New PCOS guidelines: What's relevant to general practice

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Conflict of interest

I declare that in the past three years I have:

- Received royalties from: **None**
- Performed consulting work for: **Merck Sharp and Dome and Gedeon Richter**
- Given presentations for: **Ferring pharmaceuticals**
- Held shares in: **Virtus Health**
- Received institutional support from: **None**
- Clinical Director of **Melbourne IVF** East Melbourne.

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Presentation outline on PCOS

- Background
- International guidelines - new publication
- Diagnosis & assessment
- Management of excess weight
- Use of COCP
- Treatment of infertility
- Take home messages

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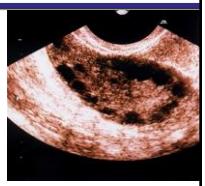
PCOS: background – what we already know

- Group of clinical features and hormone changes:
  - ovulatory dysfunction
  - Hyperandrogenemia
  - polycystic ovaries
- Most common endocrine disease in reproductive age women
- Prevalence 12-18%



(Rotterdam criteria) - Australia [1]

March et al Human Reprod 2010

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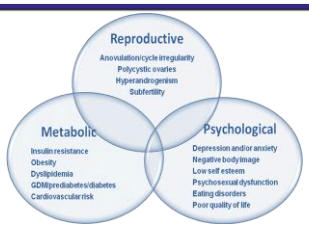
PCOS clinical features



Norman et al Lancet 2007, Teede et al BMC Medicine 2010, Teede et al MJA 2011

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International evidence based PCOS guidelines

- 1st ever internationally endorsed & evidence based guidelines
- Released July 2018
- Covers assessment, diagnosis & management of PCOS
- 5 Guideline Development Groups (GDG)
  1. Diagnosis & assessment
  2. Assessment & management of emotional wellbeing
  3. Lifestyle intervention
  4. Pharmacological treatment for non-fertility indications
  5. Assessment & management of infertility
- Followed GRADE process to rate the strength of recommendations depending upon the quality of the evidence

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Evidence-based guidelines

Developed by multi-national and multi-disciplinary team from Monash University in combination with US national institute of health NIH, NICE guidelines UK, ESHRE, ASRM

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Diagnosis of PCOS in adults:

The Rotterdam diagnostic criteria endorsed for PCOS and recommend that PCOS be diagnosed by:

- in adult women if two of the following three are present:
  - androgen excess,
  - ovulatory dysfunction, or
  - polycystic ovarian morphology are present
- disorders of exclusion are ruled out including:
  - thyroid disease (TSH screen)
  - hyperprolactinemia (serum Prl)
  - non-classic congenital adrenal hyperplasia by serum 17-OHP in all women
  - Premature ovarian failure

Rotterdam consensus, Fertility and Sterility 81;1:19-25.2004.

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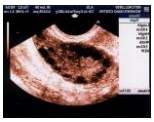
PCO – improved diagnosis with improved technology:



– Dewailly D. ***Diagnostic criteria for PCOS: Is it time for a rethink?*** Best Pract Res Clin Obstet Gynaecol. 2016 Nov;37:5-11.

- **Previous Ultrasound diagnosis:**
- 12 or more follicles 2-9 mm diameter
- +/- increased ovarian volume (>10ml)
- 1 or both ovaries

- **Proposed New Diagnosis:**
- An ***elevated follicle number per ovary (FNPO) of >20*** and/or an ovarian volume > 10 ml (using high quality ultrasound transducers)
- ensuring no corpora lutea, cysts or dominant follicles are present
- FNPO – studies vary from >19 to >28 follicles for improved diagnostic sensitivity

Lujan, M.E., et al., *Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume.* Hum Reprod, 2013. **28**(9): p. 1361-8.
Dewailly D, et al., Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2014; 20(3):334-52.

Diagnosis continued – **caution** in adolescents:

in adolescents (<20 years of age) or who are less than three years after the onset of menarche:

- only if **both** androgen excess (assessed clinically and where required biochemically) **and** ovulatory dysfunction (on menstrual history <21 or >35 day cycles and biochemically if cycles are regular and PCOS is suspected clinically) are present.
- Re-assessment recommended after 5 – 8 years

- **Ultrasound is not recommended for diagnosis in this age group**
  - Findings of multi-cystic ovaries are common in this age group with up to **70%** of the adolescent population meeting the ultrasound criteria for diagnosis!

– Kristensen, S., et al., *A very large proportion of young Danish women have polycystic ovaries: is a revision of the Rotterdam criteria needed?* Human Reproduction, 2010. **25**(12): p. 3117-3122.

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AMH – Anti-Mullerian hormone in the diagnosis of PCOS

- Serum AMH levels should not yet be used as an alternative for the detection PCOS.
- There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOS in the future.

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Assessment of Hyperandrogenism

- Clinical Hyperandrogenism
  - hirsutism
  - acne
  - male pattern hair loss
    - Be aware ethnic variation in vellus hair density
- Biochemical Hyperandrogenism
  - bioavailable testosterone,
  - calculated free testosterone
  - or free androgen index
  - consider androstenedione & DHEAS if total testosterone or free testosterone not elevated

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Management of excess weight in PCOS

- Lifestyle interventions
  - Diet
    - energy deficit of 30% is required
    - no specific energy equivalent diet is better than another
  - Exercise
    - moderate intensity: > 250 mins/week
    - vigorous intensity: > 150 mins/week
- Behavioural
  - includes goal setting, slower eating, self monitoring
- Metformin (+ lifestyle)
- Anti-obesity pharmacological agents (+ lifestyle)
- Bariatric surgery

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The top 25 items in Australian supermarkets

1. Coca-Cola 375mls
2. Coca-Cola 1 litre
3. Coca-Cola 2 litres
4. Diet coke 375mls
5. Cherry Ripe
6. Nestle's condensed milk
7. Tally Ho cig papers
8. Mars Bar
9. Kit Kat
10. Crunchie Bar
11. Eta 5 star margarine
12. Heinz Baked Beans
13. Golden Circle vege
14. Diet Coke 1 litre
15. Bushells tea
16. Cadbury Dairy Milk
17. Pepsi Cola 375mls
18. Coca-Cola 1.5 litre
19. Kellog's Corn Flakes
20. Maggi 2 min noodles
21. Generic lemon drink
22. Panadol tablets
23. MeadowLea margarine
24. Generic lemonade
25. Mrs McGregors margarine

Need for behavioural modification !

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Slide courtesy Dr A Clarke

Bariatric Surgery in PCOS:

No good evidence in pcos

Substantial evidence to support bariatric surgery on weight loss in women who are severely obese or with Type 2 Diabetes

Substantial efficacy of bariatric surgery on weight loss has been demonstrated in women who are severely obese

the balance between delaying infertility whilst undertaking bariatric surgery and attaining stable post-operative weight is unclear

What is the optimal type of bariatric surgery for PCOS patients??

In one study obese women who undergo bariatric surgery and subsequently conceived had more small for gestational age babies, shorter gestations, and a trend towards increased neonatal mortality compared to obese controls

- Johansson, K., et al., *Outcomes of pregnancy after bariatric surgery.* N Engl J Med, 2015. **372**(9): p. 814-24.

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Use of combined oral contraceptive pill in PCOS

- Use for clinical hyperandrogenism & irregular menstrual cycles
- Type
  - EE2&CPA OCP not 1st line due to thrombo-embolic risks
  - otherwise no specific COCP to be recommended over another
- Consider add metformin if
  - metabolic features i.e. IGT, T2DM
  - overweight/obese
- Consider add anti-androgens if
  - > 6 mths of COCP failed to adequately improve hirsutism
  - treatment of hair loss

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Prevalence, screening and treatment of emotional wellbeing:

- Health professionals and women should be aware of the adverse impact of PCOS on quality of life.
- Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents.
- A recent rigorous meta-analysis of ten studies showed increased moderate/severe anxiety symptoms in PCOS (OR: 5.38; 95% CI: 2.28, 12.67), with
- A prevalence of **41.9%** (IQR: 13.6, 52.0%) in PCOS compared to **8.5%** (IQR: 3.3, 12.0%) in controls.
- Psychological therapy and/or pharmacological treatment should be offered
- Caution is needed to avoid inappropriate treatment with antidepressants or anxiolytics particularly the use of agents that exacerbate PCOS symptoms such as weight gain.

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Aim to improve Screening, Diagnosis and Treatment of Emotional wellbeing in patients with PCOS:

- Increased:
  - Anxiety
  - Low self esteem
  - Depression
  - Poor body image
  - Eating disorder
  - Psycho-sexual dysfunction
- Management
  - Making diagnosis
  - Increase awareness
  - Consider pcosQOL tool
  - Counselling
  - Pharmacotherapy
  - Appropriate referal

Treatment of infertility in PCOS

- Lifestyle (diet, exercise) if obese
- Ovulation Induction
- Pharmacotherapy
  - Oral agents
    - Letrozole, clomiphene citrate, metformin,
    - combinations of the above
  - Gonadotropins
    - r-FSH, HMG
- Surgical
  - Laparoscopic ovarian surgery
- IVF

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Pre-pregnancy assessment in PCOS

- Offer oral glucose tolerance test
- Optimize the following factors to improve reproductive & obstetric outcomes
  - Weight
  - diet, exercise
  - blood glucose
  - smoking, alcohol
  - blood pressure
  - mental, emotional and sexual health

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Ovulation Induction in PCOS

- Exclude pregnancy prior to starting OI
- Infertile anovulatory women with no other infertility factors
- **Letrozole** is 1st line pharmacological therapy [1]
  - Risk of multiple pregnancy is less with letrozole compared with clomiphene citrate [2]
  - Consider monitoring to reduce risk of multiple pregnancy

1. *Wang, Costello et al BMJ 2017 PCOS Australian Guidelines 2015*
2. *2. Wang, Costello et al BMJ 2017*

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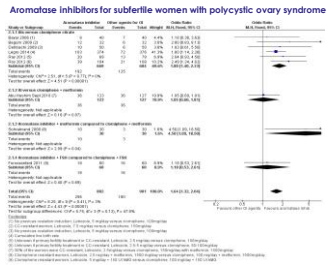

Letrozole Ovulation Induction in PCOS

- Start with spontaneous or progestogen induced period
- Dose/duration: 2.5-5.0-7.5 mg for 5 days
- Off label use – discuss with the patient

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Adjuvant metformin use

- Addition of metformin to FSH OI improves ovulation, pregnancy and live-birth rates[1]
- Addition of metformin to IVF treatment improves clinical pregnancy rate and lowers the risk of OHSS[2,3]

1. *Bordewijk, Costello et al Cochrane SRV 2017*
2. *2. Lo, Costello et al Cochrane SRV 2014*
3. *3. Lo, Costello et al Fert Steril 2015*

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Summary:

- 1st International evidence based guidelines on PCOS to be published in 2018
- Evidence based guidelines incorporate
  - best evidence from research +
  - clinical expertise +
  - patient values +
  - cost-effectiveness
- New published criteria for diagnosis of PCOS
- Ultrasound not recommended for diagnosis of PCOS in adolescents
- Letrozole first line recommendation for ovulation induction

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Take home messages in general practice

- Management of excess weight in PCOS may involve the interventions of
  1. Lifestyle (diet, exercise, behavioural)
  2. Metformin
  3. Anti-obesity pharmacological agents
  4. ? Bariatric surgery
- Use COCP for treatment of clinical hyperandrogenism & irregular menstrual cycles
  - No specific OCP is to be recommended over another – use lowest effective dose
- Don't forget Quality of life and emotional wellbeing
  - Screen all patients with pcos and consider treatment where required

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Take home messages in general practice

- Optomising health in pre pregnancy
- Ovulation induction indicated in infertile anovulatory PCOS women with no other infertility factors
- Letrozole is 1st line pharmacological therapy
- Addition of metformin to ovulation induction and IVF can improve success rates and outcomes

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Thank you

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