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When should I suspect polycystic ovary syndrome?

- **Suspect polycystic ovary syndrome (PCOS) if the woman has one or more clinical features of:**

o Infrequent or no ovulation — for example infertility, oligomenorrhoea, or amenorrhoea.

o Hyperandrogenism — for example hirsutism, acne vulgaris occurring after adolescence, or alopecia.

- Although it is not in the diagnostic criteria, women may have indirect evidence of insulin resistance, for example:

o Obesity, especially central obesity.

o Acanthosis nigricans. The skin is dry and rough, with grey-brown pigmentation; and is palpably thickened, and covered by a papillomatous elevation, giving it a velvety texture. The condition commonly affects the axillae, perineum, or extensor surfaces of the elbows and knuckles. When the neck is affected, there is often a thin necklace of warty fissures that can spread as a wide band.

- **Increase the level of suspicion if there is a family history of PCOS.**

- **Exclude other conditions that have similar clinical presentations,** as PCOS is a diagnosis of exclusion.

What are the diagnostic criteria for polycystic ovary syndrome?

- **The Rotterdam diagnostic criteria have been generally accepted** and state that polycystic ovary syndrome (PCOS) should be diagnosed if two of three of the following criteria are present, as long as other causes of menstrual disturbance and hyperandrogenism are excluded [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Ehrmann, 2005]:

o Infrequent or no ovulation (usually manifested as infrequent or no menstruation).

o Clinical or biochemical signs of hyperandrogenism (such as hirsutism, acne, or male pattern alopecia), or elevated levels of total or free testosterone.

o Polycystic ovaries on ultrasonography, defined as the presence of 12 or more follicles in at least one ovary, measuring 2–9 mm diameter, or increased ovarian volume (greater than 10 mL).

- **Polycystic ovaries do not have to be present to make the diagnosis,** and the finding of polycystic ovaries does not alone establish the diagnosis [Ehrmann, 2005].

- The Androgen Excess and PCOS Society Task Force has challenged the Rotterdam criteria [Azziz et al, 2006; Azziz et al, 2009].

o Only a minority of this task force considered that PCOS could exist without hyperandrogenism and suggested that PCOS should be defined by two criteria:

o The presence of hyperandrogenism (biochemical or clinical).

o Ovarian dysfunction (oligo- or anovulation or polycystic ovaries).

o However, the Rotterdam consensus definition provides a helpful framework, and too exclusive a definition would leave many women with PCOS who are at the milder end of the spectrum without a diagnosis [Balen et al, 2009].

What investigations should I perform?

▪ **Measure the following to help diagnose polycystic ovary syndrome (PCOS).**

o **Total testosterone** — this is normal to moderately elevated in women with PCOS.

o If the testosterone level is greater than 5 nanomol/L, test for 17-hydroxyprogesterone and seek specialist advice.

o **Sex hormone-binding globulin** — this is normal to low in women with PCOS. It provides a surrogate measurement of the degree of hyperinsulinaemia.

▪ **Calculate the free androgen index** (the normal range is usually less than 5, but this depends on local laboratories) — this is normal or elevated in women with PCOS. It provides an assessment of the amount of physiologically active testosterone present.

o To calculate the free androgen index, divide the total testosterone value (in nanomol/L x 100) by the sex hormone-binding globulin value (in nanomol/L).

▪ **Measure the following to rule out other causes of oligomenorrhoea and amenorrhoea (such as premature ovarian failure, hypothyroidism, and hyperprolactinaemia):**

o Luteinizing hormone and follicle-stimulating hormone — may be increased in women with premature ovarian failure and decreased in women with hypogonadotropic hypogonadism.

o Prolactin (normal range is less than 500 mU/L) — may be mildly elevated in women with PCOS.

o Thyroid-stimulating hormone (normal range 0.4–4.5 mU/L).

▪ Estradiol measurement is not recommended.

▪ Refer for pelvic ultrasonography (unless the diagnosis of PCOS is obvious on clinical and biochemical grounds):

o To look for the classic picture of polycystic ovaries (12 or more follicles in at least one ovary, measuring 2–9 mm in diameter) or increased ovarian volume (greater than 10 mL) in women who satisfy only one of the above two criteria.

▪ Exclude pregnancy and other diagnoses as appropriate — see Differential diagnosis.

Basis for recommendation

Recommended blood tests

- These recommendations are based on guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007].

o Total testosterone level is normal to moderately elevated in women with PCOS.

o High testosterone levels (greater than 5.0 nanomol/L) warrant investigation to exclude conditions such as late-onset congenital adrenal hyperplasia, Cushing's syndrome, or an androgen-secreting tumour [RCOG, 2007].

o A proportion of women with PCOS do not have an abnormality in their circulating androgens [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004]. A study of 1741 women with PCOS found that only 29% had elevated serum testosterone (greater than 2.5 nanomol/L) [Balen et al, 1995].

o Combined oral contraceptives may normalize testosterone levels [Legro, 2007].

o Sex hormone-binding globulin (SHBG) provides a surrogate measure of the degree of hyperinsulinaemia.

o Insulin suppresses SHBG [Jayagopal et al, 2003; Balen et al, 2005].

o If the SHBG level is low despite an apparently normal total testosterone level, the amount of free testosterone (which is the bioactive form) may be increased, therefore elevating the free androgen index (FAI) [Balen et al, 2005].

o A small cross-sectional study of 12 women with PCOS found that serum SHBG levels were a useful marker for insulin resistance [Jayagopal et al, 2003].

o The FAI (or free testosterone) measurement is the most sensitive method of assessing hyperandrogenaemia [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004]. If the SHBG and total testosterone levels are known, the FAI can be calculated. The FAI provides a simple assessment of the amount of physiologically-active testosterone present. Free testosterone may reflect the combined effects of:

o Insulin resistance (increased insulin level and decreased SHBG level).

o Ovarian and adrenal hyperandrogenism (increased total circulating testosterone) [Legro, 1998].

- Thyroid-stimulating hormone and prolactin.

o Prolactin levels may be normal or mildly elevated in PCOS [Balen et al, 2005]. About 10–25% of women with PCOS have mildly elevated prolactin levels [Practice Committee of the American Society for Reproductive Medicine, 2008].

o Although thyroid-stimulating hormone is a useful screening test, the incidence of thyroid dysfunction among women with hyperandrogenism is no higher than that in women without hyperandrogenism who are of reproductive age [Balen et al, 2005].

Tests not recommended for the diagnosis of PCOS but essential for the diagnosis of other conditions that may present with amenorrhoea

▪ Luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratios are no longer considered useful in diagnosing PCOS because of their inconsistency [RCOG, 2007].

o The FSH level is normal in PCOS [Azziz et al, 2009].

o The LH level may be moderately elevated in PCOS [Azziz et al, 2009]. A single blood sample may fail to detect an increased LH level because of the pulsatile nature of gonadotrophin release [Dunaif, 1997; McIver et al, 1997]. A study of 1741 women with polycystic ovaries and other features of PCOS found that 39% had increased LH (greater than 10 IU/L) [Balen et al, 1995].

o Measurement of FSH and LH are essential in the diagnosis of other conditions that may present with amenorrhoea [Balen et al, 2005].

▪ Estradiol measurement is not recommended, as levels tend to fluctuate, and can be normal or low in both PCOS and hypothalamic amenorrhoea [Practice Committee of the American Society for Reproductive Medicine, 2008]. Estrogenization may be confirmed by endometrial assessment [Balen et al, 2005].

Pelvic ultrasonography

▪ The recommendation to do pelvic ultrasonography to assess ovarian morphology is based on expert advice in a textbook [Balen et al, 2005].

▪ Polycystic ovaries do not have to be present to make the diagnosis, and the finding of polycystic ovaries does not alone establish the diagnosis. In some women, the combination of irregular menses and biochemical hyperandrogenism may obviate the need for pelvic ultrasonography if there is confidence in the diagnosis.

What else might it be?

▪ The diagnosis of polycystic ovary syndrome involves the exclusion of all of the following disorders, which may have a similar clinical presentation:

o Simple obesity.

o Primary hypothyroidism.

o Premature ovarian failure.

o Hyperprolactinaemia.

o Non-classic congenital adrenal hyperplasia.

o Cushing's syndrome.

o Androgen-secreting neoplasm.

o Hypogonadotropic hypogonadism (that is central origin of ovarian dysfunction).

- Hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome.
- High-dose exogenous androgens.
- Acromegaly.

- Also consider drug-related conditions.
- The following drugs may cause hirsutism:
- Androgenic drugs, including testosterone, danazol, gestrinone, adrenocorticotropic hormone, high-dose corticosteroids, androgenic progestogens in oral contraceptives, and anabolic steroids.
- Non-androgenic drugs, including ciclosporin, diazoxide, minoxidil, and phenytoin; rarely, carbamazepine, sodium valproate, and acetazolamide.
- The following drugs may cause hypertrichosis: ciclosporin, diazoxide, minoxidil, and phenytoin.

Table 1. Conditions for exclusion in the diagnosis of polycystic ovary syndrome.

Condition	Hyperandrogenaemia or hyperandrogenism (or both)	Oligomenorrhoea or amenorrhoea	Distinguishing features	
			Clinical	Hormonal or biochemical
Simple obesity	Often	Not often	Diagnosed by exclusion	None
Hyperprolactinaemia or prolactinoma	None or mild	Yes	Galactorrhoea	Elevated plasma prolactin level
Non-classic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase	Yes	Not often	Family history of infertility, hirsutism, or both; common in Ashkenazi Jewish people	Elevated basal 17-hydroxyprogesterone level in the morning or on stimulation
Cushing's syndrome	Yes	Yes	Hypertension, striae, easy bruising	Elevated 24-hour urinary free cortisol level
Androgen-secreting tumour (virilizing adrenal or ovarian neoplasm)	Yes	Yes	Clitoromegaly, extreme hirsutism, or male pattern alopecia	Extremely elevated plasma androgen levels
Acromegaly	None or mild	Often	Enlargement of the extremities, coarse features, prognathism	Increased plasma insulin-like growth factor level
Primary hypothyroidism	None or mild	May be present	Goitre may be present	Elevated thyroid-stimulating hormone and subnormal plasma thyroxine levels. Prolactin level may also be increased
Premature ovarian failure	None	Yes	May be associated with other	Elevated plasma follicle-stimulating hormone and normal

			autoimmune endocrinopathies	or subnormal estradiol level
Drug-related conditions	Often	Variably	Evidence provided by drug history, for example use of androgens, sodium valproate, ciclosporins	None

Data from: [Ehrmann, 2005]

[Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Ehrmann, 2005; Aronson, 2006; Micromedex, 2009]

Polycystic ovary syndrome – Management

Scenario: Polycystic ovary syndrome

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Overview of management

- Encourage a healthy lifestyle to reduce possible long-term risks to health (Type 2 diabetes and cardiovascular disease). Emphasize that becoming overweight makes the condition worse.
- Offer screening for impaired glucose tolerance and Type 2 diabetes annually.
- Do not initiate treatment with insulin-sensitizing drugs in primary care.
  - Refer the woman if this treatment is being considered.
- Offer regular screening for cardiovascular risk factors.
  - Advise measures to reduce cardiovascular risk.
  - Refer the woman for specialist advice if glucose intolerance is present or if dyslipidaemia requires treatment.
- Ask about snoring and daytime fatigue/somnolence.
  - Refer for investigation and treatment if there are symptoms of obstructive sleep apnoea.
- For women who are overweight, advise weight loss.
- For women with oligomenorrhoea or amenorrhoea:
  - Induce a withdrawal bleed and then refer for ultrasonography to assess endometrial thickness.
  - If the endometrium fails to shed, endometrial thickening is present (greater than 10 mm), or the endometrium has an unusual appearance, refer for endometrial sampling to exclude endometrial hyperplasia or cancer.

- If the endometrium is of normal thickness, advise treatment to prevent endometrial hyperplasia. Offer women the choice of either regular withdrawal bleeding at least once every 3 months (using a combined oral contraceptive or cyclical progestogen) or the levonorgestrel intrauterine system.

- For women with hirsutism, offer advice about cosmetic measures and consider treatment with:

- A standard combined oral contraceptive or co-cyprindiol (Dianette®), *or*

- Topical eflornithine if hormonal treatment is contraindicated, ineffective, or inappropriate.

- For women with infertility:

- Carry out an assessment to identify the possible causes of infertility, which might not be due to polycystic ovary syndrome.

- Strongly advise the woman to lose weight, if appropriate.

- Consider referring to secondary care for fertility treatment.

- For women who are pregnant:

- Screen for gestational diabetes and impaired glucose tolerance with an oral glucose tolerance test before 20 weeks' gestation.

- Refer to a specialist obstetric diabetic service if abnormalities are detected.

- Be aware that there is an increased risk of pregnancy-induced hypertension, pre-eclampsia, and pre-term birth.

When should I screen for glucose intolerance?

- **Screen women with polycystic ovary syndrome (PCOS) annually for impaired glucose tolerance and Type 2 diabetes mellitus.**

- **Offer an initial oral glucose tolerance test** to all women presenting with PCOS.

- In women who have impaired glucose tolerance, offer an annual oral glucose tolerance test thereafter.

- **Also consider offering an annual glucose tolerance test to women at particular risk of Type 2 diabetes** because they have:

- A strong family history of diabetes.

- A body mass index greater than 30 kg/m^2 (or 25 kg/m^2 in Asian women).

- A history of gestational diabetes.

- **In all women not offered an annual glucose tolerance test, measure fasting glucose annually.**

- If the fasting glucose level is 5.6 mmol/L or greater, perform an oral glucose tolerance test.

- For information on how to treat Type 2 diabetes, see the CKS topic on Diabetes type 2.

Basis for recommendation

Association between Type 2 diabetes mellitus and polycystic ovary syndrome (PCOS)

- Prospective studies provide evidence that the prevalence of both Type 2 diabetes mellitus and impaired glucose tolerance is higher in women with PCOS than in age- and weight-matched women without PCOS.
- There is evidence from a non-systematic review and small case-control and cross-sectional studies that women with PCOS are more likely to have insulin resistance, and that this is more marked if the woman is obese.
- Good evidence from prospective cohort studies indicates that women with PCOS have an increased risk of developing Type 2 diabetes or impaired glucose tolerance in middle age. Obesity increases the risk of impaired glucose tolerance and diabetes [Legro, 2001].
- Limited evidence from a prospective study indicates that women who have had gestational diabetes mellitus are more likely to have PCOS.

Screening

- These recommendations are based on expert advice from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007], a position statement from the Androgen Excess Society [Salley et al, 2007], and the opinion of CKS expert reviewers.
- It is not known whether or how often women with PCOS should be screened for impaired glucose tolerance or Type 2 diabetes.
  - Three cohort studies provide evidence that fasting glucose levels alone are a poor predictor of impaired glucose tolerance and that a family history of diabetes in a first-degree relative may be significant. The evidence suggests that if a test is done, an oral glucose tolerance test is the most appropriate. However this is not always practical in primary care.
  - The Royal College of Obstetricians and Gynaecologists suggest an approach to screening that does not involve performing an oral glucose tolerance test on all women with PCOS; it recommends regular (perhaps annual) fasting glucose tests in all women with PCOS but performing an oral glucose tolerance test in women who have a body mass index (BMI) greater than 30 kg/m^2, a strong family history of Type 2 diabetes, or a fasting glucose level of 5.6 mmol/L or greater [RCOG, 2007].
  - The International Diabetes Federation suggests that if the fasting glucose level is greater than 5.6 mmol/L, an oral glucose tolerance test should be done [International Diabetes Federation, 2005].
  - A position statement from the Androgen Excess Society suggests that all women with PCOS should have an oral glucose tolerance test. Most members of the Androgen Excess Society Board suggest screening all women with PCOS at least every 2 years with an oral glucose tolerance test, or more frequently if additional risk factors are present. Women with impaired glucose tolerance should be screened annually for Type 2 diabetes. A few members of the Board suggested an oral glucose tolerance test only in women with a BMI of 30 kg/m^2 or in lean women with additional risk factors [Salley et al, 2007].
- Taking into account the practicalities of screening in primary care, these recommendations are based on:

- The position statement from the Androgen Excess Society that all women with PCOS should have an oral glucose tolerance test [Salley et al, 2007] and the opinion from some CKS expert reviewers that all women with PCOS should have an initial oral glucose tolerance test.

- The position statement from the Androgen Excess Society that all women with impaired glucose tolerance should be screened annually for Type 2 diabetes mellitus [Salley et al, 2007].

- The pragmatic recommendation from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007], and also from some CKS expert reviewers, of annual fasting glucose measurement for all women with PCOS.

- The suggestion from the Androgen Excess Society of doing oral glucose tolerance tests more frequently than once every 2 years in women at particular risk of Type 2 diabetes [Salley et al, 2007].

▪ CKS has also recommended considering women who have had gestational diabetes mellitus or Asian women with a BMI greater than 25 kg/m^2 to be at particular risk of Type 2 diabetes; CKS expert reviewers agreed with this suggestion.

Should I prescribe an insulin-sensitizing drug?

▪ **Do not initiate treatment with insulin-sensitizing drugs in primary care.**

- Insulin-sensitizing drugs may be initiated by a specialist.

- Insulin-sensitizing drugs are not licensed in the UK for the treatment of polycystic ovary syndrome, and the woman should be counselled before beginning treatment.

▪ There is no consensus on which women should be referred for consideration of insulin-sensitizing drugs. Some CKS expert reviewers recommend referring women with:

- Severe oligomenorrhoea or amenorrhoea.

- Impaired glucose tolerance or impaired fasting glucose.

- Hirsutism.

- Low sex hormone-binding globulin levels (as this is a surrogate marker for insulin resistance).

Additional information

▪ The potential for the long-term use of insulin-sensitizing drugs in women with polycystic ovary syndrome is of interest because hyperinsulinaemia is important in the development of hyperandrogenaemia and disrupted folliculogenesis. Metformin and other insulin-sensitizing drugs decrease insulin secretion and may restore normal endocrinological function, but evidence from good-quality randomized controlled trials is lacking to show they produce clinical benefits.

▪ Metformin is the most commonly used insulin-sensitizing drug and is the most extensively studied.

▪ Other insulin-sensitizing drugs include the thiazolidinediones, rosiglitazone and pioglitazone, which are currently being evaluated in randomized controlled trials [Harborne et al, 2003].

Basis for recommendation

- Guidelines from the Royal College of Obstetricians and Gynaecologists make the following points about the use of these drugs in women with polycystic ovary syndrome [RCOG, 2007]:

  - There is no evidence of long-term benefit.
  - Evidence suggests that metformin may have short-term effects on insulin resistance in women without diabetes.
  - Metformin may reduce androgen levels by about 11% compared with placebo.
  - Evidence regarding metformin and reduction in body weight is conflicting.
  - Women with a body mass index greater than 37 kg/m^2 may not respond to metformin.
  - No evidence supports the use of insulin-sensitizing drugs in the prevention of cardiovascular disease.
  - Evidence suggests that metformin is no better than diet and lifestyle at improving metabolic risk and progression to Type 2 diabetes.
  - There has been recent concern that myocardial infarction and death are increased in women with diabetes treated with rosiglitazone.
  - Metformin and the thiazolinediones are unlicensed for use in polycystic ovary syndrome.

- As there is uncertainty about the benefits and safety of insulin-sensitizing drugs, CKS recommends that they be initiated by a specialist.

- There is no expert consensus on which women should be referred for treatment with metformin.

How should I manage cardiovascular risk factors?

- **Explain that women with polycystic ovary syndrome (PCOS) appear to have more risk factors for, and may be at a higher risk of, cardiovascular disease compared with women of a similar weight who do not have PCOS.**

  - These risk factors include obesity, hyperandrogenism, hyperlipidaemia, and hyperinsulinaemia.
  - Despite this apparent increased risk, mortality and morbidity from cardiovascular disease is not as high as would be expected, although the incidence of stroke is slightly increased.

- **Screen regularly for cardiovascular risk factors.**

- **Calculate the cardiovascular risk score.**

  - For more information, see the CKS topic on CVD risk assessment and management.
  - Of note, conventional cardiovascular risk calculators have not been validated in women with PCOS.

- **Advise measures to reduce cardiovascular risk,** including:

  - Weight loss, if the woman is overweight or obese.
  - Diet.

- Exercise.

▪ Refer for specialist advice if glucose intolerance is present or if dyslipidaemia requires treatment.

Basis for recommendation

These recommendations are based on guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007].

Risk factors for cardiovascular disease

▪ Limited evidence from a non-systematic review, a small cross-sectional study, and a case-control study suggests that women with polycystic ovary syndrome (PCOS) have more risk factors for cardiovascular disease than other women of the same age. In particular, they may have central obesity, hypertriglyceridaemia, and reduced high-density lipoprotein (HDL) cholesterol levels.

- There is evidence from a non-systematic review and case-control studies that women with PCOS frequently have abnormal lipid profiles, with increased triglyceride and total and low-density lipoprotein cholesterol levels. However the effect of PCOS on HDL cholesterol is controversial [RCOG, 2007].

- A systematic review found that evidence linking PCOS and hypertension was conflicting.

- Central obesity is observed in 35–60% of women with PCOS [Balen and Glass, 2005].

- Hyperandrogenism is associated with a preponderance of fat localized to truncal abdominal sites, and women with PCOS have greater truncal abdominal fat distribution (demonstrated by a higher waist-to-hip ratio).

- This central distribution of fat is independent of body mass index and is associated with higher plasma insulin and triglyceride concentrations and lower HDL cholesterol concentrations.

- Limited evidence from a small cross-sectional study indicates that women with PCOS have elevated concentrations of plasminogen activator inhibitor 1, which is a potent inhibitor of fibrinolysis, and has been linked to insulin resistance and an increased risk of thrombotic vascular events [Hopkinson et al, 1998; Kelly et al, 2000].

- Hyperhomocysteinaemia is a recognized risk factor for atherosclerosis. Limited evidence from a small case-control study suggests that plasma homocysteine levels are higher in women with PCOS than in an ethnically matched control group.

Risk of cardiovascular disease

▪ It is not known whether women with PCOS are at greater risk of cardiovascular disease.

- Limited evidence from epidemiological studies shows that morbidity and mortality from coronary heart disease in middle-aged women with a history of PCOS is not as high as predicted, despite their increased cardiovascular risk factors [Wild, 2002b; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004].

- However, the cohorts of women studied so far have been relatively young (around 55 years) [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004].

- Unknown factors in PCOS may protect the heart despite the presence of other risk factors [Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004].

- Limited evidence suggests an increased risk of stroke.

- It is not clear whether PCOS is an independent risk factor for cardiovascular disease [Wild, 2002b].

Recommendations for screening for cardiovascular risk factors

- At present, it is unclear which women should be screened for cardiovascular risk and when this should occur. These recommendations are based on expert opinion and consensus.

- Guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007] suggest that it is prudent to screen women with PCOS for cardiovascular risk factors.

- It has been suggested that only women 35 years of age or older with PCOS should be screened [Lobo and Carmina, 2000] because abnormal lipid levels in younger women usually do not require treatment [Harborne et al, 2003].

Recommendations for treatment

- Although women with PCOS are more likely to have abnormal lipid profiles, which may put them at higher risk of cardiovascular disease, it is not known whether modifying the risk factors in women with PCOS reduces cardiovascular events. No studies have been sufficiently powered to assess the effects of preventive therapy on cardiovascular morbidity and mortality in women with PCOS [Wild, 2002b].

- Although conventional cardiovascular risk calculators have not been validated in women with PCOS, guidelines from the Royal College of Obstetricians and Gynaecologists recommend that clinicians should continue to identify cardiovascular risk factors in women with PCOS and treat them according to current guidance [RCOG, 2007].

- CKS recommends that, in view of the possible increased risk of cardiovascular events, clinicians should give advice on measures to reduce cardiovascular risk.

How should I manage sleep apnoea?

- Ask about snoring and daytime fatigue or somnolence.

- Offer referral for investigation and treatment if obstructive sleep apnoea is suspected.

Basis for recommendation

- Guidelines from the Royal College of Obstetricians and Gynaecologists recommend asking all women with polycystic ovary syndrome whether they have symptoms of obstructive sleep apnoea [RCOG, 2007].

- Limited evidence from observational studies indicates that obstructive sleep apnoea is more prevalent in women with polycystic ovary syndrome than can be explained by obesity alone.

How should I manage women who are overweight?

- Advise the woman if she is overweight that the most effective treatment is to lose weight, and encourage her to do this.
- Explain that weight loss may reduce hyperinsulinism and hyperandrogenism and:
  - Reduce the risk of Type 2 diabetes and cardiovascular disease.
  - Result in menstrual regularity.
  - Improve the chance of pregnancy, if that is what she wants.
- Consider referral to a dietitian.
- Consider offering orlistat or sibutramine to assist with weight loss. For further information, see the CKS topic on Obesity.
- Consider bariatric surgery (gastric bypass or banding) in women who are morbidly obese (body mass index greater than 40 kg/m^2).

Basis for recommendation

Advise weight loss if appropriate

- It is estimated that 40–50% of women with polycystic ovary syndrome (PCOS) are obese [Lobo and Carmina, 2000]. Obesity worsens insulin resistance and increases the risk of Type 2 diabetes and cardiovascular disease. Unfortunately, weight loss is difficult to achieve.
- Weight gain is associated with worsening of symptoms, whereas weight loss may improve the endocrine and metabolic profile [Balen, 2000].
  - Limited evidence from small randomized controlled trials and a within-group comparison study suggests that even moderate weight loss can lead to an improvement in hyperinsulinism and hyperandrogenism.
  - Good evidence from a Cochrane systematic review and small prospective studies suggests that weight reduction in infertile obese women with PCOS improves ovulation and the chances of pregnancy.
  - Expert opinion from a textbook is that if more than 5% of body weight can be lost, there is an excellent chance of restoring menstrual regularity, and an increased incidence of pregnancies has been reported [Balen and Glass, 2005].

Use of orlistat and sibutramine

- Guidelines from the Royal College of Obstetricians and Gynaecologists recommend the use of either of these drugs, as they may reduce body weight and hyperandrogenism in women with PCOS [RCOG, 2007].
- Very limited evidence from a small randomized controlled trial and two small prospective studies suggests that orlistat and sibutramine may reduce body weight and hyperandrogenism in women with PCOS.

Use of bariatric surgery

▪ This intervention is suggested in guidelines from the Royal College of Obstetricians and Gynaecologists for selected women with morbid obesity [RCOG, 2007]. A small prospective non-randomized study followed up 12 of an original cohort of 17 women with PCOS and morbid obesity who had undergone bariatric surgery. The mean weight loss was 41 +/– 9 kg, and menstrual cycle regularity was restored in all 12 women. In one woman, diabetes and dyslipidaemia resolved, and in another woman, the diabetes reverted to glucose intolerance. However, one of the women undergoing bariatric surgery died of post-operative complications [Escobar-Morreale et al, 2005].

How should I manage oligomenorrhoea or amenorrhoea?

▪ **Rule out other causes of oligomenorrhoea or amenorrhoea.** For more information, see the CKS topic on Amenorrhoea.

▪ **Induce a withdrawal bleed, and then refer for ultrasonography to assess endometrial thickness.**

o **If the endometrium fails to shed, endometrial thickening is present (greater than 10 mm), or the endometrium has an unusual appearance,** refer for endometrial sampling to exclude endometrial hyperplasia or cancer.

o **If the endometrium is of normal thickness, advise treatment to prevent endometrial hyperplasia.** The choice of treatment depends on whether the woman wishes to have regular withdrawal bleeds (at least once very 3 months) and whether she has acne or hirsutism. Options include:

o Combined oral contraceptive. For prescribing information, see the CKS topic on Contraception.

o A cyclical progestogen, such as medroxyprogesterone 10 mg daily for 14 days, every 1–3 months.

o The levonorgestrel-releasing intrauterine system (LNG-IUS). For prescribing information, see the CKS topic on Contraception.

▪ **If the woman is unwilling to take cyclical hormone treatment or use the LNG-IUS, seek specialist advice or refer.** Regular ultrasonography is likely to be required (every 6–12 months) to assess endometrial thickness and morphology.

▪ **Encourage the woman to lose weight** if appropriate, as this alone may restore menstrual regularity.

▪ **Osteoporosis prophylaxis is unnecessary** for women with polycystic ovary syndrome who are amenorrhoeic, as they are not oestrogen deficient.

Basis for recommendation

Encourage weight loss

▪ This recommendation is based on expert advice in a non-systematic review [Balen and Anderson, 2007].

▪ If more than 5% of body weight can be lost, there is an excellent chance of restoring menstrual regularity [Balen and Anderson, 2007].

Risk of endometrial cancer

▪ Severe oligomenorrhoea and amenorrhoea in the presence of premenopausal levels of oestrogen can lead to endometrial hyperplasia, which in some women could develop into endometrial cancer [RCOG, 2007]. Inter-menstrual intervals of more than 3 months may be associated with endometrial hyperplasia [RCOG, 2007].

▪ **The true risk of endometrial cancer in women with polycystic ovary syndrome (PCOS) is unknown.** Studies are small or have been done on women with infertility, including those with causes of infertility other than PCOS [Balen, 2001]. Other studies have been uncontrolled, and their interpretation is complicated by the variety of diagnostic criteria used to define the syndrome [Hardiman et al, 2003]. There are anecdotal reports of endometrial cancer developing in teenagers with amenorrhoea [Wild, 2002a].

▪ Endometrial cancer has a mean age of occurrence of 61 years in the UK. Cases in women younger than 35 years of age are exceptionally rare and usually occur when anovulation is secondary to PCOS or oestrogen-secreting tumours [Balen, 2000].

Induce withdrawal bleeding and then refer for ultrasonography to assess endometrial thickness

▪ These recommendations are based on expert opinion in a review article [Balen, 2000] and advice from CKS expert reviewers.

Prescribe treatment to induce withdrawal bleeding

▪ These recommendations are based on guidance from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007] and expert opinion in a review article [Hardiman et al, 2003].

o Although evidence is lacking about the risk of endometrial cancer in women with oligomenorrhoea or amenorrhoea, expert opinion is that there is little option other than to advise women to take treatment to induce regular bleeding, at least every 3 months [RCOG, 2007].

o Another option is a progestogen-secreting intrauterine system, such as the levonorgestrel-releasing intrauterine system [Balen and Glass, 2005].

o Cyclical progestogen treatment using less-androgenic progestogens, such as medroxyprogesterone acetate, can be used to induce withdrawal bleeding [Balen, 2000]. However, evidence is lacking about the optimal progestogen, dosage, or treatment regimen [Hardiman et al, 2003]. Guidelines from the Royal College of Obstetricians and Gynaecologists recommend at least a 12-day course of progestogens each month. Medroxyprogesterone is recommended because it is licensed for endometrial protection from oestrogenic hormone replacement therapy as a 14-day course within each 28-day oestrogen hormone replacement therapy cycle.

Women unwilling to take cyclical hormone treatment

- These recommendations are based on expert advice in a non-systematic review [Balen, 2001].

Women who are amenorrhoeic do not need osteoporosis prophylaxis

- **Women with PCOS have some ovarian activity [Crosignani and Vegetti, 1996].** Follicular development and oestrogen production continue but are arrested at some stage short of full maturation of an ovulatory follicle. Therefore, although these women are anovulatory, they do not show signs of oestrogen deficiency [Baird, 1997].

o A small case-controlled study of 45 adolescent women with amenorrhoea or oligomenorrhoea (14 had polycystic ovaries) matched with 45 women with regular menstruation found that, although overall the women with amenorrhoea or oligomenorrhoea had lower bone mineral density than those with regular menstruation, those with polycystic ovaries had a bone mineral density similar to that of the control group [To and Wong, 2005].

o A subgroup of 51 women with PCOS in a case-controlled study found that amenorrhoeic women with PCOS had only a marginal decrease in bone mass. Bone protection was thought to be due to adequate oestrogen production and overproduction of androgenic steroids [Adami et al, 1998].

How should I treat hirsutism?

- **Rule out other causes of hirsutism.**

o Measure serum testosterone and seek specialist advice if the level is greater than 5 nanomol/L (see Diagnostic investigations).

- **Advise the woman to lose weight,** if appropriate.

- **Advise about cosmetic measures.**

o Mild hirsutism can usually be managed by cosmetic measures alone.

o For more severe hirsutism, drug treatment may be required in addition to cosmetic measures.

- **If additional treatment is required,** offer co-cyprindiol (Dianette®) or a combined oral contraceptive (COC) containing drospirenone (for example Yasmin®).

o Co-cyprindiol (Dianette®; a combination of ethinylestradiol and the anti-androgen cyproterone acetate) is licensed for the treatment of moderately-severe hirsutism but should be stopped three or four menstrual cycles after the woman's hirsutism has completely resolved because of an increased risk of venous thromboembolism.

o Yasmin® (a combination of ethinylestradiol and drospirenone) is not licensed specifically for hirsutism but is an alternative to co-cyprindiol for women who require long-term treatment. Yasmin® is more expensive than co-cyprindiol.

o See the CKS topic on Contraception for a full discussion of the risks of COCs.

▪ **Advise the woman that hirsutism may take 6–9 months (or longer) to improve on hormonal treatment.**

o Co-cyprindiol should be stopped three or four menstrual cycles after the woman's hirsutism has resolved (on advice from the Committee on Safety of Medicines). Other COCs can be continued indefinitely.

o Relapse is likely once treatment with co-cyprindiol is stopped. Options include:

o Intermittent use of co-cyprindiol — stopping treatment after resolution occurs, and starting again if symptoms reappear (licensed use).

o Switching to a COC containing drospirenone (Yasmin®).

o Some experts recommend continuing treatment with co-cyprindiol if the above measures fail. This may be the best option for otherwise healthy young women, as hirsutism causes considerable distress.

▪ **Consider offering topical eflornithine** for facial hirsutism if hormonal treatment is contraindicated, ineffective, or inappropriate.

o The cream should be applied thinly twice a day. Advise the woman that transient stinging may occur, that she must wait at least 5 minutes before applying any makeup, and that eflornithine cream can sometimes cause acne.

o Benefit may be noticed after 8 weeks.

o Relapse is rapid once treatment is stopped. However, there are no safety data on long-term use.

▪ **Refer the woman if:**

o Excess hair growth is particularly severe.

o Hair growth is of recent onset and rapidly progressive.

o A COC, co-cyprindiol, or topical eflornithine combined with cosmetic measures is not adequate (as there are further options for treatment available in secondary care).

Additional information

Cosmetic measures

▪ Cosmetic treatment is not usually available on the NHS.

▪ Cosmetic procedures that can be applied in a domestic setting are not generally recommended, especially in more severe hirsutism, as their effect is only temporary [Archer and Chang, 2004; Moghetti and Toscano, 2006].

o Shaving does not increase the rate of hair growth or thicken hair, contrary to popular belief. It is a useful technique and yields instant results. However, it does leave stubble that is unpleasant, unsightly, and sharp, and it may irritate the skin.

o Waxing and plucking are effective, but can be painful and may cause scarring, folliculitis, and hyperpigmentation. These techniques can also lead to resistance to electrolysis.

o Bleaching can improve appearance in the short term, but may also lead to skin irritation.

o Skin irritation is problematic, as it is itchy and unsightly and, paradoxically, can lead to increased hair growth.

▪ Cosmetic procedures carried out in specialist clinics tend to have a longer effect, although they are not usually permanent [Archer and Chang, 2004]:

o Electrolysis uses a localized electric charge to destroy hair cells at the bulb. It is effective, but is time-consuming and painful, and it may leave scars or cause pigmentation changes.

o Lasers are used selectively in the process of photothermolysis, a more recent technique that generally yields better results than electrolysis [Balen, 2000]. It affects hair only in the growing phase and thus must be repeated over several months. A woman with dark hair and light skin is the ideal candidate [Balen et al, 2005].

Secondary care treatments

▪ Systemic treatments that may be used in secondary care include:

o Anti-androgens (such as high-dose cyproterone acetate, spironolactone, and flutamide).

o 5-alpha-reductase inhibitors (such as finasteride).

o Insulin-sensitizing drugs (such as metformin and the glitazones [pioglitazone and rosiglitazone]).

o Gonadotrophin-releasing hormone analogues (such as goserelin and leuprorelin).

Basis for recommendation

These recommendation are based on advice in guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007], a non-systematic review [Koulouri and Conway, 2009], a textbook [Balen et al, 2005], and guidelines from the Endocrine Society (US) [Endocrine Society, 2008].

Causes of hirsutism

▪ The most common underlying causes for hirsutism are polycystic ovary syndrome (PCOS) or idiopathic hirsutism [Koulouri and Conway, 2009].

▪ Hirsutism is present in 60–80% of women with PCOS [Archer and Chang, 2004].

▪ Other causes of hirsutism are rare and include late-onset congenital adrenal hyperplasia, androgen-secreting tumours (ovarian or adrenal), Cushing's syndrome, acromegaly, or drugs.

Test for elevated androgens

▪ This recommendation is based on guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007].

Advise weight loss if the woman is obese

▪ Good evidence from a systematic review suggests that obesity negatively influences treatment for hirsutism.

Cosmetic measures

▪ Cosmetic measures may be helpful because drug treatments may take 6–9 months or longer before any improvement is noticed [Balen et al, 2005].

▪ Limited evidence from a Cochrane systematic review suggests that some laser and photoepilation treatments may lead to temporary short-term hair removal.

Treatment of hirsutism

▪ As hirsutism is caused by excess circulating androgenic hormones, it can be treated with anti-androgenic agents. Other topical and systemic drugs can also be used to treat the specific symptoms. The principal treatment for hirsutism caused by PCOS is to reduce or block the effect of circulating androgenic hormones.

Choice of hormonal treatment

▪ Oestrogen and progestins suppress gonadotrophin secretion from the pituitary, resulting in decreased androgenic hormones. In addition, oestrogen increases sex hormone-binding globulin levels, which results in decreased free testosterone levels. Progestins can act as an androgen antagonist.

▪ Combined oral contraceptives (COCs) may be used to reduce ovarian androgen production and treat hyperandrogenism. Some COCs may be more effective than others because of their progestogen content (although there is little direct evidence to support this idea) [Archer and Chang, 2004]. No specific COC has been shown to be superior in treating hirsutism in PCOS, and the best COC for women with PCOS is unknown [Balen et al, 2005].

▪ The rationale for using COCs to treat the symptoms of PCOS remains controversial. Whilst treatment is undoubtedly of benefit for many symptoms, there is some concern that use of COCs may negatively affect insulin resistance, glucose tolerance, vascular reactivity, and blood coagulation [Ehrmann, 2005].

▪ CKS expert reviewers recommend co-cyprindiol (Dianette®) or a COC containing drospirenone as the preferred COCs for women with hirsutism.

o Co-cyprindiol contains the anti-androgen cyproterone acetate.

o Cyproterone acetate inhibits 5-alpha reductase activity, increases sex hormone-binding globulin levels, and has significant anti-gonadotrophin effects.

o There is limited evidence from a Cochrane systematic review that suggests that co-cyprindiol is more effective than placebo for treating hirsutism.

o Co-cyprindiol is licensed for the treatment of moderately-severe hirsutism [ABPI Medicines Compendium, 2008].

o Drospirenone also has anti-androgenic properties [Martin et al, 2008].

o COCs containing drospirenone (such as Yasmin®) may be an alternative to co-cyprindiol in women with hirsutism, especially as long-term treatment is often necessary.

o There is conflicting poor quality evidence for its use in women with PCOS.

▪ CKS expert reviewers did not recommend second generation COCs (containing levonorgestrel and norethisterone) and third generation COCs (containing desogestrel, norgestimate, and gestodene) for the management of hirsutism.

o COCs containing levonorgestrel and norethisterone are more androgenic and could potentially exacerbate hirsutism [Koulouri and Conway, 2009].

o There is some concern that COCs containing desogestrel, norgestimate, and gestodene may have a greater risk of venous thromboembolism than those containing drospirenone, levonorgestrel, or norethisterone, although the absolute risk is is still low (about 25 per 100,000 women per year of use) [BNF 57, 2009].

Treatment of relapse when co-cyprindiol is stopped

▪ The advice on whether to continue to use co-cyprindiol continuously or intermittently, or to switch to an alternative COC, is advice based on the opinions of CKS expert reviewers.

Onset of improvement with drug treatment

▪ An individual hair follicle takes months to pass through the anagen (active growing), catagen (involutional), and telogen (resting) phases. All systemic treatments for hirsutism reduce stimulation of the anagen growth phase by testosterone, but enough follicles must enter the anagen phase before a clinical effect is noticeable [Koulouri and Conway, 2009].

Length of hormonal treatment

▪ **Co-cyprindiol (Dianette®)** may take 6 months or longer to produce an improvement in hirsutism, so advise the woman to be patient during this period [Balen et al, 2005; Butts and Driscoll, 2006].

▪ The Committee on Safety of Medicines has recommended that co-cyprindiol should be discontinued three or four menstrual cycles after the woman's acne or hirsutism has resolved, owing to the risk of serious adverse effects, such as thromboembolism [CSM, 2002].

o There is a two- to four-fold increase in the risk of venous thromboembolism with co-cyprindiol compared with conventional second-generation COCs, although the absolute risk remains low [Vasilakis-Scaramozza and Jick, 2001; Seaman et al, 2003].

▪ The recommendation to continue to use co-cyprindiol continuously or intermittently, or to switch to an alternative COC, is pragmatic advice from CKS.

Eflornithine

▪ **Eflornithine** is an irreversible inhibitor of ornithine decarboxylase, an essential enzyme involved in the production of hair [Moghetti et al, 2000]. Inhibition of this enzyme reduces hair growth.

o Limited evidence from randomized controlled trials suggests that it is effective at reducing hirsutism, although this effect is rapidly reversed after stopping treatment [Moghetti and Toscano, 2006].

o No data are available on the long-term safety of eflornithine [Butts and Driscoll, 2006].

o The advice to consider prescribing topical eflornithine for women in whom standard treatment is ineffective, contraindicated, or considered inappropriate is consistent with the restricted use advice given by the Scottish Medicines Consortium [Scottish Medicines Consortium, 2005].

▪ Limited evidence from a Cochrane systematic review suggests that some laser and photoepilation treatments may lead to temporary short-term hair removal.

Treatments available in secondary care

▪ Weak evidence from systematic reviews suggests that spironolactone and other anti-androgens are effective in the treatment of hirsutism.

▪ Spironolactone has moderate anti-androgenic effects. It is not licensed in the UK for the treatment of hirsutism.

Referral

▪ These recommendations are based on expert advice in a review article [Koulouri and Conway, 2009].

How should I treat acne?

▪ **For women with polycystic ovary syndrome and acne, consider using a hormonal contraceptive** instead of, or in addition to, topical treatment for acne.

o Offer either a standard combined oral contraceptive or co-cyprindiol (Dianette®), as for the treatment of hirsutism.

▪ For further information on treatments for acne and when to refer women with acne, see the CKS topic on Acne vulgaris.

▪ For information on contraindications, cautions, management of adverse effects, and interactions with combined oral contraceptives, see the CKS topic on Contraception.

Basis for recommendation

Use of a hormonal contraceptive

▪ A Cochrane systematic review provides evidence that combined oral contraceptives (COCs) are effective in the treatment of acne vulgaris. In general, the efficacy of COCs in treating acne vulgaris is independent of the particular oestrogen or progestogen component used; however, evidence suggests that the addition of cyproterone acetate as the progestogen component may further increase effectiveness.

▪ In most women, the safety profile of COCs is good, and they have additional benefits for women who require contraception.

▪ **Carry out an assessment** to identify the possible causes of infertility, which might not be due to polycystic ovary syndrome (PCOS).

o Carry out the initial investigations on the couple rather than the individual. For further information, see the CKS topic on Infertility.

▪ **Consider referral for fertility treatment.**

o The decision to refer should always be based on the couple's concerns and preferences.

o Some women may wish to try lifestyle measures, including weight loss, before referral.

o Such factors as age may prompt earlier referral.

▪ **Advise the couple to adopt a healthy lifestyle** (if they are not already doing so). In particular, advise the woman to eat healthily and do regular exercise.

▪ **Strongly advise the woman to lose weight, if appropriate.**

o Women with a body mass index greater than 29 kg/m^2 are likely to take longer to conceive.

o Women with a body mass index greater than 29 kg/m^2 who are not ovulating should be informed that losing weight is likely to increase their chance of conception.

o Consider referral to a dietitian.

o Inform the woman that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone.

o If the woman is being referred for anti-oestrogen treatment and is obese, explain that obesity is likely to inhibit the response to treatment.

Basis for recommendation

These recommendations are based on advice from the National Institute for Health and Clinical Excellence for obese women in general, including those with polycystic ovary syndrome (PCOS) [National Collaborating Centre for Women's and Children's Health, 2004].

Weight loss

▪ Lifestyle modification through sensible eating and exercise may improve insulin sensitivity and restore ovulation, even though minimal weight loss is achieved [Balen et al, 2006; Balen and Anderson, 2007].

▪ Good evidence from a Cochrane systematic review suggests that weight reduction in infertile obese women with PCOS improves ovulation and the chances of pregnancy.

▪ Most women with PCOS will ovulate in response to clomifene citrate. An increased body mass index is the only factor which is consistently associated with a decreased response to clomifene citrate. Therefore,

weight reduction is also an important part of treatment for anovulatory women who are considering treatment with anti-oestrogens [Kousta et al, 1997].

What treatments are available for infertility in secondary care?

▪ **Clomifene citrate remains the first-line treatment to induce ovulation in women with polycystic ovary syndrome (PCOS).**

o GPs should prescribe clomifene citrate only as part of a formal shared-care agreement between primary and secondary care.

o The National Institute for Health and Clinical Excellence (NICE) recommends that:

o Women with PCOS should be offered clomifene citrate or tamoxifen as first-line treatment for up to 12 months, because it is likely to induce ovulation.

o Women should be informed of the risk of multiple pregnancies associated with both clomifene citrate and tamoxifen.

o Women undergoing treatment with clomifene citrate should be offered ultrasonographic monitoring during at least the first cycle of treatment, to ensure that they receive a dose that minimizes the risk of multiple pregnancy.

o Women with PCOS who ovulate with clomifene citrate but have not become pregnant after 6 months of treatment should be offered clomifene citrate-stimulated intrauterine insemination.

▪ NICE recommends that women with PCOS who have not responded to clomifene citrate should be offered treatment with gonadotrophins or laparoscopic ovarian drilling.

▪ **Laparoscopic ovarian drilling** is not associated with an increased risk of multiple pregnancy, but it takes longer to achieve pregnancy compared with treatment with gonadotropins.

▪ **Gonadotrophins** are ovulation induction agents and may be recommended for some women with PCOS who have not responded to clomifene citrate. They should always be prescribed under specialist supervision, as careful monitoring is required to reduce the risk of multiple pregnancy.

o Human menopausal gonadotrophin is a purified extract from human postmenopausal urine. It contains both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

o FSH alone is either derived from human menopausal urine or as a recombinant peptide produced by cultured cells.

o NICE recommends that:

o Women with PCOS who do not ovulate with clomifene citrate (or tamoxifen) can be offered treatment with gonadotrophins. Human menopausal gonadotrophin, urinary FSH, and recombinant FSH are all equally effective in achieving pregnancy.

o Women with PCOS who are being offered treatment with gonadotrophins should not be offered concomitant treatment with a gonadotrophin-releasing hormone agonist, because it does not improve pregnancy rates and there is a higher risk of ovarian hyperstimulation syndrome.

- **Metformin is no longer recommended** for the routine management of anovulatory PCOS.

Basis for recommendation

Clomifene citrate

These recommendations are based on guidelines from the National Institute for Health and Clinical Excellence for people with fertility problems [NICE, 2004] and a review article [Balen and Rutherford, 2007].

- Anti-oestrogens, such as clomifene citrate and tamoxifen, occupy hypothalamic oestrogen receptors but do not activate them. This interferes with the binding of estradiol and thus prevents negative feedback inhibition of follicle-stimulating hormone secretion.

- Randomized controlled trials provide evidence from randomized controlled trials that clomifene citrate is effective at increasing pregnancy rates.

- Women may benefit from receiving clomifene citrate in up to 12 cycles, as cumulative pregnancy rates continue to increase after six treatment cycles before reaching a plateau similar to that of the normal fertile population by cycle 12. Alternative treatments should be considered after 12 cycles if results are poor [National Collaborating Centre for Women's and Children's Health, 2004]. This is because evidence suggests that the use of clomifene citrate for more than 12 cycles is associated with an increased risk of ovarian cancer.

Ovarian hyperstimulation syndrome (OHSS)

- Mainly retrospective and prospective studies provide evidence that women with polycystic ovary syndrome (PCOS) are at increased risk of developing OHSS. This is characterized by massive enlargement of the ovaries and ascites, that can lead to rapid and symptomatic enlargement of the abdomen, intravascular contraction, hypercoagulability, and systemic organ dysfunction [Legro, 2001].

- OHSS has been reported rarely in women who have taken clomifene citrate [Brown et al, 2005].

Laparoscopic ovarian drilling (LOD)

- There is evidence that LOD is less likely than gonadotrophin therapy to result in multiple pregnancies in the management of clomifene-resistant PCOS. However, LOD is effective in less than 50% of women, who then need to be treated with additional ovulation induction.

- LOD is recommended as a second-line option if ovulation induction with clomifene citrate has failed [Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008].

- The aim of surgery is to destroy ovarian androgen-producing tissue [Farquhar et al, 2007].

o Intraovarian androgen production decreases, which results in a decreased circulating androgen concentration. A reduction in total and free testosterone by 40–50% after LOD has been found [Pirwany and Tulandi, 2003].

o The destruction of the ovarian stroma seems to have an indirect modulating effect on the pituitary gland. Luteinizing hormone concentrations decrease and follicle-stimulating hormone concentrations tend to increase, thus restoring the normal luteinizing hormone/follicle-stimulating hormone ratio. This leads to recruitment of a new set of follicles and resumption of normal ovarian function [Pirwany and Tulandi, 2003].

o These endocrine changes occur rapidly after surgery and are sustained for several years [Pirwany and Tulandi, 2003]. However, there is ongoing concern about the long-term effects of LOD [Farquhar et al, 2007].

▪ During LOD, either laparoscopic ovarian cautery or laser vaporization (using CO_2, argon or Nd:YAG lasers) is used to create multiple perforations (about 10 holes per ovary) in the ovarian surface and stroma. The procedure can be done on a day-case basis. There is a risk of peri-adnexal adhesions, and LOD should only be offered as a second-line treatment for clomifene citrate-resistant anovulatory women [Pirwany and Tulandi, 2003; Farquhar et al, 2007].

▪ Ovarian wedge resection is no longer recommended. This was the first established surgical treatment for PCOS and has been used for years but is now obsolete because of the risk of post-surgical adhesions and the introduction of medical ovulation induction [Farquhar et al, 2007].

Gonadotrophins

▪ There is evidence that gonadotrophins are effective in inducing ovulation in anovulatory women with PCOS who have not responded to clomifene citrate.

▪ Gonadotropins require careful monitoring to reduce the risk of multiple pregnancy, and low-dose regimens are now used to prevent overstimulation and multiple pregnancies [Balen and Rutherford, 2007].

▪ Gonadotrophins are recommended as a second-line option if ovulation induction with clomifene citrate has failed [Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008].

Multiple pregnancy

▪ Women with PCOS are at increased risk of multiple pregnancy with both clomifene citrate and human menopausal gonadotrophin treatment [Balen and Rutherford, 2007].

Metformin

▪ A Cochrane systematic review found no evidence that metformin improves live birth rates when used alone or in combination with clomifene citrate.

▪ Expert opinion in a consensus workshop [Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008] and a non-systematic review [Balen and Rutherford, 2007] is that metformin is no longer recommended as first-line treatment in infertile women with PCOS. Its use should be restricted to women with glucose intolerance [Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008].

How do I manage a woman who has PCOS and is pregnant?

▪ Screen all women with known polycystic ovary syndrome (PCOS) before 20 weeks' gestation, for gestational diabetes and impaired glucose tolerance, with an oral glucose tolerance test.

▪ Refer the woman to a specialist obstetric diabetic service if abnormalities are detected.

▪ Be aware that:

o The risks of pregnancy-induced hypertension, pre-eclampsia, and pre-term birth are increased.

o Women with PCOS have a higher rate of spontaneous miscarriage after assisted reproduction.

▪ Consider whether any changes to drug treatment should be made. For example:

o Metformin is not recommended in pregnancy. Seek specialist advice.

o Any hormonal treatment (such as medroxyprogesterone for inducing cyclical bleeding) should be stopped.

o Eflornithine cream (for hirsutism) is contraindicated in pregnancy.

Basis for recommendation

Screening for gestational diabetes

▪ These recommendations are based on guidance from the Royal College of Obstetricians and Gynaecologists. Good evidence from a meta-analysis suggests that women with PCOS have an increased risk of gestational diabetes mellitus.

Pregnancy complications

▪ Good evidence from a meta-analysis suggests that women with PCOS have an increased risk of pregnancy-induced hypertension, pre-eclampsia, and pre-term birth, and that the baby is at increased risk of neonatal complications.

Spontaneous miscarriage after assisted reproduction

▪ There is evidence that women with PCOS have a higher rate of spontaneous miscarriage after assisted reproduction.

Use of metformin

▪ The use of metformin in pregnancy is not recommended in guidelines from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007] until further randomized prospective trials are available to provide adequate evidence of safety and efficacy.

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Anti-androgen and oestrogen (co-cyprindiol)

Age from 14 to 50 years

Cyproterone acetate 2mg + ethinylestradiol 35micrograms

Co-cyprindiol 2000microgram/35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 14 years to 50 years
NHS cost: £3.92
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

COCs monophasic: EE 30mcg plus drospirenone

Age from 13 to 50 years

Yasmin: drospirenone 3mg + ethinylestradiol 30mcg

Yasmin tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £14.70
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a healthcare professional.

Eflornithine cream

Age from 12 years onwards

Eflornithine 11.5% cream: apply twice a day

Eflornithine 11.5% cream
Apply thinly to the affected area(s) twice a day.
Supply 60 grams.

Age: from 12 years onwards
NHS cost: £52.08
Licensed use: yes

Patient information: This cream must be rubbed in thoroughly. Wait 5 minutes after applying this cream before applying any makeup. Do not wash your face for 4 hours after applying this cream.

Medroxyprogesterone (to induce withdrawal bleeds)

Age from 16 years onwards

Medroxyprogesterone tablets: 10mg once a day for 14 days

Medroxyprogesterone 10mg tablets
Every one to three months, take one tablet once a day for 14 days.
Supply 42 tablets.

Age: from 16 years onwards
NHS cost: £10.37
Licensed use: no - off-label dose

Levonorgestrel-releasing intrauterine system

Age from 13 to 60 years

Levonorgestrel 20mcg/24hrs intra-uterine system (Mirena®)

Levonorgestrel 20micrograms/24hours intrauterine system
For insertion into the uterine cavity.
Supply 1 device.

Age: from 13 years to 60 years
NHS cost: £83.16
Licensed use: yes

Patient information: You may experience irregular bleeding for about 6 months after insertion of the device. Seek medical advice if this persists.