

Polycystic Ovarian syndrome and Infertility – An update for General Practice 2015

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PCOS

1. Definitions
2. Diagnosis
3. Pathophysiology
4. Common presentations
5. Common misdiagnosis
6. Investigations
7. Long term complications
8. Treatment
9. Take home message



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- No conflict of interest



PCOS

Most common female endocrine disorder and
one of the most common female conditions in
Australia

Group of clinical features and hormone
changes:
Anovulation
Androgenisation
insulin resistance

Name is inaccurate and misleading



Prevalence

12-21% of Australian women
21% in indigenous Australian women

70% mis or undiagnosed

40% develop type 2 diabetes



Diagnosis - Rotterdam Criteria most commonly used

Any 2 of the following:

1. **PCO on ultrasound examination**
2. **Clinical and/or biochemical evidence of hyperandrogenism**
3. **Oligo or anovulation with menstrual dysfunction**



*ESHRE and ASRM PCOS symposium, Rotterdam, 2003.
Fertility and Sterility 81:1:19-25.2004.*



Diagnosis continued:

Exclusion of other endocrinopathies:

Hypothalamic causes ie wt loss or weight gain
 Hypothyroidism
 Congenital adrenal hyperplasia
 Androgen secreting tumours
 Cushing's syndrome
 Functional ovarian cysts
 Premature ovarian failure



PCO – Ultrasound Definition of Polycystic ovaries:

Ultrasound diagnosis:

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



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



Diagnosis of biochemical hyperandrogenism

↑ Testosterone (free or sensitive)
 ↑ Free androgen index (t/shbg x 100)
 ↑ Androstenedione
 ↑ Dheas

17 oh progesterone (exclude delayed onset congenital adrenal hyperplasia)

Controversies

Difficult to assess biochemically
 Variations – diurnal, cyclical, seasonal, age related and ethnic background



PCOS - PATHOPHYSIOLOGY

Genetic factors interact with environmental factors
 Often associated with weight gain ?trigger in some patients
 Insulin resistance
 Hyperandrogenism



PCOS – genetic aetiology

Complex multigenic disorder

GWAS – genome wide association studies:

Several focus genes: FSHR, LHCGR, INSR, RAB5B and DENND1A

these candidates comprise a hierarchical signalling network through adapter proteins and associated downstream signalling cascades to regulate theca cell androgen biosynthesis.



PCOS – Clinical features:

Reproductive Features:

Sub-fertility
 Menstrual irregularity – oligo or amenorrhoea
 ?Miscarriage (may be obesity related)
 Pregnancy complications
 -gestational diabetes
 -operative delivery
 -hypertensive disorders of pregnancy



Non-reproductive features:

Metabolic
 Obesity
 increased risk of cardiovascular disease
 impaired glucose tolerance
 type 2 diabetes
 Hyper-androgenism
 Obstructive sleep apnoea
 Endometrial hyperplasia and carcinoma
 Mood disorder
 poor self-esteem
 anxiety
 depression



Who has PCOS? – common presenting problems

Infrequent irregular menses	90%
Amenorrhoea	50 - 75%
Anovulatory infertility	>90%
Acne in women (late onset)	>95%
Hirsutism	>95%
IDD in women	up to 50%
Female caucasian population	10%-15%
UK south asian population	30-50%



PCO vs PCOS - Common misdiagnoses

A patient with PCO on ultrasound and absence of ovulatory disorder or hyperandrogenism **DOES NOT HAVE PCOS (syndrome)**

PCO alone was found in 20-25% of healthy reproductive age women in UK and NZ studies.

Not all patients with Obesity and irregular menses have PCOS

Polson et al, Lancet, 1988;1:870-872.



Investigations:

Ultrasound - transvaginal

Blood tests

Testosterone – free or sensitive if available
 Dheas
 SHBG – sex hormone binding globulin
 Mid-luteal or serial progesterone assessment
 TSH
 Prolactin
 FSH and LH
 +/- AMH



Long term complications PCOS

Hypercholesterolaemia
 Impaired glucose tolerance - 23-35%
 T2 diabetes melitis - 4-10%
 Cardio-vascular disease
 Endometrial hyperplasia and carcinoma
 Obstructive sleep apnoea
 Non-alcoholic fatty liver disease



PCOS and Metabolic syndrome:

PCOS associated with increased risk of development of the metabolic syndrome
 -46% of PCOS women (23% in general population)
 Increased risk of metabolic syndrome in siblings of women with PCOS
 Risk for developing type 2 DM, HT, coronary and other vascular disease
 Increased conversion in PCOS from IGT to T2DM compared with matched controls (annual incidence 10% cw 1%)



PCOS Management

Obesity
 Irregular cycles
 Subfertility
 Hirsutism and hyperandrogenism
 Metabolic syndrome
 Prevention endometrial pathology
 Mood disorder



Management

Obesity

Lifestyle modification

Weight loss program

Dietitian

Education of healthy balanced eating
 Avoid repeat dieting

Exercise

Institute exercise program
 Strategies for improving self-esteem
 Improved outcomes in group environment

Consider Lap banding



Which diet/eating pattern?

Many have been proposed
 Studies are poor with no good quality prospective studies in PCOS

Some groups promote low GI diet

- Low fat, moderate protein, mod CHO probably best (Scalzo, 2000)

- High vs low protein doesn't make much difference (Moran et al 2003)

- Low GI probably good, reduces fasting insulin but may not change insulin sensitivity. Better success in patients with T2DM

(Brand 1991, Jarvi et al 1999)



Effect of weight loss on reproductive function

Improved hormone profiles
 Increases menstrual regularity
 Improved ovulation rates
 Improved pregnancy rates
 Effects seen with modest weight loss (10%)
 Ave 7-10 kg

Clark et al. 1998 and Hollman et al 1996.



Results of RWH lifestyle group: (N=285)

67% of participants entered the program with the hope of trying to conceive

60% of these have conceived so far, of which > 50% of the pregnancies are spontaneous

16% of these women miscarried – similar to miscarriage rates reported in other groups



Management - Irregular cycles

Pelvic us

Exclude endometrial hyperplasia or other pelvic pathology

Oral contraceptive pill

Low dose oestrogen

Cyclical progesterone

Metformin

may be helpful where oestrogen is relative contraindication



MANAGEMENT OF Hyperandrogenism

- Weight loss and exercise
- Cosmetic measures
- Laser hair removal
- Oral contraceptive pill
- Anti-androgen medication to reduce hair growth
 - Cyproterone acetate
 - Spironolactone
- Other treatments
 - Flutamide, finasteride, eflornithine
 - Vaniqa – topical inhibitor linear hair growth



Management - Infertility

- Weight management
 - Lifestyle advice
- Folate
- Ovulation induction
- +/- Ovarian drilling (golf balling)
- IVF



PCOS-MANAGEMENT

- if overweight, weight loss/exercise program is **first line treatment**
- Improved reproductive outcomes
- Improves long term risks
- Can combine with other treatments
 - Eg ovulation induction



Methods of Ovulation Induction

- Weight correction
- Clomiphene citrate
 - Oestrogen antagonist
 - Increases FSH and increases follicular growth
 - Oral administration – 5 days only
- Gonadotrophins (Recombinant FSH)
 - Clomiphene resistant PCOS
 - Administered by sc injection
 - Increased side effects of multiple pregnancy and ovarian hyperstimulation
- Metformin
 - Clomiphene resistance
 - Laparoscopic ovarian drilling (Golf balling)
 - Possible benefit
 - Resumption of ovulation often temporary
- Aromatase Inhibitor – eg Letrozole**
 - ovulation rates and pregnancy rates comparable or better than cc - not approved by pbs for this indication



Clomiphene Citrate (Clomid or Serophene)

- Now over 5000 publications
- 1961 first used to induce ovulation
- A competitive anti-oestrogen
- Depends on adequate oestrogen to work
- FSH by competing for E2 receptor sites
- May also have direct effect on the ovary



clomiphene citrate

- ovulation rates 70-80% (Messinis 2002)
- pregnancy rates 30-40% (Messinis 2002)
- clomiphene resistance :
 - add metformin
 - golf balling
 - letrozole
 - gonadotrophins



Clomiphene citrate-Side Effects

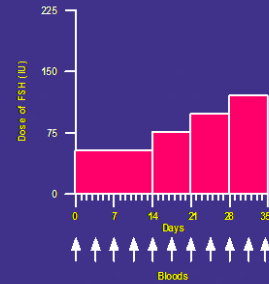
Multiple pregnancy 10%
 Bloating
 Headaches
 Abdo discomfort
 Nausea and vomiting
 Flushing
 Dryness or loss of hair



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Low dose gonadotrophins

- Give slowly increasing doses of gonadotrophin until oestradiol rises
- Puregon/ Gonal F/ Menopur



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Side effects of gonadotrophins

Ovarian hyperstimulation – severe 1%
 Multiple pregnancy - 20%
 Nausea and vomiting
 Mood change
 Abdominal tenderness and distention



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Laparoscopic ovarian drilling



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Gonadotrophins v Ovarian drilling

- Equally effective
- Conceptions happen more slowly in ovarian drilling
- Multiple pregnancy less common with ovarian drilling
- Case reports of ovarian failure with drilling



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Letrozole

Aromatase inhibitor

Meta-analysis of 13 RCTs found higher pregnancy rates when compared to clomiphene citrate

Blocks conversion of androgens to oestrogen leading to reduced negative feedback to pituitary and hypothalamus increasing endogenous GnRH and FSH

Higher pregnancy rates than laparoscopic surgery

Off label in Australia



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Metformin– Cochrane Sys Review 2012

No evidence that metformin improves live birth rate:

Clinical pregnancy rates are improved:
Metformin versus placebo
OR 2.31, 95% CI 1.52 to 3.51

Metformin + CC versus CC alone
OR 1.51, 95% CI 1.17 to 1.96



Use of Metformin

Metformin not recommended as part of first line treatment for PCOS

Reserve metformin for second line treatment for women with clomiphene resistance
Use currently outweighs good evidence from clinical trials

(Cochrane database systematic review 2012)

Recent study indicated adjuvant use of metformin reduced risk of OHSS in patients undergoing assisted reproduction



options after failure of medical OI

weight loss (+/- consider laparoscopic gastric banding if other methods fail)

laparoscopic ovarian drilling

IVF



IVF

Different medication protocols are available:

Standard protocols:

Antagonist protocol - most common, better for PCOS – reduced chance of OHSS

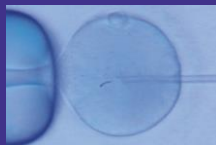
Down Regulation protocol - longer

Flare protocol



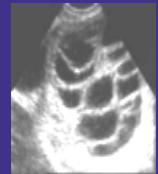
IVF

ICSI



Ovarian Hyper Stimulation Syndrome

- after egg collection most cases
- More prevalent in PCOS
- Over-response to FSH stimulation
- > 20 eggs collected Fluid retention, abdominal swelling and discomfort, nausea
- Occurs mildly in 1-10% of IVF cycles (severe in <1%).
Contact fertility clinic if suspected



Role of GP

- GPs play an important role in providing:
 - pre-pregnancy advice
 - undertaking initial investigations
 - Helping to emphasize lifestyle changes and provide referral to experienced dietitian
 - Detection of non reproductive sequelae in patient and family
- Earlier referral / younger age best to enable the highest chance for a successful pregnancy



Take home message:

Commonly under diagnosed – consider diagnosis

Check all newly diagnosed for IGT or T2DM

Do not miss endometrial pre-malignant or malignant pathology

Modify other CVD risk factors

