Human Reproduction, Vol.36, No.3, pp. 523–528, 2021
Advance Access Publication on December 17, 2020 doi:10.1093/humrep/deaa331

human reproduction

OPINION

Harmonizing research outcomes for polycystic ovary syndrome (HARP), a marathon not a sprint: current challenges and future research need

Bassel H. Al Wattar[1,2,*], Aurora Bueno[3,4,5], Miguel Garcia Martin[3,4,5], Naomi Cano Ibáñez[3,4,5], Klejda Harasani[6], Rhonda Garad[7,8], Steve Franks[9], Adam Balen[10], Priya Bhide[11,12], Terhi Piltonen[13], Daniela Romualdi[14,15], Joop Laven[16], Ngawai Moss[12], Caroline Andrews[17], Rachel Hawkes[17], Ben W. Mol[18,19] Helena Teede[7,8], Shakila Thangaratinam[20], and Khalid Saeed Khan[3]

[1]Warwick Medical School, University of Warwick, Coventry, UK [2]Reproductive Medicine Unit, Institute for Women's Health, University College London Hospitals, London, UK [3]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain [4]Consortium for Biomedical Research in Epidemiology & Public Health (CIBER Epidemiología y Salud Pública-CIBERESP), Madrid, Spain [5]Inst Invest Biosanitaria Ibs GRANADA, Granada, Spain [6]Department of Pharmacy, University of Medicine of Tirana, Tirana, Albania [7]National Health and Medical Research Council Centre for Research Excellence in PCOS, Monash Centre for Health Research and Implementation, Monash University Melbourne, Melbourne, VIC, Australia [8]Monash Centre for Health Research and Implementation, School Public Health, Monash University, Clayton, VIC, Australia [9]Imperial College School of Medicine, Institute of Reproductive and Developmental Biology, Hammersmith Hospital, London, UK [10]Leeds Fertility, Seacroft Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK [11]Homerton University Hospital NHS Foundation Trust, London, UK [12]Barts Research Centre for Women's Health (BARC), Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK [13]Department of Obstetrics and Gynecology, PEDEGO Research Unit, Medical Research Centre, Oulu University Hospital, University of Oulu, Oulu, Finland [14]Department of Women's and Children's Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy [15]Department of Woman and Child Health, Azienda Ospedaliera Card.Panico, Tricase, Italy [16]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Erasmus University Medical Centre, Rotterdam, The Netherlands [17]Verity—The PCOS Self Help Group, Surry, UK [18]Department of Obstetrics and Gynaecology, University of Monash, Melbourne, Australia [19]Aberdeen Centre for Women's Health Research, University of Aberdeen, Aberdeen, UK [20]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

*Correspondence address. Warwick Medical School, University of Warwick, Coventry, UK. E-mail: dr.basselwa@gmail.com

Submitted on July 15, 2020; resubmitted on September 14, 2020; editorial decision on November 2, 2020

ABSTRACT: Investing in clinical research and evidence-based medicine has helped to improve the care for women with polycystic ovary syndrome (PCOS). However, several important questions remain unanswered on the optimal prevention and management strategies for PCOS. Addressing this uncertainty is often hindered by suboptimal research conduct leading to inefficient evidence synthesis and research wastage. PCOS research is often practised by varied specialized teams in silo leading to disharmonious and fragmented efforts neglecting the lifelong impact of PCOS on women's wellbeing. Poor engagement among key stakeholders and lay consumers continues to limit the impact and benefits of research to society. Selective reporting on surrogate outcomes with a 'significant' *P*-value is a common malpractice in PCOS outputs. Effective adoption of the harmonizing research outcomes for PCOS (HARP) core outcome set is needed to minimize heterogeneity in reporting and promote research excellence. Small single-centre studies offer limited value to assess the varied PCOS phenotypes. Efficient large scale data-sharing is needed to address complex research questions and glean the benefits of big data research. We propose a roadmap to address these challenges and remedy future research need by promoting patient and public involvement in PCOS research to guide research efforts and address real patients' needs; engaging all key stakeholder groups to promote a multi-disciplinary lifelong approach to new research; continuously refining research needs and priorities to revise the knowledge gap and allocate resources judiciously; standardizing outcomes definitions and measurement tools to harmonize reporting and promote excellence in research; and by investing in large data-sharing infrastructure to facilitate big data research and govern ethical data sharing.

Key words: polycystic ovary syndrome / stakeholder / core outcomes / reporting / big data / public involvement

Introduction

Caring for women with polycystic ovary syndrome (PCOS) has progressed over the last few decades thanks to an increasing, still shy, investment in clinical research and evidence-based medicine (Azziz et al., 2019). What was a vaguely reported syndrome by Stein and Leventhal in 1935 has transformed today into a common endocrine condition attracting the attention of women, health professionals and researchers worldwide (Azziz and Adashi, 2016). While certain aspects of the PCOS pathophysiology remain unknown (Dumesic et al., 2015), investing in research helped to substantially improve the care for women with PCOS (Teede et al., 2018). Examples include the ESHRE/American Society for Reproductive Medicine standardized PCOS diagnostic criteria, which not only helped to improve clinical care but also enabled a more homogeneous amalgamation of research findings (Fauser et al., 2012). Public investment in large randomized trials and their meta-analyses helped to regulate the use of insulin sensitizers and ovulation stimulation agents to reduce the risk of adverse outcomes in women affected by PCOS (Wang et al., 2017; Sharpe et al., 2019). Epidemiological studies helped to crystallize the risk of endometrial cancer in this group and prompted the introduction of preventative treatments into routine care (Lauretta et al., 2016; MacKintosh and Crosbie, 2018). However, aspiring beyond the status quo, a major paradigm shift is needed to improve research quality and bridge the current knowledge gaps.

Several interventions helped the scientific community to improve the quality of research over the last 20 years such as prospective trial registration (DeAngelis et al., 2005), standardized reporting checklists (Begg et al., 1996) and mandatory disclosure of conflict of interest (Blum et al., 2009). Still, increasing research efficiency remains a major challenge yielding a recurrent wastage in health research outputs. A problem estimated to consume as much as 85% of the global research in biomedical and applied clinical sciences yearly budget (Macleod et al., 2014). Clearly, PCOS research is not immune to this issue.

The recent international guideline on the diagnosis and management of PCOS included 40 systematic and 20 narrative reviews to address 60 prioritized clinical questions (Teede et al., 2018). It generated 31 evidence-based recommendations where sufficient evidence was available to inform the guideline development group and 57 clinical consensus recommendations where, in the absence of sufficient evidence, a consensus was needed; highlighting the need for more evidence synthesis to inform practice.

To address this expressed need, as we start a new decade of research, we highlight some of the key challenges and suggest a roadmap to increase efficiency, reduce wastage and increase the impact of PCOS research on women's health.

Current challenges

Poor engagement of key stakeholders

PCOS is unique in its multi-systemic effects and varied clinical presentation. As such, affected women were often cared for by health professionals within different specialized teams. Yet, for many years this segregated approach not only led to disharmonious and fragmented care but also produced isolated research efforts neglecting the lifelong impact of PCOS on women's wellbeing (Tay et al., 2018). To date, more than 14 evidence-based guidelines and consensus statements have been published on the diagnosis and management of PCOS, but only two of those guidelines adopted a lifelong view to PCOS in consultation with patient representatives (Teede et al., 2011, 2018). Such a segregated approach further hinders the translation and implementation of evidence into practice, leading to a persistent knowledge gap (Dokras et al., 2017) and poor patient experience (Gibson-Helm et al., 2017). Until recently, the dialogue between lay consumers and their caring professionals was largely absent from the research cycle, often pushing PCOS researchers astray from real patients' needs (Teede et al., 2014). For example, engaging patient representatives and lay consumers in our recently published core outcome set (Al Wattar et al., 2020) emphasized the importance of reporting on the psychological impact of PCOS on women's mental health, outcomes that were traditionally poorly reported in most published trials.

Going forward, the practice of silo research should be avoided. This can be achieved by investing in setting up joint research efforts within multidisciplinary teams to continuously refine research priorities (Legro et al., 2006), engage all key stakeholder groups including lay consumers (Al Wattar et al., 2020) and promote a lifelong approach in PCOS research (Weiss and Bulmer, 2011).

P-hacking, heterogeneity and varied outcomes reporting

Selective reporting on surrogate outcomes with a 'significant' *P*-value is a common malpractice in health research permeating to the pages of leading medical journals (Chuard et al., 2019). This is particularly prevalent in PCOS outputs mostly in small single-centre studies reporting on outcomes of limited significance (Teede et al., 2018). Several research initiatives and journals are now promoting the practice of transparent and meaningful reporting on key outcomes of importance in clinical studies (Williamson et al., 2011; Khan and O'Donovan, 2014). While this could help to improve the quality of evidence synthesis, systematic reviewing and meta-analyses, effective implementation in practice remains an important obstacle. For example, in a current systematic review (CRD42020186571), we identified 59 randomized clinical trials that evaluated lifestyle interventions (dietary, physical, behavioural, pharmacological and their combinations) in women with PCOS. Yet only 12 of these trials reported on both BMI and weight changes, 16 reported exclusively on BMI, 10 exclusively reported on weight and 18 (1084 women) reported on neither. Such selective reporting is yielding a net data loss towards evidence synthesis and increasing wastage (Fig. 1).

The harmonizing research outcomes for PCOS (HARP) core outcome set was published as an international effort to address this issue, promoting higher research homogeneity (Al Wattar et al., 2020). While a positive step, its adoption and impact in practice are yet to be determined. Searching clinicaltrials.gov, we identified 29 ongoing trials registered since the HARP core set was published: we call upon their investigators to adopt this core outcome set when reporting their findings (Fig. 2). We do acknowledge that some trials might not be able to collect all of the core outcomes. However, the HARP set should provide a strong incentive to argue for adequate funding to adopt a standardized reporting of those core outcomes. Of course, other outcomes outside the core set should also be further explored and

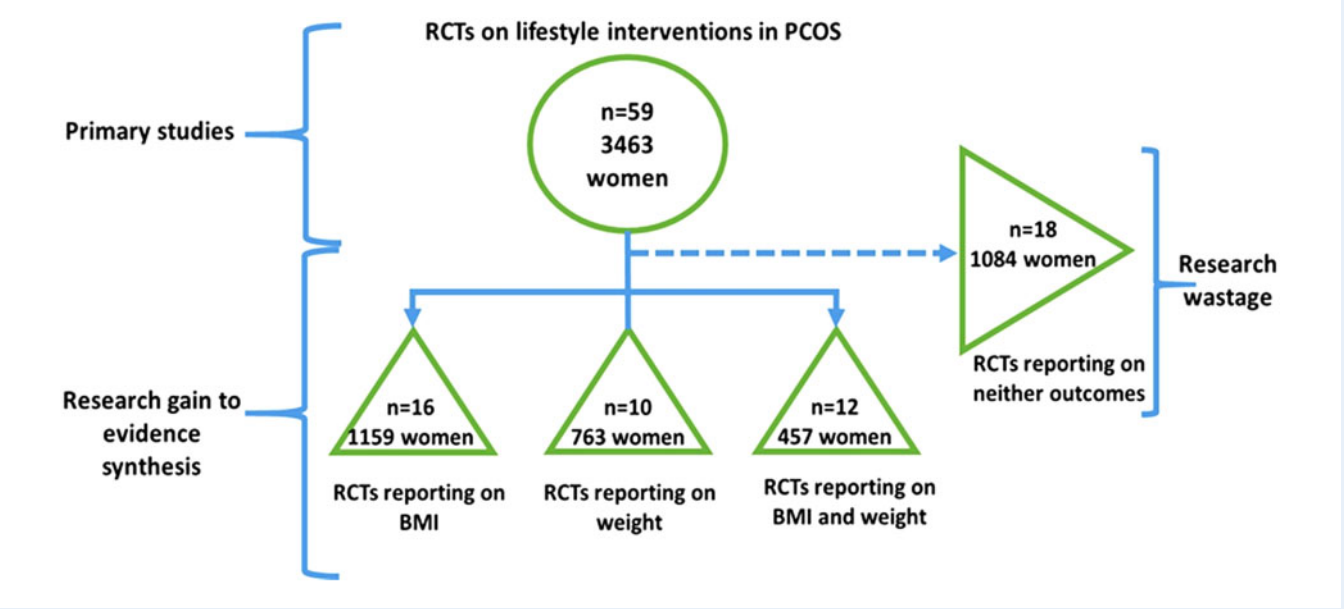

Figure 1. Research wastage for the outcomes of BMI and weight in randomized controlled trials on lifestyle interventions in women with polycystic ovary syndrome. RCT, randomized controlled trial; PCOS, polycystic ovary syndrome.

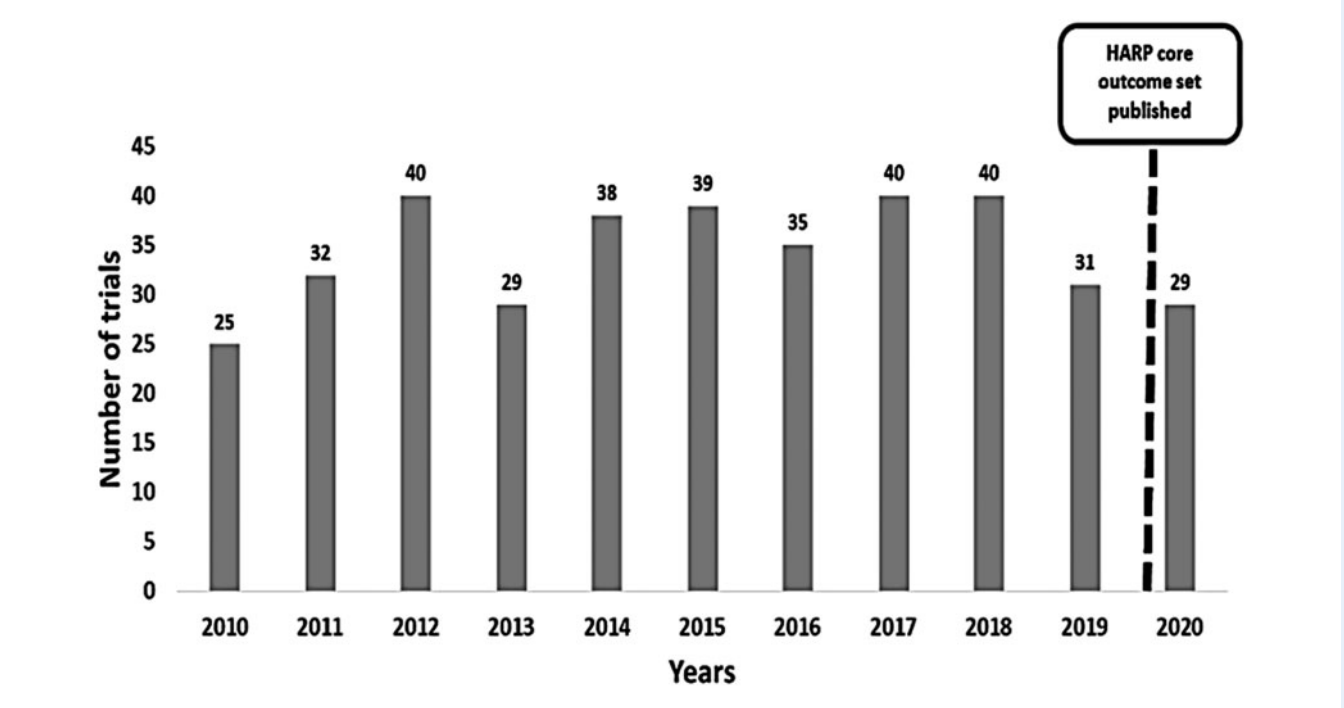

Figure 2. Number of yearly registered trials on polycystic ovary syndrome on clinicaltrials.gov. HARP, harmonizing research outcomes for polycystic ovary syndrome.

sample size (power) calculations should not be based on a core outcome exclusively. Finally, we acknowledge that standardized definitions and measurement tools for some of those core outcomes are lacking. More consensus work is needed among stakeholders to address this research need.

Limited scope for data sharing and joint research efforts

As we enter into the third age of computing innovation (Miailhe and Hodes, 2017), a remarkable shift towards digitalized healthcare and healthinformatics is taking place worldwide (Herland *et al.*, 2014). Harvesting this emerging computing power to enable large scale 'big data' health research is all but inevitable (Yang et al., 2017). Yet, this practice remains scarce in PCOS research. The benefits of investing in a platform to enable big data research are numerous and specific to PCOS. Put simply, current means are unable to address several key questions such as the differential effect of different treatments across the PCOS phenotypes and the epigenetic expression of PCOS manifestation across generations and families (Legro *et al.*, 2006). Furthermore, as treatment algorithms get more complex with many competing treatment options and higher patient expectations for increased safety, it would be naïve to expect randomized controlled trials (RCTs) to address such large questions efficiently. For example, direct evaluation of the effectiveness and safety of all available ovulation stimulation agents to reduce the risk of ovarian hyperstimulation syndrome in women with PCOS would require a six arms multicentre RCT, not counting treatments' combinations with huge sample size, a near-impossible task at least in the near future. Capturing long-term safety outcomes (e.g. stroke and thrombotic events) is particularly difficult in RCTs but could be recorded efficiently using digitalized health records. Therefore, serious investment in collaborative efforts to enable large scale cohort studies (Azziz *et al.*, 2019) and quality big data research is a priority to address those impenetrable, yet important, questions.

Research need

A proposed roadmap to address the above challenges and remedy future research need could include the approaches outlined below.

Promote patient and public involvement in future research

A key priority is to establish a true partnership between the academic and lay community to deliver impactful research that directly addresses patients' health needs. This entails involving lay consumers in the evidence synthesis and translation ecosystem. Women's needs and preferences should advise future research design, resources allocation and evidence dissemination strategies via multi-faceted, multi-modal communication channels. Therefore, there is a need to invest in training both health researchers and lay partners on patient and public involvement (PPI) methodology (Dudley *et al.*, 2015). While several generic resources exist (Bagley *et al.*, 2016), a PCOS specific PPI toolkit is needed.

Adopt a multidisciplinary lifelong approach to new research

All new treatments and preventions for PCOS will have implications on the wellbeing of affected women encompassing their endocrine, reproductive, and mental health. Therefore, new trials should engage representatives from all stakeholder groups to plan and report their findings keeping in mind the lifelong impact of PCOS on women's wellbeing. International professional societies and women health regulators should invest in disseminating new research across their membership to boost collaboration across disciplines and facilitate the participation of all relevant stakeholders beyond geographical boundaries. Establishing such an international cross-disciplines collaboration platform could boost the participation of traditionally absent stakeholders in PCOS research.

Continuously refine research needs and priorities

With ever finite research resources, there is a need to continuously refine the current research need, assess the knowledge gap, guide future research efforts and reallocate resources judiciously. As the findings of existing initiatives are likely to become obsolete (Legro *et al.*, 2006), investing in an efficient platform to produce regular updates is needed. This is particularly relevant to translational research where experimental treatments could be evaluated and introduced into practice, safely bridging the gap between experimental and applied clinical research.

Standardize outcome definitions and measurement tools

To date, the definitions of several key clinical outcomes remain elusive such as insulin resistance and eating disorders. Similarly, key outcomes, such as depression and anxiety, are commonly measured and reported using several measurement tools, which hinders evidence synthesis. Consensus work is needed among all stakeholders (academic, clinical, industry and lay groups) to harmonize these elements and promote excellence in outcomes reporting.

Invest in data sharing infrastructure

Innovation is key to reap the benefits of big data research (Rothstein, 2015; Sharon, 2016). Investing in a common platform is needed to facilitate and standardize data collection and harmonization. Initial consensus steps could include standardized recommendations for enhanced routine data collection, unified data time points and a shared data dictionary for PCOS core outcomes' definitions and characteristics. This should be complemented with guidance on joint international efforts to govern ethical reporting, safeguard co-investigators and empower lay consumers.

Conclusion

Collaborative efforts are needed to improve the quality of PCOS research conduct and increase its impact. The HARP initiative aims to address the identified challenges and deliver the proposed solutions to

harmonize outcomes' reporting, increase research transparency and promote excellence in PCOS research.

Data availability

No new data were generated or analysed in support of this research.

Authors' roles

B.H.A.W. drafted the first manuscript and conducted supportive literature searches. All remaining co-authors provided critical contribution to refine the content and edit the final manuscript.

Funding

No direct funding was received in support of this work. B.H.A.W. holds a personal Lecturership from the UK National Health Institute of Research. K.S.K. is Distinguished Investigator at University of Granada funded by the Beatriz Galindo (senior modality) program of the Spanish Ministry of Education. H.T. is funded through an NHMRC fellowship.

Conflict of interest

None.

References

Al Wattar BH, Teede H, Garad R, Franks S, Balen A, Bhide P, Piltonen T, Romualdi D, Laven J, Thondan M *et al*. Harmonising research outcomes for polycystic ovary syndrome: an international multi-stakeholder core outcome set. *Hum Reprod* 2020;**35**:404–412.

Azziz R, Adashi EY. Stein and Leventhal: 80 years on. *Am J Obstet Gynecol* 2016;**214**:247–2e1.

Azziz R, Kintziger K, Li R, Laven J, Morin-Papunen L, Merkin SS, Teede H, Yildiz BO. Recommendations for epidemiologic and phenotypic research in polycystic ovary syndrome: an androgen excess and PCOS society resource. *Hum Reprod* 2019;**34**:2254–2265.

Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, Young B, Williamson PR. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials–a work in progress. *Res Involv Engagem* 2016;**2**:15.

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;**276**:637–639.

Blum JA, Freeman K, Dart RC, Cooper RJ. Requirements and definitions in conflict of interest policies of medical journals. *JAMA* 2009;**302**:2230–2234.

Chuard PJC, Vrtílek M, Head ML, Jennions MD. Evidence that nonsignificant results are sometimes preferred: reverse P-hacking or selective reporting? *PLoS Biol* 2019;**17**:e3000127.

DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJPM *et al*. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Arch Dermatol* 2005;**141**:76–77.

Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. *Fertil Steril* 2017;**107**:1380–1386.e1.

Dudley L, Gamble C, Allam A, Bell P, Buck D, Goodare H, Hanley B, Preston J, Walker A, Williamson P *et al*. A little more conversation please? Qualitative study of researchers' and patients' interview accounts of training for patient and public involvement in clinical trials. *Trials* 2015;**16**:190.

Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. *Endocr Rev* 2015;**36**:487–525.

Fauser BCJM, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JSE *et al*. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 2012;**97**:28–38.

Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2017;**102**:604–612.

Herland M, Khoshgoftaar TM, Wald R. A review of data mining using big data in health informatics. *J Big Data* 2014;**1**:2–35.

Khan K, O'Donovan P. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *BMC Pregnancy Childbirth* 2014;**14**:199.

Lauretta R, Lanzolla G, Vici P, Mariani L, Moretti C, Appetecchia M. Insulin-sensitizers, polycystic ovary syndrome and gynaecological cancer risk. *Int J Endocrinol* 2016;**2016**:8671762.

Legro RS, Azziz R, Giudice L. A twenty-first century research agenda for polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab* 2006;**20**:331–336.

MacKintosh ML, Crosbie EJ. Prevention strategies in endometrial carcinoma. *Curr Oncol Rep* 2018;**20**:101.

Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JPA, Salman RA-S, Chan A-W, Glasziou P. Biomedical research: increasing value, reducing waste. *Lancet* 2014;**383**:101–104.

Miailhe N, Hodes C. The third age of artificial intelligence. *F Actions Sci Reports J F Actions* 2017;(Special Issue 17):6–11.

Rothstein MA. Ethical issues in big data health research: currents in contemporary bioethics. *J Law Med Ethics* 2015;**43**:425–429.

Sharon T. The Googlization of health research: from disruptive innovation to disruptive ethics. *Per Med* 2016;**13**:563–574.

Sharpe A, Morley LC, Tang T, Norman RJ, Balen AH. Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2019;**12**:CD013505. doi:10.1002/14651858.CD013505.

Tay CT, Moran LJ, Wijeyaratne CN, Redman LM, Norman RJ, Teede HJ, Joham AE. Integrated model of care for polycystic ovary syndrome. *Semin Reprod Med* 2018;**36**:086–094.

Teede H, Gibson-Helm M, Norman RJ, Boyle J. Polycystic ovary syndrome: perceptions and attitudes of women and primary health

care physicians on features of PCOS and renaming the syndrome. *J Clin Endocrinol Metab* 2014;**99**:E107–E111.

Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ, Andersen M, Azziz R *et al.*; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod* 2018;**33**:1602–1618.

Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BGA, Wong JLA, Norman RJ, Costello MF. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 2011;**195**:65.

Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, Ng EHY, Legro RS, Bhattacharya S, Norman RJ *et al.* Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. *BMJ* 2017; **356**:j138.

Weiss TR, Bulmer SM. Young women's experiences living with polycystic ovary syndrome. *J Obstet Gynecol Neonatal Nurs* 2011;**40**: 709–718.

Williamson PR, Altman DG, Blazeby JM, Clarke M, Gargon E. The COMET (core outcome measures in effectiveness trials) initiative. *Trials* 2011;**12**:A70.

Yang C, Huang Q, Li Z, Liu K, Hu F. Big Data and cloud computing: innovation opportunities and challenges. *Int J Digit Earth* 2017;**10**: 13–53.