New PCOS guidelines: What's relevant to general practice

Dr Michael Costello
Fertility Specialist

How do we know if something is **new**?

Louvre Museum, Paris 2016

Conflict of interest

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

Presentation outline on PCOS

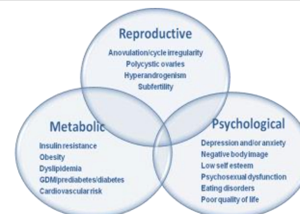
- Background
- International guidelines
- Diagnosis & assessment
- Management of excess weight
- Use of COCP
- Treatment of infertility
- Take home messages

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

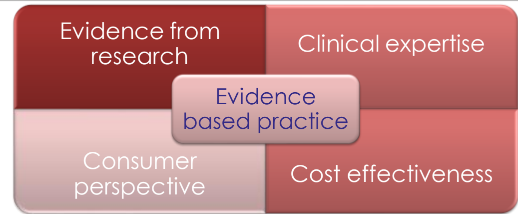


Norman et al Lancet 2007, Teede et al BMC Medicine 2010, Teede et al MJA 2011

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



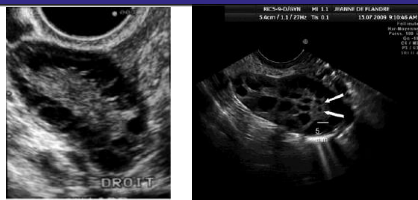
Diagnosis of PCOS in Adults

- 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)

Diagnosis of Polycystic Ovarian Morphology

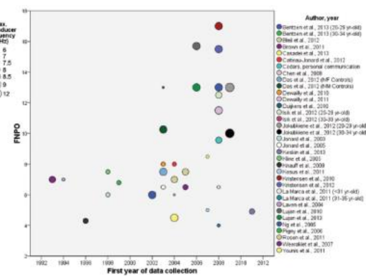
- Use transvaginal ultrasound
  - Follicle # per ovary $\geq$ 18 &/or ovarian volume $\geq$ 10ml if using **new technology**
  - Follicle # per ovary $\geq$ 12 &/or ovarian volume $\geq$ 10ml if using **old technology**
- Transabdominal ultrasound
  - Ovary volume $\geq$ 10ml

Comparing US images



Old technology New technology

Changes in the mean or median of **follicle number per ovary (FNPO)** in healthy women with regular menstrual cycles over time.



Dewailly 2014

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

IVFAustralia

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

IVFAustralia

Management of excess weight in PCOS

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

IVFAustralia

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

IVFAustralia

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

IVFAustralia

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

IVFAustralia

Ovulation Induction in PCOS

- Exclude pregnancy prior to starting OI
- Infertile anovulatory women with no other infertility factors
- Letrozole is 1st line pharmacological therapy [1,2]
- Risk of multiple pregnancy is less with letrozole compared with clomiphene citrate [3]
- Consider monitoring to reduce risk of multiple pregnancy

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

ORIGINAL ARTICLE: INFERTILITY

First reported case of sextuplets conceived via letrozole for ovulation induction

Gunwant Warraich, M.D. and Tannys D. R. Vause, M.D.
Ottawa Fertility Centre, Ottawa, Ontario, Canada

Fertility and Sterility® Vol. 103, No. 2, February 2015

20/30

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

Potential Teratogenic Effect of Letrozole

Biljan et al. Oral abstract presentation ASRM Oct 14-19 2005

Retrospective cohort study

150 babies born to women following letrozole treatment

compared to

36,050 babies born from low risk women in a community hospital

Increased risk of bone and cardiac defects with Letrozole

Health Canada Endorsed Important Safety Information on Femara* (letrozole)

November 17, 2005

Dear Health Care Professional:

Subject: Contraindication of Femara* (letrozole) in premenopausal women

Following discussions with Health Canada, Novartis is advising you of concerns about the use of the aromatase inhibitor Femara* (letrozole) for the purpose of ovulation induction in the treatment of infertility. Novartis is aware that Femara* has been or is being used to treat infertility even though statements in the Canadian Product Monographs warn physicians about potential embryo- and fetotoxicity with or without teratogenicity. There have been post-market reports of congenital anomalies in infants of mothers exposed to Femara* for the treatment of infertility.

Femara* (letrozole) is contraindicated in women with premenopausal endocrine status, in pregnancy, and/or lactation due to the potential for maternal and fetal toxicity and fetal malformations.

Novartis is committed to the safe use of its medications. As a manufacturer and distributor of Femara* (letrozole), it is our regulatory and compliance responsibility to duly remind all concerned physicians that the use of letrozole for the purpose of ovulation induction is not within the scope of the approved indications. For your information, the approved indications for Femara* and important information on contraindications and reproductive toxicology are described below:

MIMS AUSTRALIA : Letrozole

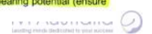
MIMS Abbreviated Product Listing

Femara

Generic Ingredients: letrozole
Company Novartis Pharmaceuticals Australia Pty Ltd
Pregnancy Category D*

Banned in sport
ARTG: **Registered medicine**

Use: Nonsteroidal aromatose inhibitor. Hormone receptor +ve breast cancer in postmenopausal women
Contra: Premenopausal endocrine status; pregnancy, lactation
Prec: Not for hormone receptor -ve breast cancer; neoadjuvant use; monitor bone health; renal (ClCr < 30 mL/min), hepatic (Child-Pugh C) impairment; perimenopause; recent postmenopause; women of childbearing potential (ensure adequate contraception)



Letrozole: risk of congenital anomalies in **published** literature

n = 10 studies

Appendix 39 Congenital malformations in newborns conceived through letrozole vs control.

Study ID	Country	Study design	Congenital malformation	
			Control	Letrozole
Dehbashi 2009[1]	Iran	RCT	CC: 16.6% (1/6)[a]	0% (0/10)
Ray 2012[2]	India	RCT	CC: 0% (0/13)	0% (0/20)
Roy 2012[3]	India	RCT	CC: 0% (0/21)	0% (0/39)
Legro 2014[4]	USA	RCT	CC: 1.5% (1/66)[b]	3.9% (4/102)[c]
Diamond 2015[5]	USA	RCT	CC: 4.3% (3/70)[d]	3.6% (2/56)[e]
Tulandi 2006[6]	Canada	observational	CC/CC+FSH: 4.8(19/397)[f]	Letrozole/Letrozole+FSH: 2.4% (14/514)[g]
Forman 2007[7]	Canada	observational	2.6% (7/271)[h]	0% (0/94)
Sharma 2014[8]	India	observational	CC:4.0% (10/251)[i]; Natural conception: 2.9% (5/171)[k]	2.5% (5/201)[j]
Wu 2016[9]	China	RCT	Berberine: 0% (0/48)	Letrozole alone: 1.2%(1/84)[l]; Letrozole+Berberine: 1.2%(1/81)[m]
Tatsumi 2016[10]	Japan	observational	Natural cycle IVF/ICSI: 1.9% (44/2287)[n]	Letrozole + IVF/ICSI: 2.2%(15/694)[o]
Total			**2.50% (90/3601)**	**2.20% (42/1895)**

25/30

Wang Costello et al BMJ 2017

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. *Lo, Costello et al Cochrane SRV 2014*
3. *Lo, Costello et al Fert Steril 2015*

Take home messages: 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

Take home messages in general practice

- Use Rotterdam 2003 criteria for diagnosis of PCOS
- Ultrasound not recommended for diagnosis of PCOS in adolescents
- Use COCP for treatment of clinical hyperandrogenism & irregular menstrual cycles
- No specific OCP is to be recommended over another

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

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

Thank you

IVFAustralia
Leading minds dedicated to your success