

Manuscript version: Author's Accepted Manuscript

The version presented in WRAP is the author's accepted manuscript and may differ from the published version or Version of Record.

Persistent WRAP URL:

<http://wrap.warwick.ac.uk/130772>

How to cite:

Please refer to published version for the most recent bibliographic citation information. If a published version is known of, the repository item page linked to above, will contain details on accessing it.

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions.

Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:

Please refer to the repository item page, publisher's statement section, for further information.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk.

1 **Metabolic inflexibility in women with polycystic ovary syndrome: A systematic**
2 **review**

3 Michael Rimmer¹, Bee K Tan², Helena Teede^{3,4}, Shakila Thangaratinam⁵, Bassel H.Al
4 Wattar^{5,6}

5

6 ¹ MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK

7 ² University of Leicester

8 ³ National Health and Medical Research Council Centre for Research Excellence in
9 PCOS, Monash Centre for Health Research and Implementation, Monash University

10 Melbourne, Vic., Australia

11 ⁴ Endocrine and Diabetes Units, Monash Health, Melbourne, Vic., Australia

12 ⁵ Women's Health Research Unit, Barts and the London School of Medicine and Dentistry,
13 Queen Mary University of London, London UK

14 ⁶ Warwick Medical School, University of Warwick, Coventry, UK

15

16 **Short Title:** Metabolic inflexibility in PCOS

17 **Corresponding author:** Bassel H.Al Wattar - Women's Health Research Unit, Barts and
18 the London School of Medicine and Dentistry, Queen Mary University of London,
19 London UK

20 b.wattar@qmul.ac.uk

21

22

23 **Keywords:**

24 Metabolic flexibility, inflexibility, polycystic, syndrome, systematic review.

25

26 **Abstract:**

27 **Context:** Polycystic ovary syndrome (PCOS) is a risk factor for dysglycemia, insulin
28 resistance, and type 2 Diabetes Mellitus (T2DM). Inefficient energy oxidation, metabolic
29 inflexibility, is a marker of blunted metabolism. We conducted a systematic review on
30 metabolic inflexibility in women with PCOS.

31 **Evidence Acquisition:** We searched MEDLINE, EMBASE and Cochrane central
32 (inception-October 2018) for studies evaluating metabolic inflexibility and reporting on
33 changes in Respiratory Quotient (Δ RQ). We extracted data and assessed quality using The
34 Newcastle-Ottawa Scale.

35 **Evidence Synthesis:** We included five prospective cohort studies (461 women). Three
36 compared PCOS women to unaffected subjects, one to women with obesity or T2DM, and
37 one to adolescent girls; all had medium quality. Three studies showed higher metabolic
38 inflexibility in women with PCOS (Δ RQ range 0.05-0.098) compared to unaffected
39 subjects. Women with PCOS had similar metabolic inflexibility compared to those with
40 T2DM (Δ RQ 0.05 ± 0.03 vs 0.06 ± 0.04 , $p=0.98$) and obesity ($p=0.06$). Inflexibility was
41 higher in hyperandrogenemic women with PCOS (Δ RQ 0.091 ± 0.060 vs 0.120 ± 0.010 ,
42 $p=0.014$). Δ RQ was lower in PCOS women with insulin resistance vs those with normal
43 insulin sensitivity (0.04 ± 0.02 vs. 0.07 ± 0.04 , $p=0.007$).

44 **Conclusions:** Women with polycystic ovary syndrome appear to have higher metabolic
45 inflexibility associated with hyperandrogenemia and insulin resistance.

46

47

48 **Introduction**

49 Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder affecting women
50 of reproductive age with an estimated prevalence between 8–13% ¹. It is a known risk
51 factor for dysglycemia; 75% to 95% of women with PCOS demonstrate insulin resistance,
52 with a four-fold increased risk for developing gestational and type 2 diabetes mellitus
53 (T2DM) ^{2,3}.

54 Impaired glucose metabolism could be attributed to the increased insulin resistance,
55 inadequate glucose uptake in target tissues, impaired glycogen synthesis and inefficient
56 switching from lipids to glucose oxidation in affected subjects⁴. Additionally, the reduced
57 metabolic capability to switch from lipid oxidation in fasting conditions to lipid
58 availability in glucose rich conditions, termed metabolic inflexibility, leads to lipids
59 accumulation in ectopic tissues (e.g skeletal muscles) inducing lipotoxicity with
60 worsening insulin resistance ⁵. Thus a vicious cycle of hyperinsulinemia, ectopic fat
61 storage in peripheral tissues and inefficient metabolism develops ⁶.

62 Evidence of metabolic inflexibility is well documented in obese and diabetic subjects
63 suggesting an association with insulin resistance ⁵. Hypothesising a common pathway,
64 women with PCOS might have a disposition for both insulin resistance and metabolic
65 inflexibility. We conducted a systematic review of the literature to evaluate the available
66 evidence on metabolic inflexibility in women with PCOS.

67

68 **Methods:**

69 We undertook a systematic review using a prospectively registered protocol
70 (CRD42018116809) and reported in line with the PRISMA guidelines ⁷.

71

72 *Literature search*

73 We searched major electronic databases (MEDLINE, EMBASE and Cochrane central) for
74 all primary studies evaluating metabolic inflexibility in women with PCOS from inception
75 until October 2018. We combined the following Mesh search terms using the Boolean
76 operators AND/OR to screen for relevant articles (polycystic ovary, polycystic ovaries,
77 PCO, polycystic ovarian syndrome, ovary, inflexibility, flexibility, metabolic, metabolism,
78 lipids, carbohydrate, clamp, oxidation) (Appendix 1). We did not employ any search
79 filters or language restrictions. We manually searched the bibliographies of relevant
80 articles to identify studies not captured by our electronic search. We contacted the authors
81 of relevant studies to obtain any missing additional data.

82

83 *Study selection and inclusion*

84 Two independent reviews (MR and BW) completed the study selection and inclusion
85 process in two stages, any discrepancies were resolved in consensus with a third reviewer
86 (ST). First, we screened titles and abstracts to identify potentially relevant articles; then
87 we reviewed full copies of relevant articles against our inclusion criteria. We included all
88 primary studies of any design reporting on the metabolic inflexibility (or flexibility)
89 between women with and without PCOS using respiratory exchange ratio or respiratory
90 quotient (RQ) as surrogate markers to evaluate metabolic inflexibility. We excluded
91 studies on animals, case reports, case series, and studies with no appropriately matched
92 comparison groups.

93

94 *Quality assessment of the included studies*

95 We used the Newcastle-Ottawa Scale (NOS) ⁸ to assess the quality of the included studies
96 in duplicate by two reviewers (MR) and (BW). Studies were awarded a maximum of four
97 stars for selection, two for comparability and three for assessment of outcomes. Those

98 which scored four stars for selection, two stars of comparability and three stars for
99 assessment of outcomes were considered to be of high quality. Scores of one star or less
100 for selection, comparability or outcome assessment were considered to be of low quality.
101 Any other score combinations were considered of medium quality.

102

103 *Data extraction and analysis*

104 Two reviewers (MR and BW) extracted data in duplicate using a piloted electronic data
105 extraction tool on the study design, number of included participants, inclusion and
106 exclusion criteria of each study, protocols of the used euglycemic clamp and calorimetry
107 studies, journal of publication and year of publication. We extracted data on the reported
108 outcomes including insulin sensitivity, substrate oxidation (carbohydrate and protein),
109 levels of testosterone, free testosterone, sex hormone binding globulin, free androgen
110 index, luteinizing hormone, body mass index, fat mass, and free fat mass. We reported the
111 findings narratively using natural frequencies and percentages. All analyses were
112 conducted in Microsoft Excel 2013 (Microsoft Inc, Washington 2013).

113

114 **Results**

115 *Characteristics of included studies*

116 Our electronic search revealed 17 potentially relevant citations, we removed three
117 duplicates and assessed 14 articles in full against our inclusion criteria. We included five
118 prospective cohort studies reporting on 461 women (Figure 1). Two were carried out in
119 the United States of America, two in Poland and one in Italy. All were published in
120 specialist journals on endocrinology, nutrition, or metabolism.

121

122 All studies were relatively small with a median sample size of 98 (range 42-122). Three
123 compared women with PCOS to unaffected women with normal weight, one to
124 overweight or obese women and women with T2DM, and one study compared adolescent
125 girls with PCOS to unaffected subjects (Table 1). All included women were diagnosed
126 with PCOS based on the National Institute of Health or Rotterdam criteria ⁹. All studies
127 evaluated metabolic inflexibility by calculating the difference between the mean RQ in the
128 fasting state and the mean RQ in the insulin rich state. Metabolic inflexibility was
129 diagnosed in the group with a significantly lower mean difference (Δ RQ). All studies
130 employed a calometric breath analysis to evaluate lipid oxidation and used euglycemic
131 clamp studies to evaluate carbohydrate oxidation between fasting and insulin rich status
132 (Table 1).

133

134 *Quality of included studies*

135 Overall, the quality of included studies was medium; three studies scored highly for the
136 selection process, and two were of low quality. The majority of studies (80%, 4/5) had a
137 medium quality for comparability, primarily due to small sample size with a limited
138 variation in the comparison cohorts in view of the varied phenotype of PCOS in the
139 general population. Most studies (60%, 3/5) had an adequate assessment of outcomes and
140 follow up process. (Figure 2) (Appendix 2).

141

142 *Metabolic flexibility*

143 Three of the included studies showed evidence of metabolic inflexibility in women with
144 PCOS compared to healthy, overweight or obese unaffected women ^{10,11} (Table 2), or to
145 healthy adolescents (Δ RQ 0.05 ± 0.01 vs 0.095 ± 0.009 , $p=0.004$) ¹². Hyperandrogenemic
146 women with PCOS had worse metabolic inflexibility compared to those with normal

147 androgen profile (Δ RQ 0.091 ± 0.060 vs 0.120 ± 0.010 , $p=0.014$)¹¹. Women with PCOS
148 demonstrated similar metabolic inflexibility to unaffected women with T2DM (Δ RQ
149 0.05 ± 0.03 vs. 0.06 ± 0.04 , $p=0.98$)¹⁰.

150

151 In contrast, two studies from the same research group suggested no difference in
152 metabolic flexibility between women with PCOS and healthy adults^{13,14}. Both studies had
153 a high risk of bias for cohort selection (Appendix 2). Due to variations in the included
154 controls and selective outcomes reporting, a quantitative pooling of data was not possible
155 (Table 2).

156

157 *Metabolic and endocrine outcomes*

158 All included studies reported higher insulin resistance in women with PCOS compared to
159 unaffected subjects¹⁰⁻¹², with similar levels compared to unaffected obese women and
160 those with T2DM^{10,13,14}.

161

162 Fasting glucose levels were higher in women with PCOS^{10,11}, but this was not consistent
163 across all included cohorts^{12,14}. There was mixed evidence on the efficiency of glucose
164 and lipid oxidation in women with PCOS with some studies reporting significantly higher
165 glucose oxidation before the CLAMP study and reduced lipid oxidation before and during
166 the CLAMP study¹². A clear conclusion could not be reached, due to variations in
167 reporting across studies.

168

169 Three studies reported lower levels of sex hormone binding globulin in women with
170 PCOS compared to matched controls¹⁰⁻¹². This was associated with an increase in both

171 total ^{11,12} and free testosterone ¹⁰⁻¹². Similarly, free androgen index was higher in women
172 with PCOS compared to unaffected lean and obese women ^{10,14} (Table 2).

173

174 **Discussion**

175 The findings of our review support an overall association between PCOS and metabolic
176 inflexibility, however, this was not consistent in all studies included. Inflexibility was
177 reported in both adult and adolescent women with PCOS suggesting an association
178 independent to age. It was more pronounced with high BMI, hyperandrogenemia, and
179 worsening insulin resistance, signifying an impaired metabolism with worsening features
180 of PCOS. Insulin resistance and blunted carbohydrates oxidation were common features in
181 all included women, thus a common pathway of inappropriate energy oxidation, metabolic
182 inflexibility and response to insulin in women with PCOS is apparent.

183

184 *Strengths and limitations*

185 To our knowledge, our review is the first to synthesis evidence on the prospect of
186 metabolic inflexibility in women with PCOS. We used a prospective protocol following a
187 standardised methodology and a comprehensive search strategy. We included all studies
188 reporting on elements of metabolic inflexibility and reported on all relevant outcomes
189 across included studies. We assessed the quality of in included studies and extracted data
190 in duplicate. The main limitation of this review was the small number of included studies
191 and the limited number of women included. PCOS has varied phenotypes and thus, the
192 population reported on in this review might not fully represent all women with PCOS.
193 There was variation in the reported outcomes with few studies reporting primary
194 quantitative endpoints in a standardised manner which limited our ability to pool data
195 quantitatively.

196

197 *Wider implications*

198 Women presenting with symptoms and signs of PCOS often suffer from delayed diagnosis
199 and fragmented care ¹⁵. The associated metabolic risk factors are seldom discussed or
200 evaluated at diagnosis, driven by a heterogeneous care provision for women with PCOS
201 across disciplines. Our findings help to define the metabolic risks associated with a
202 diagnosis of PCOS, aligned with the known increased insulin resistance, T2DM and
203 cardiovascular risk factors. The majority of included studies reported worsening metabolic
204 inflexibility with higher BMI, and hyperandrogenemia, thus, establishing those risk
205 factors at the time of diagnosis could facilitate a more targeted management plan and
206 better response to treatment.

207

208 The use of CLAMP studies is cumbersome, expensive and invasive; other measures of
209 insulin resistance lack accuracy as noted in the recent international evidence based
210 guideline on PCOS management ¹⁵. There is a need to establish more efficient surrogate
211 markers of metabolic inflexibility for use in everyday clinical practice. Kim et al ¹²
212 suggested a clinical model to evaluate metabolic inflexibility based on fasting insulin,
213 triglycerides, and adiponectin levels which explained 62% of the variance in metabolic
214 inflexibility in the study participants. Developing predictive models with standardised and
215 easy to record metabolic predictors could help to determine individual metabolic risk
216 factors in women newly diagnosed with PCOS ¹⁶. Other methods could also be employed
217 to further evaluate the metabolic inflexibility in women with PCOS such as the measuring
218 lactate and fat to carbohydrate oxidation in exercise settings ¹⁷. More studies are needed to
219 investigate the metabolic response to high-fat diets in women with PCOS as well as the

220 role of glucose disposal rate, adipose tissue lipid storage, and mitochondrial function on
221 metabolic inflexibility ⁵.

222

223 Weight loss, lifestyle and exercise interventions were shown to improve the metabolic
224 inflexibility in individuals with obesity and T2DM ⁴. Losing 10% of body weight with
225 lifestyle interventions ¹⁸ or 30% with bariatric surgery also improved the metabolic
226 performance and the associated insulin resistance in obese patients ¹⁹. There is a need to
227 evaluate such interventions in women with PCOS to establish their feasibility and
228 effectiveness in alleviating the established risk factors associated with this condition. To
229 date, evidence on the benefit of lifestyle interventions in PCOS is varied and limited to a
230 specific range of outcomes ²⁰. Adjusting lifestyle interventions to the individualised
231 metabolic characteristics of women with PCOS could increase their effectiveness and
232 improve compliance. Combining lifestyle interventions with insulin sensitising drugs such
233 as metformin or myoinositol could help to reduce the associated insulin resistance,
234 promote weight loss and stabilise the metabolic status in women with PCOS ^{21,22}.

235

236 Our study summaries current evidence on metabolic inflexibility in women with PCOS.
237 However, larger cohorts with better adjustment for confounding factors (age, ethnicity,
238 BMI, baseline diet, and phenotype), more standardised reporting of relevant outcomes are
239 needed ²³.

240

241 **Conclusion**

242 Women with polycystic ovary syndrome appear to have higher metabolic inflexibility
243 compared to unaffected women associated with hyperandrogenemia and insulin resistance.
244 More research is needed to investigate this metabolic feature among all PCOS phenotypes.

245 **Disclosure of interest:** The authors report no conflict of interest

246 **Acknowledgement:** None

247 **Funding:** BHA is funded through an NIHR lectureship.

248

249

250

251 **References**

- 252 1. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and
253 phenotypic features of polycystic ovary syndrome: a systematic review and meta-
254 analysis. *Hum Reprod.* 2016;31(12):2841-2855.
- 255 2. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin
256 resistance in polycystic ovary syndrome: a systematic review and meta-analysis of
257 euglycaemic–hyperinsulinaemic clamp studies. *Hum Reprod.* 2016;31(11):2619-
258 2631.
- 259 3. Boomsma CM, Eijkemans MJC, Hughes EG, Visser GHA, Fauser B, Macklon NS.
260 A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome.
261 *Hum Reprod Update.* 2006;12(6):673-683.
- 262 4. Corpeleijn E, Saris WHM, Blaak EE. Metabolic flexibility in the development of
263 insulin resistance and type 2 diabetes: effects of lifestyle. *Obes Rev.*
264 2009;10(2):178-193.
- 265 5. Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. *Am J*
266 *Physiol Metab.* 2008;295(5):E1009-E1017.
- 267 6. Thyfault JP, Rector RS, Noland RC. Metabolic inflexibility in skeletal muscle: a
268 prelude to the cardiometabolic syndrome? *J Cardiometab Syndr.* 2006;1(3):184-
269 189.
- 270 7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for
271 systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.*
272 2009;151(4):264-269.
- 273 8. Wells G, Shea B, O'Connell D, et al. Newcastle-Ottawa quality assessment scale
274 cohort studies. 2015-11-19] [http://www.ohri](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
275 [ca/programs/clinical_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). 2014.

- 276 9. Carmina E, Azziz R. Diagnosis, phenotype, and prevalence of polycystic ovary
277 syndrome. *Fertil Steril*. 2006;86:S7-S8.
- 278 10. Broskey NT, Tam CS, Sutton EF, et al. Metabolic inflexibility in women with
279 PCOS is similar to women with type 2 diabetes. *Nutr Metab (Lond)*. 2018;15(1):75.
- 280 11. Di Sarra D, Tosi F, Bonin C, et al. Metabolic inflexibility is a feature of women
281 with polycystic ovary syndrome and is associated with both insulin resistance and
282 hyperandrogenism. *J Clin Endocrinol Metab*. 2013;98(6):2581-2588.
- 283 12. Kim JY, Tfayli H, Michaliszyn SF, Arslanian S. Impaired Lipolysis, Diminished
284 Fat Oxidation, and Metabolic Inflexibility in Obese Girls With Polycystic Ovary
285 Syndrome. *J Clin Endocrinol Metab*. 2017;103(2):546-554.
- 286 13. Straczkowski M, Kowalska I, Adamska A, et al. Normal metabolic flexibility
287 despite insulin resistance in lean and obese women with polycystic ovary
288 syndrome. In: *11th European Congress of Endocrinology*. Vol 20. BioScientifica;
289 2009.
- 290 14. Adamska A, Karczewska-Kupczewska M, Nikolajuk A, et al. Normal metabolic
291 flexibility despite insulin resistance women with polycystic ovary syndrome.
292 *Endocr J*. 2013;60(9):1107-1113.
- 293 15. Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic
294 ovary syndrome: summary of an evidence-based guideline. *Med J Aust*.
295 2011;195(6):65.
- 296 16. Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary
297 syndrome and risk for myocardial infarction: evaluated from a risk factor model
298 based on a prospective population study of women. *Acta Obstet Gynecol Scand*.
299 1992;71(8):599-604.
- 300 17. San-Millán I, Brooks GA. Assessment of metabolic flexibility by means of

- 301 measuring blood lactate, fat, and carbohydrate oxidation responses to exercise in
302 professional endurance athletes and less-fit individuals. *Sport Med.* 2018;48(2):467-
303 479.
- 304 18. Kelley DE, Goodpaster B, Wing RR, Simoneau J-A. Skeletal muscle fatty acid
305 metabolism in association with insulin resistance, obesity, and weight loss. *Am J*
306 *Physiol Metab.* 1999;277(6):E1130-E1141.
- 307 19. Friedman JE, Dohm GL, Leggett-Frazier N, et al. Restoration of insulin
308 responsiveness in skeletal muscle of morbidly obese patients after weight loss.
309 Effect on muscle glucose transport and glucose transporter GLUT4. *J Clin Invest.*
310 1992;89(2):701-705.
- 311 20. Domecq JP, Prutsky G, Mullan RJ, et al. Lifestyle modification programs in
312 polycystic ovary syndrome: Systematic review and meta-Analysis. *J Clin*
313 *Endocrinol Metab.* 2013;98(12):4655-4663.
- 314 21. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ.
315 Metformin and lifestyle modification in polycystic ovary syndrome: systematic
316 review and meta-analysis. *Hum Reprod Update.* 2015;21(5):560-574.
- 317 22. Pundir J, Psaroudakis D, Savnur P, et al. Inositol treatment of anovulation in
318 women with polycystic ovary syndrome: a meta-analysis of randomised trials.
319 *BJOG An Int J Obstet Gynaecol.* 2018;125(3):299-308.
- 320 23. Khan K. The CROWN Initiative: journal editors invite researchers to develop core
321 outcomes in women's health. *BJOG.* 2016;123 Suppl:103-104. doi:10.1111/1471-
322 0528.14363
- 323
- 324