Lothian Guideline for the Diagnosis of Polycystic Ovary Syndrome (PCOS) in Primary Care

Summary

A diagnosis of PCOS requires at least 2 of the following 3 criteria:-

- Oligomenorrhoea or amenorrhoea
- Clinical and / or biochemical signs of excessive androgen secretion, ie hirsutism, acne, raised total testosterone or a raised Free Androgen Index (FAI). *Although raised LH, with a normal FSH, may be found in PCOS, gonadotrophin results no longer form part of the diagnostic criteria.*
- Presence of at least 12 follicles measuring 2-9 mm in diameter, an ovarian volume > 10ml, or both.

Lothian guidance is that a scan for suspected PCOS is not required unless there are other indications eg pelvic symptoms. THEREFORE THE DIAGNOSIS IS PRIMARILY MADE ON CLINICAL AND BIOCHEMICAL FEATURES.

Other possible causes of presenting features should be considered and excluded: congenital adrenal hyperplasia, androgen secreting tumour, Cushing's syndrome, thyroid dysfunction, hyperprolactinaemia and perimenopause etc

Laboratory investigation of patients with suspected PCOS

Sample Timing

Unless the patient is amenorrhoeic, the sample should be taken on days 1-5 of the menstrual cycle (since misleading increases in testosterone may occur later in the cycle).

Clinical details

- State the LMP
- If there is amenorrhoea, state this on the request form. *In cases of amenorrhoea, with a raised testosterone, the laboratory will add an estradiol (E2) measurement to try to establish if sampling is within the (preferred) early follicular phase.*
- Provide clinical details eg hirsutism, irregular periods etc: crucial if the laboratory is to add additional tests - see below.

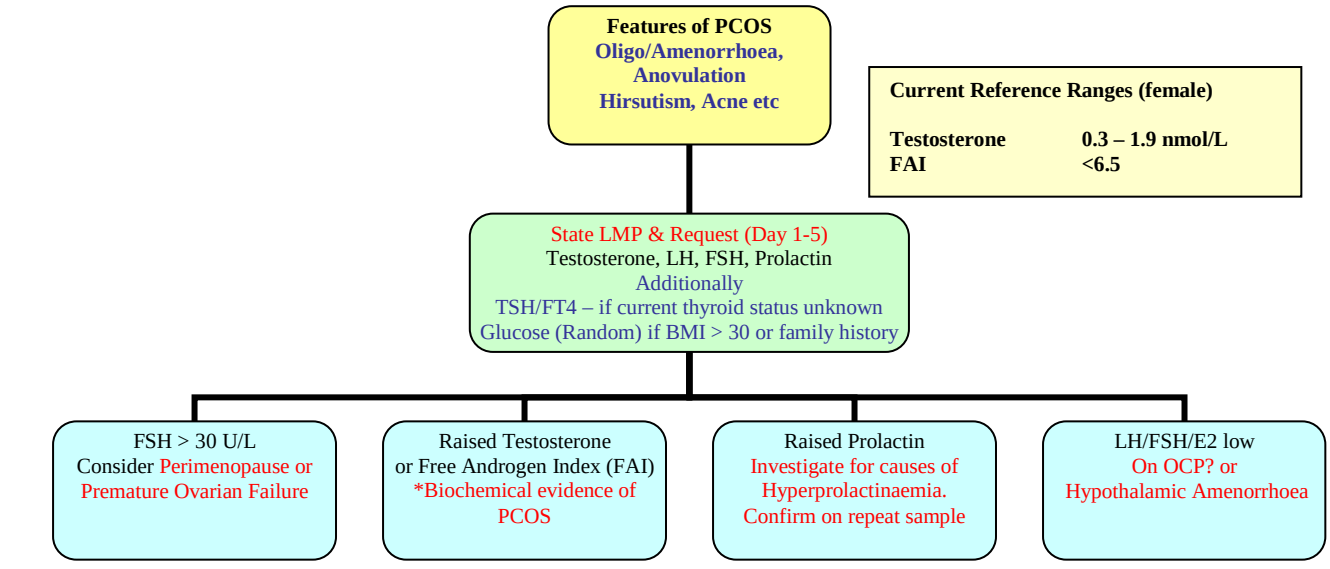
Test requests

- **LH, FSH, Testosterone & Prolactin as first line**
- **TFTs if current thyroid status unknown**
- **Random glucose (if BMI is > 30 or family history of diabetes)**

The laboratory will add any necessary additional tests (eg FAI or E2) in the light of the results and the clinical details provided. To facilitate the selection of further appropriate tests **it is crucial to provide all relevant clinical details.**

Reporting

An interpretative comment will be given and any requirement for additional sampling will be advised. **The Endocrine Duty Biochemist can be contacted on 0131 242 6880**



*** It is unusual for PCOS to present with a testosterone of >4 nmol/L: in such patients the test should be repeated as soon as possible. If confirmed on repeat sampling, the patient should be referred for an endocrine opinion.**

Background

PCOS is very common having prevalence in women of child bearing age of 5-10% and may be higher in women of South Asian origin. There is no single diagnostic criterion to confirm the clinical diagnosis. Clinical manifestations include infrequent or absent menses, anovulatory infertility, signs of androgen excess (hirsutism, acne or seborrhoea). Many women with the condition are overweight or obese. Biochemical abnormalities include hyperandrogenaemia (raised testosterone and / or free androgen index). However, the gonadotrophins - LH and FSH - are often normal. (Although LH may be raised this is no longer part of the diagnostic criteria - see below).

Women with PCOS have an increased risk of insulin resistance which, with the high prevalence of obesity, is a powerful risk factor for progression to Type 2 diabetes. They also have an increased long-term risk of endometrial hyperplasia/cancer. Currently, despite having a number of risk factors for cardiovascular disease, it is unclear whether the actual risk is increased. Investigation of glucose tolerance (initially by a random glucose) should be considered in women with PCOS with relevant *additional* risk factors such as obesity and a family history.

Definition

An international consensus definition of PCOS has been published which defines patients with PCOS as having at least 2 of the following 3 criteria:-

- Oligomenorrhoea or amenorrhoea
- Clinical and / or biochemical signs of excessive androgen secretion, ie hirsutism, acne, raised total testosterone and / or a raised Free Androgen Index (FAI: see below for definition). *Although raised LH, with a normal FSH, may be found in PCOS, gonadotrophin results no longer form part of the diagnostic criteria.*
- Presence of at least 12 follicles measuring 2-9 mm in diameter, an ovarian volume > 10ml, or both. Only one ovary needs to meet this criterion. An ultrasound scan is therefore not essential to make the diagnosis.

Lothian radiology guidance is that a scan for suspected PCOS is not required unless there are other indications eg pelvic symptoms. THEREFORE THE DIAGNOSIS IS PRIMARILY MADE ON CLINICAL AND BIOCHEMICAL FEATURES.

Other causes of the presenting clinical features should be considered and excluded:- in patients with clinical or biochemical features of marked hyperandrogenism, or acute onset of clinical symptoms, congenital adrenal hyperplasia, androgen secreting tumour & Cushing's syndrome should be considered.
It is unusual for PCOS to present with a testosterone of >4 nmol/L and in such patients the test should be repeated as soon as possible. *If confirmed on repeat sampling, the patient should be referred for an endocrine opinion.*

LH and PCOS

Although increases in LH and the LH/FSH ratio occur in many women with PCOS, it is generally established that a serum LH is not required for the diagnosis. LH is often normal in PCOS, and a raised LH and LH/FSH ratio is commonly found in women who do not have the syndrome, reflecting the pulsatile nature of LH secretion (or blood sampling shortly before ovulation). However, measurement of LH (and FSH) can be useful in identifying *other* causes of amenorrhoea eg the low gonadotrophins and estradiol found in 'functional' or 'hypothalamic' amenorrhoea associated with weight loss, stress and excess exercise.

Testosterone and free androgen index (FAI) and PCOS

A large proportion of circulating testosterone is bound to a protein called sex hormone binding globulin (SHBG). SHBG-bound testosterone is biologically inactive, in contrast to the unbound or 'free' form of the hormone. The concentration of serum SHBG is decreased (and therefore active testosterone increased) in: PCOS, insulin resistance, obesity, hyperprolactinaemia, hypothyroidism and when there are high serum androgens. Conversely serum SHBG is increased (and active testosterone reduced) by: oestrogen, pregnancy, hyperthyroidism, excess alcohol, liver disease and anticonvulsants.

The free androgen index (FAI) is a simple method of estimating the circulating free testosterone in women but may be unreliable in situations where there are extreme abnormalities in the concentration of SHBG. It is calculated as:

$$FAI = \frac{[\text{total testosterone}] \times 100}{[\text{SHBG}]}$$

The FAI is therefore more sensitive at detecting hyperandrogenism than total testosterone, and may be helpful in assessing androgen status in women who have a total testosterone in the upper half of the reference range. At the other

end of the scale, if the total testosterone is in the lower part of the reference range, FAI is generally not raised. As SHBG production is regulated by factors relevant in PCOS (see above), obesity and insulin resistance are associated with reduced SHBG levels, therefore tending to increase the FAI (ie *active, free* hormone), while *total* testosterone can remain normal.

Testosterone production increases approximately two-fold outside the early follicular phase of the menstrual cycle and may rise above the upper reference limit of 1.9 nmol/L. If a patient is having periods, a sample taken during/shortly after menses (day 1-5 of cycle) is the most suitable for diagnosis of PCOS: a sample taken later in the cycle may give a misleadingly-high testosterone result.

Laboratory investigation of patients with suspected PCOS

Clinical details

The laboratory will add additional tests, according to initial results obtained and the clinical picture: this service can only be provided if the GP has given relevant clinical details:

- Please state the LMP (in the space provided on the form)
- *If there is amenorrhoea, state this on the request form.
- Provide other relevant details on the request form (eg hirsutism, irregular periods etc)

* In cases of amenorrhoea, the laboratory will add an estradiol (E2) measurement to try to exclude sampling out-with the early follicular phase.

Sample Timing

If the patient is having periods, it is important to take the sample on day 1-5 of the menstrual cycle.

Test requests

Where PCOS is suspected, order the following tests:

- LH, FSH, Testosterone & Prolactin as first line
- TFTs if thyroid status unknown
- Random glucose (if BMI is > 30 or family history of diabetes)

The laboratory will add additional tests as required in the light of the results and the clinical details provided:- eg

- FAI if the total testosterone is in the upper half of the reference range (since some patients with testosterone in this range have raised FAI).
- Estradiol will be added if LH/FSH results are abnormal.
- Dehydroepiandrosterone sulphate (DHEAS), 17-hydroxyprogesterone, androstenedione will be added if a testosterone of >4 nmol/L is confirmed on a repeat sample (to investigate for an androgen-secreting tumour or congenital adrenal hyperplasia)

Reports

All results are scrutinised by the Duty Endocrine Biochemist who will issue an interpretative comment - if adequate clinical details have been provided – and indicate what additional action regarding further sampling etc is advised. Provision of full clinical details is important to ensure appropriate interpretation can be given.
The Endocrine Duty Biochemist can be contacted on 0131 242 6880

Guideline compiled October 2010 in collaboration with Primary Care Laboratories Interface Group

Dr Geoff Beckett
Consultant Clinical Biochemist
Honorary Reader in Clinical Biochemistry
Clinical Biochemistry
Royal Infirmary of Edinburgh

Professor Richard Anderson
Honorary Consultant Gynaecologist
Royal Infirmary of Edinburgh
Professor of Clinical Reproductive Science
University of Edinburgh

Dr Rebecca Reynolds
Honorary Consultant Endocrinologist
Royal Infirmary of Edinburgh
Reader in Endocrinology and Diabetes
University of Edinburgh