challenges and Guiding Treatment

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20

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38 **Abstract**

39 Polycystic Ovary Syndrome (PCOS) is one of the most common reproductive endocrine disorders in
40 women and despite this, diagnostic challenges, delayed diagnosis and less than optimal treatment
41 regimens plague the condition. The International PCOS network, consisting of geographically diverse
42 international experts in PCOS as well as consumers, engaged in a multi-year international evidence-
43 based guideline development process that was jointly sponsored by the European Society for Human
44 Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM). The
45 guideline was published in 2018 and endorsed by more than 40 international societies involved in PCOS.
46 Translation of this evidence-based guideline to medical practice and consumer groups remains a
47 priority. However, there remain many challenges to both understanding the diagnosis and treatment of
48 PCOS. Evidence suggests that both clinicians and consumers are not satisfied with the timeliness of
49 diagnosis and treatment options. This review summarizes the important findings for diagnosis and
50 treatment from the guidelines and expands on recent developments in the literature since its
51 publication. Special attention to diagnosis at the ends of the reproductive spectrum are discussed and
52 remaining areas of controversy are noted. Additionally, the review highlights some of the remaining
53 challenges in the understanding and management of PCOS to help guide clinicians and investigators in
54 this perplexing condition.

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62 **Introduction**

63 Polycystic Ovary Syndrome (PCOS) is the most common endocrinologic condition in women, affecting
64 between 8-13% of reproductive aged women^{1, 2}. It is an enigmatic condition that while extremely
65 common, creates challenges in the diagnosis and management, as leading symptoms may vary based on
66 age, and treatment may be tailored to specific requirements of individual need. The vast array of
67 possible diagnostic schemes, treatment offerings and often conflicting recommendations, led to the
68 formation of a large international consortium to examine the evidence in a rigorous way and produce
69 evidence-based guidelines on diagnosis and management published in 2018.^{3,4} What was clear however
70 in this published guideline is that there are still many challenges that remain to the diagnosis and
71 treatment of PCOS. Additionally, research has exposed the still large gap between the available evidence
72 and its translation to improved diagnostic timing and evidenced based treatments.^{5,6} There are still
73 knowledge gaps in different disciplines of medicine (e.g. OBGYN, Medicine, Pediatrics, Dermatology)
74 regarding the diagnosis and treatment of PCOS, and women with PCOS report significant delays in the
75 diagnosis⁷, dissatisfaction with the treatment and recommendations they receive⁸ and lack of
76 satisfactory treatment options. This gap is not just noted in practicing physicians who completed training
77 before the international guidelines were published, but recent assessment of OBGYN residents in
78 training identified significant deficiencies in the knowledge of the diagnostic criteria for PCOS. In this
79 survey of US based OBYGN residents, 85.4% of 347 trainees completing the survey reported using
80 Rotterdam criteria to diagnose PCOS. However, only 55% correctly identified the 3 main criteria used in
81 the diagnosis .⁹

82

83 This paper will review the diagnostic criteria and the challenges that continue to present for clear
84 diagnosis. PCOS impacts all aspects of the reproductive hormone physiology, however the precise
85 pathophysiology remains incompletely elucidated. The current evidence for leading pathophysiologic

86 disturbance in PCOS will be reviewed as well as the best evidence of reproductive, psychological and
87 metabolic consequences. Finally, an update on the best evidence based treatments for PCOS will be
88 reviewed. This review will highlight the challenges that remain in the diagnosis and treatment of PCOS
89 and bring forth the most recent evidence to support the recommendations.

90

91 *Search Strategies*

92 In addition to the literature reviewed by the international evidence-based guidelines³, PubMed was
93 searched with the header of Polycystic Ovary Syndrome, PCOS with the sub categories of clinical trials,
94 meta-analysis, systematic reviews between January 2018-June 2020.

95

96 **Pathophysiology**

97 The pathogenesis of PCOS is complex and multifactorial including genetic, environmental and
98 transgenerational components. All these sources drive the underpinnings of unbalanced hypothalamus-
99 pituitary-ovarian axis signaling, promoting ovarian and adrenal hyperandrogenism. The syndrome is also
100 burdened with insulin resistance that is worsened by hyperandrogenism -related adipose tissue
101 accumulation and dysfunction with lipotoxicity and oxidative stress .¹⁰ Thus, the full clinical spectrum of
102 the syndrome involves metabolic, reproductive and psychological impairments. Environmental factors
103 also play a role and the link between obesity and the prevalence of PCOS is undisputable; among
104 women with BMI <25 kg/m², the prevalence is 4.3%, and in women with BMI > 30kg/m² and 14%.¹¹

105

106 *Neuroendocrine link to PCOS*

107 Women with PCOS present with dysfunction within the gonadotropin-releasing hormone (GnRH)
108 neuronal network and increased pulse amplitude for pituitary activity shown as high serum LH levels and

109 high ovarian androgen response most likely relating to decreased responsiveness to steroid hormone
110 negative feedback.¹² Different animal models have successfully been able to recapitulate the
111 hyperandrogenism driven neuroendocrine pathology of PCOS and other central mechanisms involved.¹³
112 Recently aberrant neuroendocrine signaling was linked with adipose tissue dysfunction in murine
113 model¹⁴, whereas other studies have proposed high AMH promoting GnRH neuron activation and PCOS
114 onset.¹⁵ Given the central role of hyperandrogenism and obesity in the impairments in neuronal circuitry
115 and high prevalence of psychological distress among women with PCOS, the central dysfunction most
116 likely involves larger and more complex neuronal networks than previously expected^{16,17}

117

118 *Genetic factors*

119 The genetic factors and family clustering have been described already in the early PCOS literature¹⁸
120 however, as more genetic data has started to accumulate, it has become obvious that the syndrome
121 harbors multigenetic background. Indeed, the GWAS studies have identified a total of 19 risk gene loci
122 for PCOS located in the neuroendocrine, metabolic, and reproductive pathways¹⁹, the reproductive and
123 metabolic populations segregating a recent unsupervised clustering analysis.²⁰ In line with this,
124 mendelian randomization analyses suggested causal link between variants associated with body mass
125 index, fasting insulin, menopause timing, depression and male-pattern balding and PCOS.²¹ From all
126 genes of interest, the most potential gene loci namely *THADA*, *FSHR*, *INS-VNTR*, and *DENND1A*, would
127 require validation in the future. Interestingly the clinically validated PCOS cases have similar genetic
128 profile than the self-reported ones, allowing data generation in the future also through less burdening
129 and more inexpensive means.²¹ Given that genetic factors explain <10% of PCOS cases, other etiological
130 factors also have to be considered.

131 *Transgenerational transmission of PCOS*

132 Animal studies and human data show the syndrome having transgenerational origins with 5-fold risk for
133 the daughters born to PCOS mother inheriting the syndrome^{13,22} In a murine model prenatal androgen
134 excess alone can predispose to transgenerational transmission of PCOS.²² In humans, early androgen
135 exposure is also likely the cause for susceptibility to the syndrome shown as higher anogenital distance
136 in infant girls born to PCOS mothers.²³ The mechanism through which the daughters are exposed to
137 hyperandrogenism still remains elusive, although for example AMH could be one of the players.
138 Interestingly, a recent study showed mice subjected to high levels of AMH at late pregnancy producing
139 PCOS offspring with high LH pulsatility and increased androgen levels.²⁴ The mechanism was thought to
140 transit via AMH effect on aromatase activity in placenta, promoting hyperandrogenism. Even though
141 AMH levels have been reported to be high in the 2nd and 3rd trimester in women with PCOS^{24, 25}, the role
142 of AMH on transgenerational transmission in humans still warrants further studies.

143

144 **Diagnosis**

145 *Criteria for diagnosis*

146 There is no specific diagnostic test that unequivocally identifies PCOS but rather the diagnosis is based
147 on the varying presence of 3 specific elements, namely oligo-anovulation, androgen excess, either
148 clinical or biochemical, and the ultrasound assessment of ovarian morphology. The international
149 evidence-based guideline³ endorsed the use of the Rotterdam criteria²⁶ that requires 2 of the 3
150 diagnostic criteria be present for the diagnosis in adult women. Exclusion of thyroid disease (thyroid
151 stimulating hormone, TSH), hyperprolactinemia (prolactin), and non-classic congenital adrenal
152 hyperplasia (screening with 17-hydroxy progesterone) is recommended with further evaluation
153 recommended in those with amenorrhea and more severe clinical features including consideration of
154 hypogonadotropic hypogonadism, Cushing's disease, or androgen producing tumors where there is a
155 more severe androgenic profile. The guidelines also endorse the use of phenotype descriptions when

156 diagnosing PCOS and present 4 phenotypes (A-D) based on the presence or absence of the 3 diagnostic
157 criteria (see Table 1). The specific clinical implications or natural history of each of the phenotypes
158 remains unclear at this time, although recent study has found genetic clustering for reproductive and
159 metabolic phenotypes.²⁰ Moreover, a review of metabolic features and phenotypes noted that while
160 androgenic phenotypes were more often associated with more severe metabolic dysfunction, this was
161 confounded in most studies by the presence of adiposity with increased adiposity leading to more
162 severe complications and not all studies controlled for BMI.^{27, 28} Diagnostic features of the condition also
163 vary across the lifespan and by ethnicity which complicates the categorization and natural history.

164

165 The recommendations for the diagnostic criteria from the international guidelines are noted in Table 2.
166 Androgenic status can be assessed by either biochemical measures or clinical measures. The presence of
167 androgenic excess is clinically indicated by cutaneous manifestations such as the presence of hirsutism
168 (indicated by modified Ferriman-Gallwey (mFG) score)²⁹, acne or alopecia.. There is significant ethnic
169 variation in clinical androgenic expression and examination is often limited by self-treatment of
170 hirsutism. There is limited data from diverse populations making the interpretation of the mFG score
171 challenging. Current recommendations in the guidelines are based on limited controlled data, with a
172 reduction in the overall mFG score consistent with hyperandrogenism. Ovulatory dysfunction is marked
173 by oligo-anovulation with irregular menses as the marker defined based on published data as noted in
174 Table 2. If irregular menses is present along with hyperandrogenism, biochemical or clinical, then the
175 use of pelvic ultrasound is not required for diagnosis, although assignment of the full phenotype is
176 limited without this measure.

177

178 *Challenges for the ultrasound diagnostic criteria and role of AMH*

179 Ultrasound morphology is the most challenging of the criteria as there has been variation in the
180 standards in the reporting of the follicle count cut offs. As technology has improved the ability to see
181 more follicles increases so the cut-offs previously published were not based on current technology³⁰ and
182 are no longer valid to distinguish populations. The Androgen Excess and PCOS society published
183 guidelines in 2014.³¹ Reviewing the literature available the guideline recommended using follicle
184 number per ovary (FNPO) for the definition of PCO morphology (PCOM) and recommended the
185 threshold be set at ≥ 25 , but only when using newer technology that affords maximal resolution of
186 ovarian follicles (i.e. transducer frequency ≥ 8 MHz). The guidelines recommend the use of ovarian
187 volume for diagnosis of PCOM if such technology was not available for routine daily practice. When
188 using ultrasound in PCOS research, use of newer technology to adequately characterize follicle count is
189 suggested. The International Evidenced Based Guideline³ included a systematic review (11 studies with
190 2961 adult participants) of ultrasound in the diagnosis of PCOM and concluded that for the criteria FNPO
191 and concluded the optimal sensitivity and specificity for FNPO was > 19 follicles per ovary. The ovarian
192 volume data available did not indicate a recommended change in the ovarian volume criteria for PCOM
193 at ≥ 10 ml.

194

195 AMH levels have been considered as a surrogate marker or as an alternative to ultrasound FNPO count
196 for the diagnosis of PCOM or as an independent marker of PCOS. Overall serum AMH levels are 2-3 fold
197 higher in women with a diagnosis of PCOS than in women with normal reproductive function and
198 correlate with FNPO ultrasound measures.³²⁻³⁵ There are recognized challenges in the AMH assay³⁶ such
199 as proteolysis, changes in the AMH dimer or interfering substances that increases poor performance of
200 the assay in predictive models. Additionally, there are variations across the reproductive lifespan in the
201 ranges of AMH.³⁷ This makes it difficult to distinguish cases from controls on this criterion. Given all this
202 and the limitations of AMH measurement, AMH alone is not sufficient to establish the diagnosis. A

203 recent systematic review of the use of AMH in replacing ultrasound in PCOS diagnosis identified the
204 research gaps that still remain before AMH can be considered in the diagnostic algorithm.³⁸

205

206 *Special age group considerations*

207 Adolescence, the period of time between 10 and 19 and the time of pubertal maturation represents a
208 distinct dilemma in the diagnosis of PCOS. The diagnosis in adolescence is challenged by the overlap of
209 normal pubertal physiology changes and those that mimic adult diagnostic criteria for PCOS, namely
210 irregular menstrual cycles and multi-follicular ovaries. Additionally, the time from menarche to full
211 maturation of the reproductive axis^{39,40} can be variable to as late as 8 years post menarche which may
212 bridge young adulthood. Since there is evidence for the underpinnings of PCOS presenting in
213 adolescence and the normal pubertal overlap, there is the risk of both under-diagnosis⁷ and that of over-
214 diagnosis without adequate support for disease. The recommendation for diagnosis in adolescence
215 cannot depend on pelvic ultrasound findings given the increased overlap with normal ovarian findings in
216 this age group and instead is based on irregular menses and hyperandrogenism. Care should be taken
217 when using biochemical evidence of hyperandrogenism to establish a normative range for the assay
218 used in this population. AMH is also unhelpful in distinguishing PCOS in this age group. In adolescents,
219 levels are high and overlap considerably between adolescents with and without diagnostic features of
220 PCOS.³⁷ Menstrual cycles may not establish a regular pattern until >2 years post menarche.⁴¹ A recent
221 study of 317 16 year olds from a Danish cohort, the majority had regular cycles within 3 years post
222 menarche.⁴² Therefore, the diagnosis should not be made within 2 years of menarche to allow for this
223 maturation. The International Guidelines however allow for consideration of an “at risk” category for
224 adolescents who begin to exhibit some symptoms of PCOS but are not yet in a development stage to
225 fully endorse the diagnosis and should be re-evaluated with maturation.⁴³

226

227 On the other end of the reproductive spectrum, there are challenges to diagnosis in women in the peri-
228 and post-menopausal reproductive spectrum. The average age of menopause is 51 years but menstrual
229 changes occur much earlier than this in normal aging,⁴⁴ so ovulatory dysfunction is unreliable as a
230 diagnostic criterion. In fact, there is evidence of increase in regular menstruation in women diagnosed
231 with PCOS as they approach perimenopause.⁴⁵⁻⁴⁷ Also ovarian volumes and follicle counts decline with
232 age. Ovarian androgen production may decline in both groups but clinical hyperandrogenism may be
233 more prevalent due to decline in estrogen levels in menopause.⁴⁸ At this point there is insufficient
234 evidence about natural history to specifically distinguish the phenotype in menopausal women. The
235 Guidelines suggest a diagnosis of PCOS could be considered if there is a past diagnosis of PCOS, a long-
236 term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive
237 years, but do not endorse specific diagnostic criteria separately.⁴⁹

238

239 **Consequences**

240 **What is known**

241 *Metabolic/Obesity*

242 PCOS is associated with an increased risk of metabolic complications starting from a young age. These
243 comorbidities include traditional cardiovascular disease (CVD) risk factors such as obesity, impaired
244 glucose tolerance (IGT), type 2 diabetes (DM), dyslipidemia and hypertension. Obesity is one of the most
245 common concerns expressed in surveys of patients with PCOS.⁷ Depending on the ethnicity and study
246 population assessed the obesity rate varies between 50-80%. On examining high quality studies in a
247 large meta-analysis, the risk of obesity was reported to be four-fold higher compared to controls and
248 also higher in white women compared to Asians.⁵⁰ Importantly, women with PCOS have been shown to
249 present with long-term overweight or obesity the onset of BMI trajectory deviation occurring as early as
250 around age 5.⁵¹ Evidence from cross-sectional studies suggests that the risk of overweight/obesity

251 persists beyond the fourth decade of life⁵² and a few longitudinal studies also suggest an increase in
252 weight with age.⁵³ The increased preference for abdominal fat deposition, seen primarily in the
253 hyperandrogenic phenotype, further predisposes this population to other cardiometabolic
254 complications.⁵⁴ The risk of IGT is three-fold higher with PCOS, independent of BMI, and highest in
255 women living in Asia and North and South America.⁵⁵ Although the risk of DM is also increased in this
256 reproductive age population, there is mixed data regarding these findings independent of weight. In
257 women over age 40, a few longitudinal studies and other cross-sectional studies indicate an increased
258 risk of type 2 DM independent of BMI.⁵² In adolescents with PCOS, there are only a few small studies
259 examining the risk of DM and show an overall low prevalence. When examining the differences based
260 on PCOS phenotype, a large cross-sectional study showed a similar risk of DM in all four phenotypes.⁵⁶
261 Dyslipidemia, reflected by high triglycerides and low HDL-C, is the commonest metabolic abnormality
262 detected in PCOS.⁵⁷ Some studies have performed deep lipid phenotyping and demonstrate high LDL-C
263 levels, increase in atherogenic lipoproteins and decrease in HDL-C efflux capacity, indicating increased
264 CVD risk.⁵⁸ When examining the risk in different age groups, there are few studies in adolescents and
265 those in older women show a higher prevalence of dyslipidemia in the hyperandrogenic phenotype.⁵⁹
266 The association between hypertension and PCOS is mixed. Most studies do not demonstrate a higher
267 risk of hypertension independent of BMI, although longitudinal data demonstrate elevated blood
268 pressure even in lean women with PCOS.⁶⁰ The few studies in adolescents and older women do not
269 show significant differences compared to control groups.⁶¹ Given that most of the data on metabolic risk
270 is derived from cross-sectional studies, the long-term significance of mild to moderately abnormal
271 values for blood pressure measurements and serum lipids is not clear. Another approach is to evaluate
272 the prevalence of metabolic syndrome as it assesses early evidence of dyslipidemia, hypertension,
273 glucose intolerance and obesity as a composite score and may predict long-term risk of DM and CVD.
274 Reproductive-age women with PCOS have a two-fold increased risk of metabolic syndrome⁶² with a

275 higher risk in the hyperandrogenic phenotype.²⁸ More importantly, in adolescents with PCOS the risk of
276 metabolic syndrome is at least 2-fold higher than girls without PCOS.⁶³

277

278 *Reproductive /obstetric*

279 Women with PCOS are at an increased risk of endometrial hyperplasia and infertility related to
280 anovulation. Premenopausal women with PCOS may have a four-fold increased risk of endometrial
281 cancer.⁶⁴ For women with PCOS seeking pregnancy, the ovulation induction agent letrozole has higher
282 live birth rates compared to clomiphene citrate.⁶⁵ Use of metformin in conjunction with these
283 medications may improve the ovulation rate in a sub-population of obese women.⁶⁶ Metformin on the
284 other hand has not been shown to reduce the risk of gestational diabetes (GDM) thus its used should be
285 targeted prior to pregnancy to facilitate weight management. Once pregnant, women are at an
286 increased risk of miscarriage, GDM, pregnancy induced hypertension and preeclampsia.⁶⁷ These
287 complications are increased in the hyperandrogenic phenotypes.

288

289 *Behavioral/emotional*

290 PCOS is associated with a higher prevalence of psychiatric disorders. Both moderate to severe
291 depressive and anxiety symptoms are increased in cross sectional studies⁶⁸, while a few longitudinal
292 studies support an increased risk of incident depression and anxiety.⁶⁹ However, there is limited data on
293 the persistent of depressive and anxiety symptoms in adolescents and beyond the fourth decade,
294 although recent data implies psychological distress prevailing long-term^{70, 71} In addition, women with
295 PCOS have a higher prevalence of disordered eating⁷² and body image distress.⁷³ Interestingly, in the
296 latter study various aspects of body image distress mediated anxiety and depressive scores, indicating
297 that improvement in body image could potentially decrease anxiety and depressive symptoms. Both
298 eating disorders and body image distress add to difficulty in losing weight, highlighting the importance

299 of routine screening for these disorders and use of interventions such as cognitive behavioral therapy
300 in.^{68, 74}

301

302 *Quality of Life*

303 PCOS symptoms and comorbidities burden women with PCOS. Women with PCOS report poorer health
304 status than non-PCOS counterparts⁷⁵ and indeed, health professionals and women should be aware of
305 the adverse impact of PCOS on health-related quality of life (QoL)^{76, 77} that seems to prevail at least up
306 till late reproductive years.⁷⁵

307

308 **What remains to be clarified**

309 *Cardiovascular disease*

310 Compared to the outcomes of obesity and IGT, fewer studies have compared the risk of dyslipidemia,
311 DM and metabolic syndrome in older women with PCOS. Most of the available data in perimenopause
312 and beyond is obtained from small cross-sectional studies including women with a presumed diagnosis
313 of PCOS limiting the validity of the findings. In order to adequately counsel patients, the prevalence of
314 traditional CVD biomarkers needs to be assessed in different phenotypes of PCOS. There is some
315 evidence for increased subclinical atherosclerosis in young women with PCOS. Increase in carotid intima
316 media thickness measurements have been described⁷⁸, with data suggesting an increased risk for stroke
317 and myocardial infarction.⁶⁰ Ultimately, we need more longitudinal studies examining the incidence of
318 CV events in this populations. Although there is some evidence from population-based studies for
319 increased CV events in late reproductive age women with PCOS, most studies lack adequate power to
320 evaluate these outcomes and do not include menopausal women with well-defined PCOS.⁷⁹

321

322 *Perimenopausal disease course*

323 In a large proportion of women, the clinical features of PCOS improve with age, such that by the fourth
324 decade menstrual cycles become more regular and serum androgen levels normalize.⁴⁷ High serum
325 levels of AMH and high antral follicle counts suggest increased ovarian reserve in early reproductive
326 years. These biomarkers also decrease with age and their trajectory suggests that women with PCOS
327 may go through menopause later than controls (Minooe et al, 2018).⁸⁰

328

329 **Management**

330 The management of comorbidities related to PCOS like obesity, type 2 diabetes (DMT2), and all health
331 impairments related to metabolic syndrome and psychological distress should be treated following the
332 current common guidelines regardless of PCOS diagnosis. What should be noted is that PCOS increases
333 the risk for all these comorbidities for at least 2-3-fold (mental distress even up to 5-fold), in many cases
334 the onset occurring several years earlier than in other women. This should be considered when
335 screening and testing for them.

336

337 The new international PCOS guideline recommends assessing weight and measuring waist during every
338 visit and otherwise every 6-12months also giving high importance for weight gain prevention and pre-
339 pregnancy weight management.³ Given that even lean women with PCOS are insulin resistant, all
340 women should be tested for glycated hemoglobin, Hba1c, for every 3 years and for oral glucose tolerance
341 test (OGTT) for every 1-3 years if any known risk factors for DMT2. In a case of pregnancy, OGTT should
342 be performed already in early pregnancy and repeated at gestational week 24-28. Obesity has been
343 shown to be a high-risk factor for GDM also in PCOS, although PCOS also presents as an independent risk
344 factor.⁸¹ Hypertension should be screened annually whereas dyslipidemia should be considered and
345 tested for all overweight and obese women at diagnosis, although according to recent Nordic study
346 among women <35 years, only minority have values warranting statin medication.⁸² Considering the

347 different PCOS phenotypes and risk profiles for different comorbidities, future studies should target
348 building algorithms or tools facilitating targeted screening for women with PCOS with high metabolic
349 risk.

350

351 Mental disorders should be tested and treated similarly to common guidelines for general population.
352 However, psychological distress should be systematically screened from all women with PCOS by using
353 the common tools and short questionnaires and further assess and/or refer for assessment if needed.
354 Regarding adolescents, there is still need to address the management of mental distress in this
355 population.

356

357 *Lifestyle Interventions*

358 Obesity worsens the presentation of the symptoms of PCOS and weight management has been
359 proposed as an initial treatment strategy.³ Lifestyle intervention consists of changes in diet, exercise and
360 behavioral interventions designed to improve weight. Women with and without PCOS have similar diet
361 and physical activity levels⁸³ suggesting interventions can focus on general healthy principles. However,
362 interventions have been studied in only small populations in PCOS and the evidence of low quality.
363 Meta-analysis of lifestyle interventions⁸⁴ demonstrated improvement in weight, Free androgen Index
364 and BMI with weight reduction from lifestyle interventions (low quality evidence). However, there was
365 no specific impact on livebirth or menstrual regularity. An additional randomized trial of behavioral
366 modification in PCOS with a primary outcome of menstrual regularity was reported in 2019.⁸⁵ A 4-month
367 intervention resulted in significant weight reduction (-2.1%) and improved menstrual irregularity but did
368 not show improvements in ovulation.⁸⁵ The majority of women in the trial had moderate to severe
369 distress in a global index of psychological wellbeing. There was evidence of improved anxiety, lower
370 depressed mood and overall higher general health in the intervention group with no change in the

371 minimal intervention group.⁸⁶ Exercise alone as intervention in PCOS has been studied.⁸⁷ Most studies
372 of exercise intervention are small and involved varying exercise interventions-aerobic, resistance and
373 combined exercise. There was little evidence of impact on exercise alone on reproductive or hormonal
374 outcomes but evidence for reduction in BMI was moderate.

375

376 Adherence to diet and physical activity recommendations for lifestyle intervention is challenging.

377 Critically such adherence is important to achieve goals and therefore real-world outcomes of lifestyle

378 interventions may be significantly less over time.⁸⁸ A review of studies in PCOS involving lifestyle

379 intervention did not provide significant data on adherence to the programs in the majority of trials.⁸⁹ A

380 detailed look at 4 randomized trials of lifestyle intervention in PCOS involving a total of 221 women

381 showed attrition from the programs was 47.1%. However, weight loss of $\geq 5\%$ occurred in 63% of the

382 women. Women who were more likely to experience attrition had higher depressive indices at baseline

383 and those who had better appointment attendance had lower attrition and greater weight reduction.⁹⁰

384 It is likely that many genetic, psychosocial, sociodemographic and physiological factors impact the

385 success of a lifestyle/weight loss intervention. The inclusion of behavioral support in these interventions

386 is suggested based on psychological factors that are present with higher attrition from these programs.

387 Overall available evidence suggests that lifestyle intervention involving weight reduction has a positive

388 effect on hyperandrogenism and metabolic features of PCOS as well as on quality of life, however there

389 is less support for improvements in reproductive and fertility outcomes.

390

391 *Medical Interventions*

392 PCOS symptoms

393 The International PCOS guideline set recommendations for treating PCOS-related symptoms core to

394 diagnosis namely, irregular cycles, hirsutism and anovulation. As hyperinsulinemia promotes

395 hyperandrogenism, medical treatment is recommended only second line after lifestyle modification. For
396 medical interventions combined contraceptives (COCs) are effective in treating irregular cycles and they
397 are superior also for the treatment of hirsutism and acne compared to progestin only preparations.
398 Given that there is no data showing superiority for any particular estrogen-progestin combination, the
399 choice for COC can be done according to administration preference and minimizing side effect profile to
400 ensure compliance.³ Of note, per WHO recommendation, 35ug estrogen in combination with
401 cyproterone acetate should only be used as a second line choice for persistent acne or hirsutism, given
402 the increased risk for vascular thromboembolism related to these preparations.
403 Metformin only therapy exerts only mild to moderate changes on cycle regularity and
404 hyperandrogenism and has been reported to be inferior to COC treatment. However, as a novel
405 approach, the new guideline encourages combining metformin with COCs, especially in overweight or
406 obese women with PCOS. This recommendation also applies to adolescents. The data regarding
407 antiandrogen medication was limited due to lack of high-quality studies and the already existing data did
408 not show antiandrogens having major advantages when combined to COCs. A recent placebo controlled
409 RCT also confirmed this, as only minimal additional benefit was shown when combining bicalutamide, an
410 androgen receptor (AR) antagonist, to COC treatment for 12 months.⁹¹ In clinical practice, when treating
411 women at fertile age, the risk of virilization of the male offspring in case of pregnancy should be noted,
412 warranting effective contraception when prescribing antiandrogens.

413

414 Metabolic outcomes

415 Metformin, especially in combination with lifestyle modifications, has the vastest data on improving
416 menstrual cycles, glucose levels and adiposity in PCOS; mild to moderate alleviation of insulin resistance
417 and minimal to moderate effect on improving lipid profile.⁹² Low cost, availability and the low adverse
418 event profile of metformin supports its use. The most common side effects related to metformin are

419 gastrointestinal symptoms that are important to notice in patient consultation to ensure adherence to
420 the treatment. The use of obesity drugs is limited by their high price and availability, but emerging
421 evidence suggest their efficacy, especially glucagon-like peptide-1 (GLP-1) receptor agonist, in treating
422 obesity in women with PCOS over metformin.⁹³ Future aim should be on assessing the efficacy of
423 combinations therapies for example metformin and GLP-1 receptor agonist and anticipating obesity
424 drugs to become available also in low-income countries and communities.

425

426 Reproductive outcomes

427 A recent meta-analysis concluded that letrozole improves live birth and clinical pregnancy rates and
428 reduces time-to-pregnancy compared to clomiphene citrate (CC) and was recommended as the first-line
429 treatment for women with PCOS and infertility.⁶⁶ As for metformin, a recent review suggests very
430 modest improvement of ovulation and live birth with metformin over placebo. However, the benefit
431 combining metformin to CC was inconclusive.⁹⁴ The data on the benefit of myoinositol improving live
432 birth rate or clinical pregnancy rate in subfertile women with PCOS undergoing IVF is poor and
433 inadequate to form recommendation.⁹⁵ Future studies should focus on assessing if priming with
434 metformin before ovulation induction with letrozole would have beneficial effects on live birth rates in
435 PCOS. In cases where IVF is needed, antagonist protocol with GnRH trigger should be preferred to
436 reduce the risk for ovarian hyperstimulation syndrome (OHSS).

437

438 *Surgical Interventions*

439 Surgical interventions can sometimes relieve PCOS -related symptoms. Bariatric surgery is an effective
440 treatment for obesity and PCOS symptoms after all other treatment options have failed and it should be
441 offered to severely obese patients.⁹⁶ The risks, however, include surgical and dietary complications and
442 pregnancy should not be pursued during the following 12 months after the surgery.

443 Laparoscopic ovarian drilling (LOD) is a procedure where ovarian tissue is destroyed with a laser beam or
444 with a surgical needle using minimally invasive laparoscopic techniques aiming to rebalance and
445 improve ovarian function in PCOS. The procedure is not commonly used, but it has still remained as an
446 option in cases of CC resistant ovaries and when letrozole is not an option due to off-label use. However,
447 the recent Cochrane Review summarized that although reducing the number of multiple pregnancies
448 and the risk for OHSS, LOD may actually decrease the live birth rate in women with anovulatory PCOS
449 and CC resistance compared with medical ovulation induction alone.⁹⁷ One should also bear in mind that
450 LOD also subjects women to risks associated with surgery, such as complications from anesthesia,
451 infection, and adhesions.

452

453 *Cognitive behavioral therapy (CBT)*

454 Recent studies have also implied cognitive behavioral therapy (CBT) being effective in treating women
455 with PCOS.⁷⁴ A recent RCT reported three component treatment, including diet, exercise, and cognitive
456 behavioral therapy, improving depression and self-esteem in obese women with PCOS.⁹⁸

457

458 **Conclusions**

459 Despite its prevalence in reproductive aged women, the diagnosis and management of PCOS remains
460 challenging. Clear diagnostic protocols should allow for more timely and accurate diagnosis which will
461 address the concerns by both clinicians and consumers resulting from diagnostic delay. The
462 pathogenesis of PCOS is complex and multifactorial. New insights into the pathophysiology of PCOS
463 suggests that there may be antenatal drivers for development of PCOS specifically, evidence of
464 hyperandrogenism in mothers appears to influence development of PCOS features in offspring. Insulin
465 resistance is a near uniform finding in PCOS and is worsened by hyperandrogenism-related adiposity.
466 The role for abnormal AMH in the pathophysiology is also emerging but AMH is not yet a diagnostic tool

467 for PCOS. Comorbidities in PCOS are well described and it is important to evaluate and address these
468 comorbidities early in the treatment course including attention to mental health and quality of life
469 measures. While metabolic abnormalities are well described, the role of PCOS in cardiovascular disease
470 remains uncertain. Evidenced based treatment guidelines include recommendations for lifestyle
471 intervention as primary management for metabolic disease, although its specific benefit in reproduction
472 is not yet defined in weight loss trials. Oral contraceptives remain a first line therapy for management of
473 hyperandrogenism and irregular cycles and the role for metformin, while limited, may still add benefit
474 for metabolic dysfunction and weight management, including in adolescents. There remains a number
475 of challenges in the management of PCOS. A high prevalence of obesity is a significant contributor to
476 morbidity. Early attention to weight gain in childhood and adolescence in those at risk for PCOS may be
477 and important measure of prevention as early markers of PCOS are better defined.

478

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Table 1. Phenotypes of PCOS based on Rotterdam criteria

Phenotype	Androgen excess	Ovulatory dysfunction	PCO morphology on ultrasound
A	√	√	√
B	√	√	
C	√		√
D		√	√

Table 2. Definitions of features of PCOS for diagnosis

Feature	Definition
Irregular menses	<ul style="list-style-type: none"> • >1 year and <3 years post menarche=<21 or >45 days • >3 years post menarche= <21 or >35 days • >1 year post menarche=any cycle >90 days • Primary amenorrhea at age 15 or >3 years post thelarche
Biochemical Hyperandrogenism	<ul style="list-style-type: none"> • Calculated free testosterone or Free androgen Index • Calculated bioavailable testosterone • Liquid chromatography/mass spectrometer with extraction is the preferred method of assay measure • Can consider androstenedione or DHEAS if testosterone is normal and high index of suspicion for hyperandrogenism
Clinical Hyperandrogenism	<ul style="list-style-type: none"> • Examination specifically for acne, alopecia and hirsutism • For adolescents use severe acne and hirsutism • Use standardized visual scale of mFG $\geq 4-6$ recognizing there are ethnic variations that are not well defined
Ultrasound criteria	<ul style="list-style-type: none"> • Ultrasound should be transvaginal and using high resolution • In this setting follicle count per ovary should be ≥ 20 or ovarian volume ≥ 10 mL • Ultrasound should not be used in those <8 years post menarche

*adapted from the International Evidenced Based Guideline for the diagnosis and management of Polycystic Ovary Syndrome 2018

https://www.monash.edu/_data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

Table 3. Highlights of controversial areas in the diagnosis and treatment of PCOS

Controversy	Current recommendation
Use of AMH in diagnosis	While AMH is typically elevated in women with PCOS and reflects the increase in follicle pool, AMH is not currently recommended as a diagnostic criteria as there is overlap with normal reproductive measures and does not sufficiently distinguish PCOS.
Diagnosis in adolescence	Adolescents must be at least 2 years post menarche to consider the diagnosis. Ultrasound is not recommended in this age group before 8 years post menarche due to overlap with normal physiologic findings. Consideration to the label “at risk for PCOS” for those in transition where the diagnostic criteria are uncertain.
Diagnosis in perimenopause	Menstrual regularity improves with aging in PCOS therefore a retrospective diagnosis is necessary in this age group.
Use of metformin without evidence of diabetes	While there is little support as a single agent for use in ovulation induction, there is evidence of improved metabolic parameters with the use of metformin. There is modest impact to reduce weight and prevention of diabetes development noted in other populations and can be considered for these indications in PCOS.
Type of oral contraceptive	There is no evidence that one type of combined oral contraceptive is better than another for either improvement in menstrual cycles or for suppression of hyperandrogenism.
Use of combination therapy with metformin	There is evidence that adding metformin to combination oral contraceptives may improve response particularly in obese women with PCOS.