

PCOS guidelines: What's relevant to general practice

Dr Lyndon Hale
Medical Director, Melbourne IVF



Conflict of interest

- Virtus Health shares
- Past sponsorship by pharmaceutical companies to present at scientific meetings



Presentation outline on PCOS

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



PCOS: background

- Characterised by ovulatory dysfunction, hyperandrogenemia and polycystic ovaries
- Most common endocrinopathy in reproductive age women
- Prevalence
 - 12-18% (Rotterdam criteria) - Australia ¹

¹ March et al Human Reprod 2010



PCOS clinical features



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



International evidence based PCOS guidelines

- 1st ever internationally endorsed & evidence based
- Not yet published – aiming for August 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



Evidence-based guidelines



MelbourneIVF 

Management in adults

Diagnosis of PCOS in adults

- Endorsed Rotterdam 2003 criteria
- 2 out of the 3 following features
 1. Ovulatory dysfunction (< 21 or > 35 days)
 2. Hyperandrogenism (clinically or biochemically)
 3. PCOM
- + exclusion of thyroid disease (TSH), hyperprolactinemia (prolactin) & NCCAH (17OHP)

MelbourneIVF 

Diagnosis of Polycystic Ovarian Morphology

- Use transvaginal ultrasound
 - Follicle # per ovary > 18 &/or ovarian volume > 10ml if using new technology
 - Follicle # per ovary > 12 &/or ovarian volume > 10ml if using old technology
- Transabdominal ultrasound
 - Ovary volume > 10ml

MelbourneIVF 

Diagnosis of PCOS in adolescents

- Rotterdam 2003 criteria but
 - A. 2 years after onset of menarche
 - B. must have both
 - ovulatory dysfunction and;
 - androgen excess
 - C. Ultrasound not recommended

MelbourneIVF 

Assessment of Hyperandrogenism

- Clinical Hyperandrogenism
 - hirsutism
 - acne
 - female pattern hair loss
- Biochemical Hyperandrogenism
 - bioavailable testosterone, calculated free testosterone or free androgen index
 - consider AD & DHEAS if total testosterone or free testosterone not elevated

MelbourneIVF 

Management of excess weight in PCOS

- Lifestyle interventions
 - Diet
 - energy deficit
 - 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

MelbourneIVF 

The top 25 items in Australian supermarkets



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

MelbourneIVF 

Use of combined oral contraceptive pill in PCOS

- Use for clinical hyperandrogenism & irregular menstrual cycles
- Type
 - EE2&CPA COCP not 1st line
 - 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 female pattern hair loss

MelbourneIVF 

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

MelbourneIVF 

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

MelbourneIVF 

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. Wang, Costello et al BMJ 2017

MelbourneIVF 

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

MelbourneIVF 

studies

Letrozole: risk of congenital anomalies in published literature

n = 10 studies

Appendix 28 Congenital malformations in newborns conceived through letrozole vs control

Study ID	Country	Study design	Congenital malformations Control	Letrozole
Dubinsky 2009 ¹	Iran	RCT	CC: 16.0% (1/62)	0% (0/30)
Roy 2012 ²	India	RCT	CC: 0% (0/10)	0% (0/20)
Roy 2012 ²	India	RCT	CC: 0% (0/21)	0% (0/39)
Legro 2014 ³	USA	RCT	CC: 1.0% (1/90)	3.0% (4/132) ²
Diamond 2015 ²	USA	RCT	CC: 4.3% (1/23) ²	3.6% (2/56) ²
Tsimaki 2008 ²	Canada	observational	CC: CC + FME 4.8 (319/397) ²	Letrozole+Letrozole+FME 2.4% (14/516) ²
Franses 2007 ²	Canada	observational	2.0% (7/27) ²	0% (0/8)
Sharma 2014 ²	India	observational	CC: 4.0% (10/251) ²	2.5% (5/201) ²
Wu 2016 ²	China	RCT	Normal conceptions: 2.3% (5/217) ²	Letrozole alone: 1.2% (3/24) ² Letrozole+Biotin: 1.2% (3/24) ²
Tamura 2016 ²	Japan	observational	Normal cycle IVF/ICSI: 1.9% (44/2287) ²	Letrozole + IVF/ICSI: 2.2% (15/687) ²
Total			2.50% (90/3601)	2.20% (42/1895)

Wang Castello et al BMJ 2017

MelbourneIVF

Adjuvant metformin use

- Addition of metformin to FSH OI improves ovulation, pregnancy and live-birth rates¹
- Addition of metformin to IVF treatment improves clinical pregnancy rate and lowers the risk of OHSS^{2,3}

1. Bordeijk, Castello et al Cochrane SRV 2017
2. Lo, Castello et al Cochrane SRV 2014
3. Lo, Castello et al Fert Steril 2015

MelbourneIVF

Current guidelines

- 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
- Use Rotterdam 2003 criteria for diagnosis of PCOS
- Ultrasound not recommended for diagnosis of PCOS in adolescents

MelbourneIVF

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

MelbourneIVF

Take home messages in general practice

- Optimising 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 FSH ovulation induction and IVF can improve outcome

MelbourneIVF

Thank you

MelbourneIVF