

# Polycystic Ovary Syndrome

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# Concise History of PCOS

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- 1844 : Sclerocystic changes in ovary first described
- 1935 : Stein- Leventhal syndrome described
- 1958 : Elevated LH levels linked with condition
- 1976 : Normal LH levels linked with condition
- 1976 : Insulin resistance linked with condition
- 1981 : Ultrasound features of condition first described
- 1985 : Diagnostic Ultrasound criteria defined

# Current Consensus?

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- ❖ Aetiology remains unclear as impossible to reach consensus
- ❖ 'Syndrome' rather than a single disease entity
- ❖ Ultrasound and endocrine features must be taken together
- ❖ Well recognised familial traits possibly due to gene defects
  - ❖ Steroid synthesis gene 'CYP11a'
  - ❖ Insulin gene
  - ❖ Follistatin gene
- ❖ Abnormal growth factors
- ❖ Heterogenous biochemical features -
  - ❖ abnormal ovarian steroidogenesis : hyperandrogenism is key
  - ❖ Abnormal extra-ovarian hormone secretion : hypersecretion of androstenedione, insulin, and LH

# PCO



Normal ovary



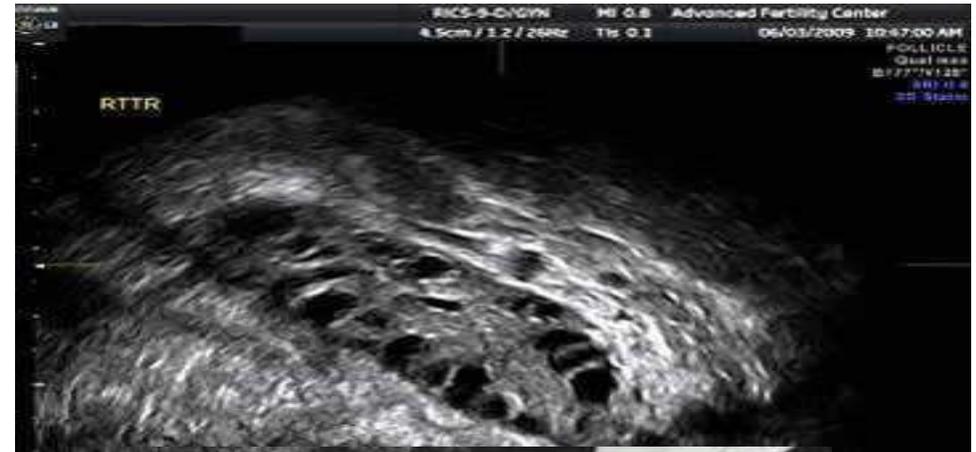
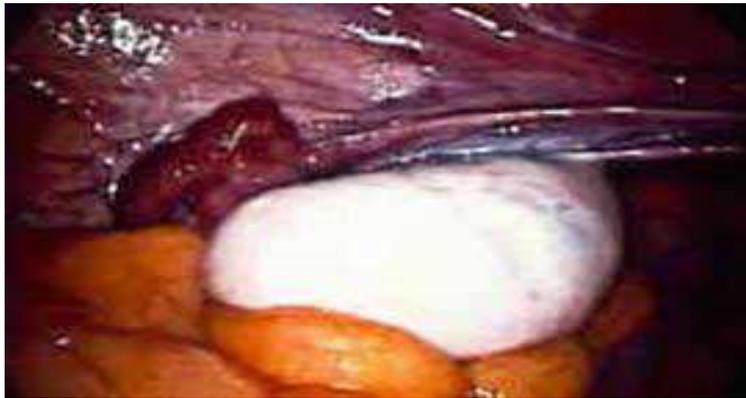
Polycystic ovary



ADAM



# PCO



# ESHRE( Rotterdam)/ASRM-PCOS Consensus Workshop Group

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- polycystic ovaries (either 12 or more peripheral follicles or increased ovarian volume (greater than 10 cm<sup>3</sup>))
- oligo- or anovulation
- clinical and/or biochemical signs of hyperandrogenism

# Polycystic Ovarian Morphology

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*Seen in all women with PCOS, many healthy women, adolescents and some cases of Hypogonadotropic hypogonadism*

1. Larger than normal ovaries (volume = >10 cc)
2. Twice the number of developing follicles
3. Increased stromal volume
4. >12 antral follicles each measuring >2mm in diameter - 'arrested maturation'

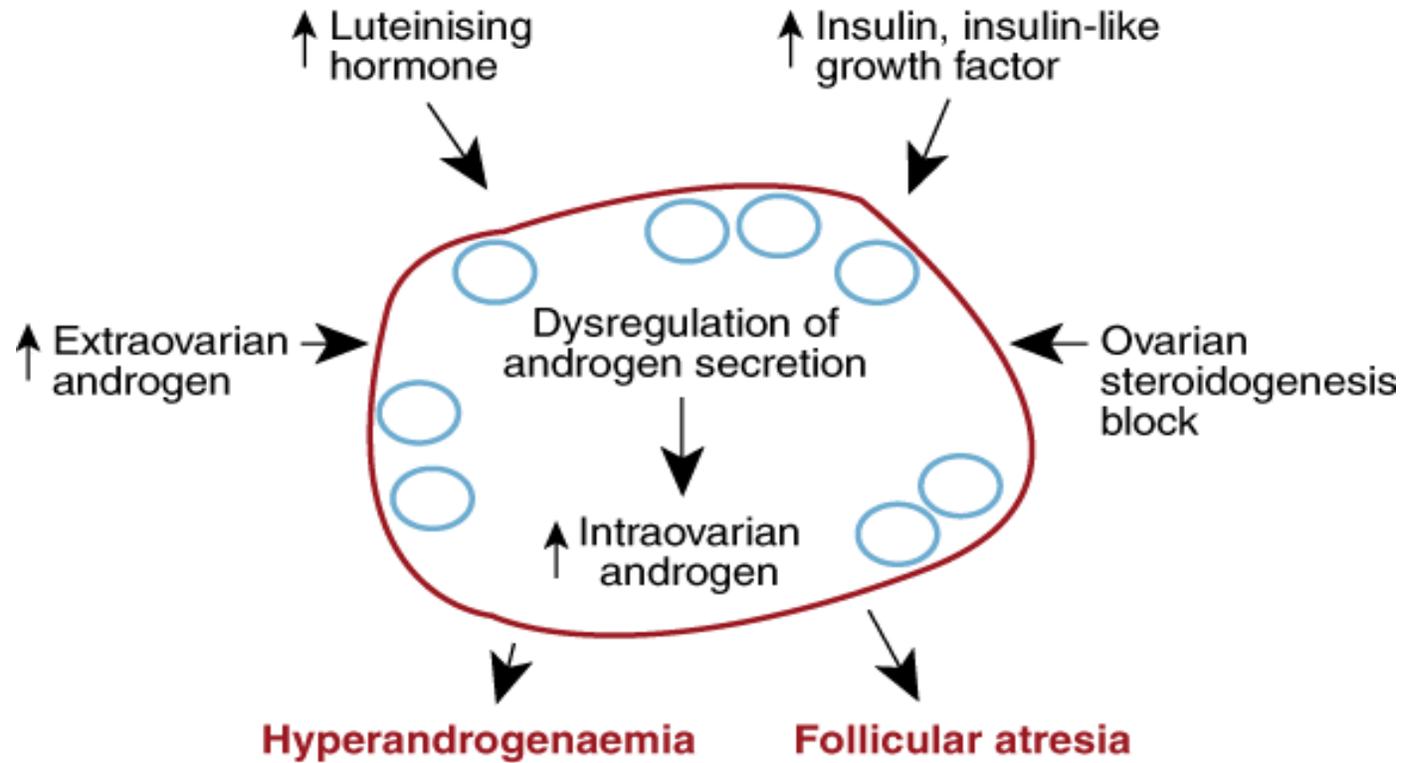
# Arrested follicular maturation

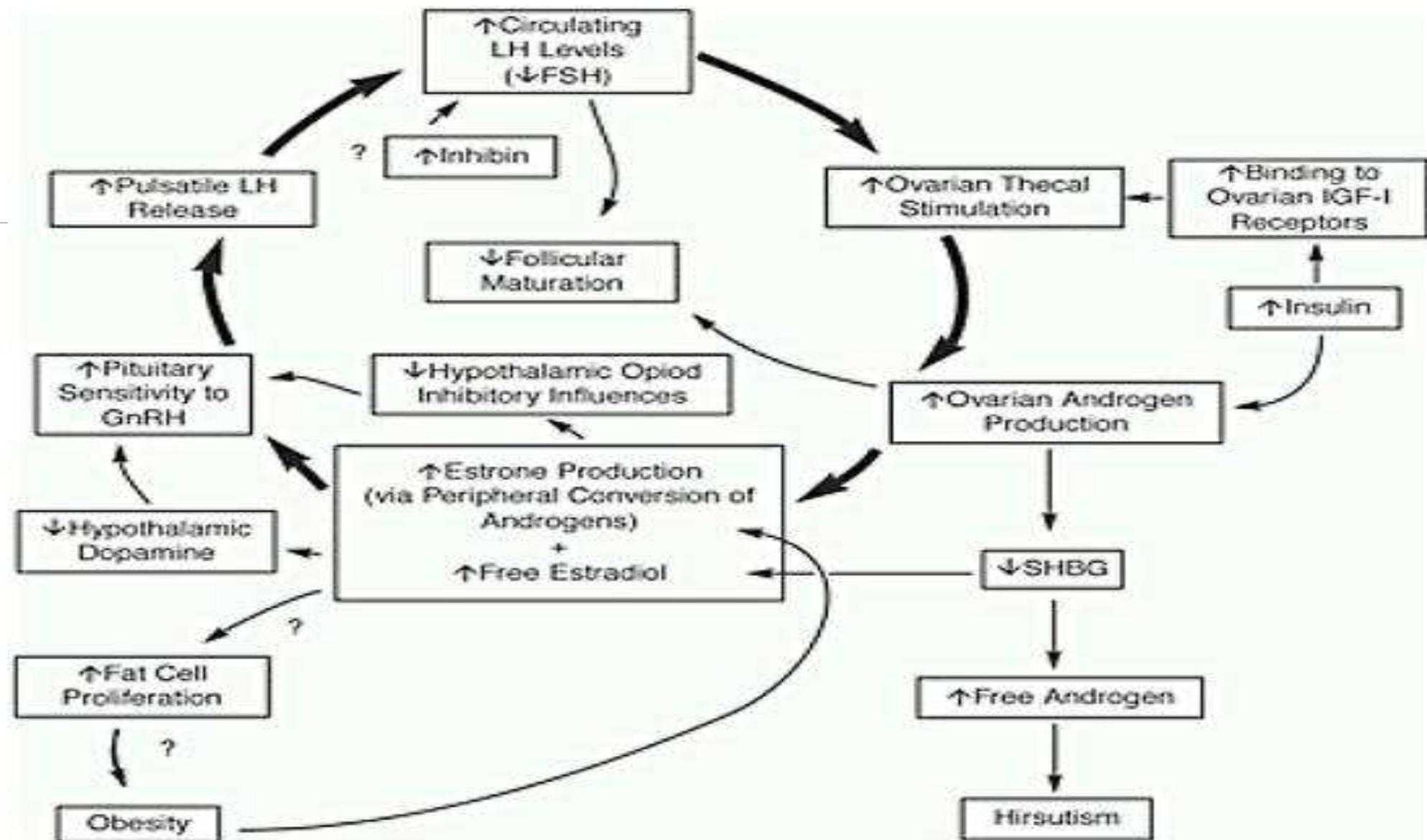
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1. Hyperfunction of EGF/TGf- $\alpha$ , Follistatin and Inhibin-b - which interfere with the action of FSH.
2. Increased sensitivity to LH due to premature expression of LH receptors
3. Excess secretion of Insulin and Androgens
4. Lack of Growth-differentiating Factor 9
5. Genetic defects can cause abnormal serine phosphorylation of Insulin receptors resulting in Insulin resistance and hyperinsulinemia.

# PCOS

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# PCOS - clinical manifestation

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## Symptoms :

1. Obesity - 38%
2. Menstrual Disturbance - 66%
3. Hyperandrogenism - 48%
4. Infertility - 30% of PCOS have anovulation
5. Asymptomatic - 20%

## Biochemical Changes:

1. High testosterone & androstenedione
2. High LH ( LH >>>FSH)
3. High Oestradiol
4. High fasting Insulin
5. High Prolactin
6. Low SHBG

# PCOS- Recommended investigations

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-FSH,LH, Estradiol, Testosterone and SHBG - Day 2-5 of menstrual cycle.

Free androgen index (total testosterone divided by sex hormone binding globulin (SHBG)  $\times 100$  to give a calculated free testosterone level).

-Serum Prolactin

-Thyroid function tests

-17-hydroxyprogesterone should be sampled in cases of clinical evidence of hyperandrogenism and total testosterone greater than 5 nmol/l,

-If clinical suspicion of Cushing syndrome-investigate according to local practice.

# Late Sequelae

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Diabetes Mellitus

Cardiovascular disease

Hyperinsulinemia

Hypercholesterolemia ( high LDLs, triglycerides and total cholesterol)

Hypertension

Endometrial Carcinoma

# Late Sequelae- Diabetes

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## Diabetes

- Literature suggests- 10-20% incidence of Type 2 diabetes and increased incidence of impaired glucose tolerance.
- PCOS is independent risk factor for diabetes in middle age- associated insulin resistance

## Screening-

- Annual fasting blood sugar. Offer glucose tolerance test if patient has PCO+ high BMI+ family history+ fasting blood glucose  $>5.6\text{mmol/l}$ .
- Fasting insulin and HOMA-IR- not routinely done in clinical practice. Results are variable .
- Screen for gestational diabetes before 20 weeks when pregnant.

# Late Sequelae- cardiovascular risks

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Increased cardiovascular risk factors with PCOS than weight-matched controls with normal ovarian function

-Obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia

Abnormal lipid profiles mainly consist of:

Raised triglycerides, total and low-density lipoprotein cholesterol. The effect of PCOS on high-density lipids is controversial.

## **In clinical practice**

Hypertension should be treated for persistent blood pressures  $\geq 140$  mmHg systolic and or 90 mmHg diastolic, not responding to lifestyle measures .

Lipid-lowering treatment is not recommended routinely and should be prescribed by a specialist

# Cancer Risks with PCOS

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Oligo- or amenorrhoea in women with PCOS may predispose to endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with progestogens to induce a withdrawal bleed at least every 3-4 months.

Cyclical progestones for at least 12 days

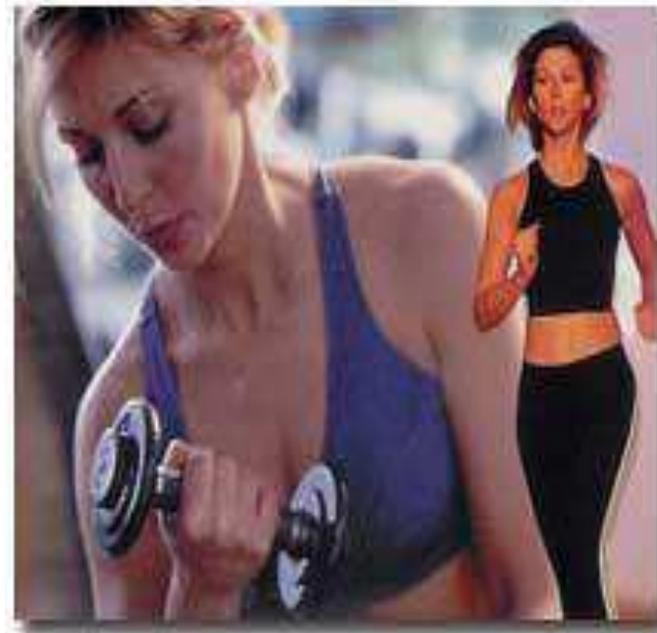
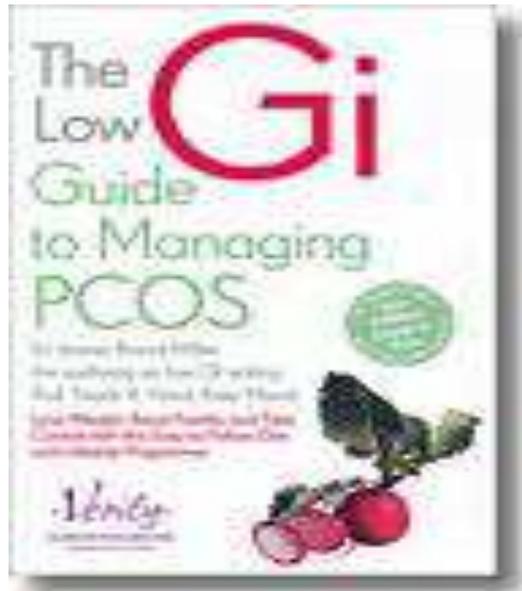
Oral contraceptive pills

Mirena intrauterine system

There does not appear to be an association with breast or ovarian cancer and no additional surveillance is needed

# Alternatives to Medication

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# Steps in primary set up to decrease risk associated with PCOS

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Life style changes- weight loss through diet and exercise

Loss of significant weight has been reported to result in

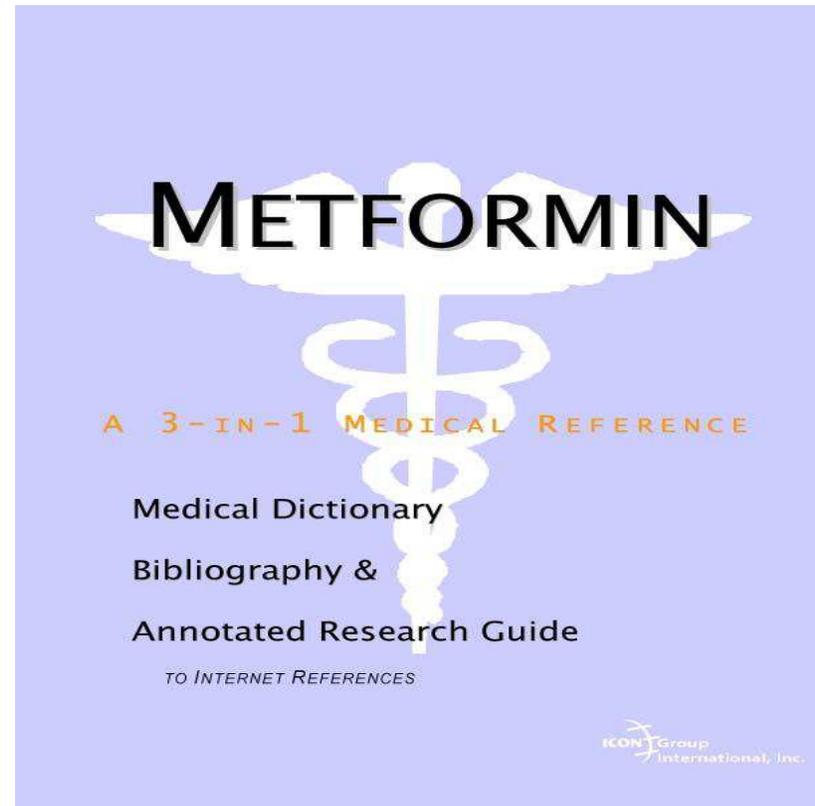
- spontaneous resumption of ovulation and improvement in fertility.

- SHBG and reduced basal level of insulin associated with normalisation in glucose metabolism

Reduce the likelihood of developing type 2 diabetes later in life.

# Treatment of PCOS

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# Use of drugs in PCOS

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1. Insulin-sensitising agents have not been licensed in the UK for use in women who are not diabetic.
2. There is currently no evidence of a long-term benefit for the use of insulin-sensitising agents.
3. Metformin and troglitazone have been shown to have only short term beneficial effects on insulin resistance in women with PCOS who are not diabetic.
4. Women with a body mass index of more than 37 may not respond well to metformin therapy

# Use of drugs in PCOS

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Use of weight-reduction drugs may be helpful in reducing insulin resistance through weight loss

Orlistat and sibutramine have been shown to significantly reduce body weight and hyperandrogenism in women with PCOS. However, the use of sibutramine is not recommended in patients with systolic hypertension

Bariatric surgery may be indicated in selected women with morbid obesity- BMI of 50 or above, some cases of BMI > 40.

# Use of drugs in PCOS- Hirsutism

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Recent Cochrane review there is insufficient evidence in favour of either metformin or the oral contraceptive pill in treating hirsutism or acne.

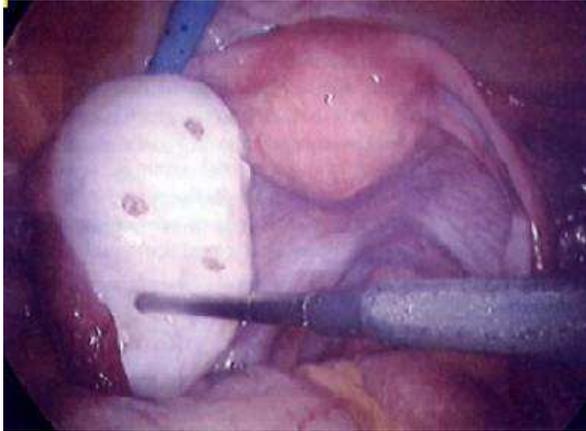
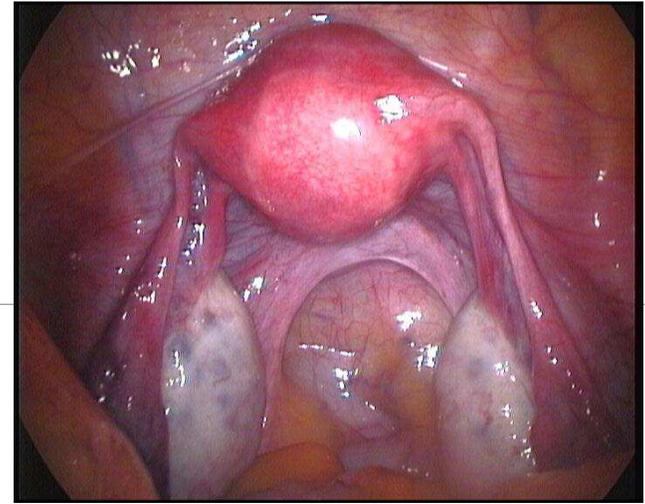
## Licensed treatments for hirsutism

- oral contraceptive pills, dianette (oestrogen and cyproterone acetate), cosmetic measures (such as laser, electrolysis, bleaching, waxing and shaving) and topical facial eflornithine (Vaniqa)

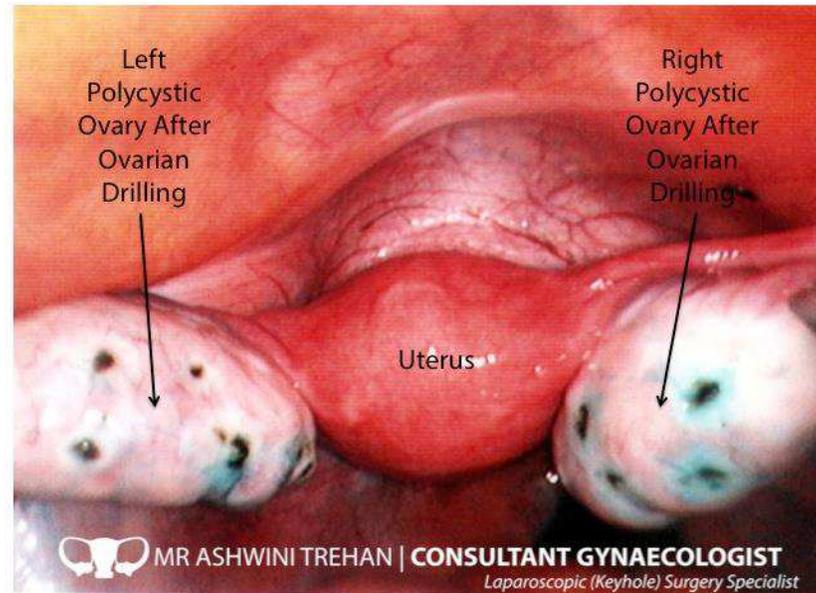
## Non-licensed treatments:

spironolactone, antiandrogens, such as flutamide, finasteride and high-dose cyproterone acetate. Metformin as an insulin sensitiser reduces androgens by 11%.

# Ovarian drilling



Completion of an ovarian drilling operation



# Ovarian Diathermy

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-Results from a longterm cohort study up to 20 years after laparoscopic ovarian electrocautery has shown persistence of ovulation and normalisation of serum androgens and SHBG in over 60% of subjects, particularly if they have a normal BMI

However, no prospective studies have been powered to look at cardiovascular risk profiles and ovarian electrocautery

Ovarian diathermy improves fertility outcome in women with PCOS.

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Thank you



NICE: Key points from the evidence

Metformin is licensed in the UK for the control of blood glucose in people with type 2 diabetes. It has also been used to treat polycystic ovary syndrome (PCOS). Metformin is not licensed in the UK for this indication so its use in PCOS is off-label.

This evidence summary relates to metformin for PCOS in women who are not planning pregnancy. The use of metformin for treating infertility in women with PCOS is not covered by this evidence summary.

Five small randomised controlled trials (RCTs) included in a Cochrane systematic review, and 4 RCTs published after the Cochrane review, provide the evidence for this summary.

There is no good evidence that regimens containing metformin are statistically significantly different from co-cyprindiol in controlling hirsutism in women with PCOS. Two small studies found no statistically significant difference between metformin and co-cyprindiol in effects on acne but the assessment methods were unclear. Metformin was less effective at improving menstrual regularity than co-cyprindiol. There was no or insufficient data in the studies included in this evidence summary from which to draw conclusions on the effectiveness of metformin for long-term outcomes such as preventing type 2 diabetes, cardiovascular events or endometrial cancer in women with PCO

Metformin use is associated with gastrointestinal adverse effects (nausea, vomiting and diarrhoea), which can be severe. The Cochrane review found that metformin caused a significantly higher incidence of gastrointestinal adverse effects that were severe (leading to treatment discontinuation) compared with co-cyprindiol, and a significantly lower incidence of other severe adverse effects (weight gain, high blood pressure, depression, chest pain and headache). Among all 9 trials there was significant heterogeneity in the rates of treatment discontinuation, which was not always because of adverse effects.

The annual cost of metformin at 1.5–2 g per day ranges from £30.03 to £83.20, depending on whether standard or modified-release tablets are prescribed.

Alternative commonly used treatments for hirsutism, acne and menstrual irregularity in PCOS in women not planning pregnancy are:

Co-cyprindiol, a combination product containing cyproterone and ethinylestradiol. Co-cyprindiol is licensed for treating severe acne refractory to prolonged oral antibiotic therapy, and moderately severe hirsutism. It is not licensed specifically for use in PCOS.

The combined oral contraceptive pill. This is not licensed for controlling menstrual irregularity in PCOS.