Polycystic ovary syndrome in adult females: biochemical investigation

Version:	1.0
Ratified by:	Clinical Biochemistry Senior Staff Meeting
Date ratified:	18 March 2021
Name of originator/author:	Dr S Stock
Director responsible for implementation:	Dr Edmund Lamb
Date issued:	26 April 2021
Review date:	2 years from issue date
Target audience:	Healthcare professionals in primary and secondary care

Version control schedule

Version	date	Author	status	comment
1.0				

Contents

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1. Policy summary

This policy gives guidance on biochemical investigation of polycystic ovary syndrome (PCOS) in adult females.

2. Introduction

PCOS is a common condition, the estimated prevalence being 5-10% in reproductive-aged women. The key clinical features are signs of hyperandrogenism (hirsuitism, acne, male-pattern hair loss) and menstrual irregularity with associated anovulatory infertility. Many (40 – 50%) women with PCOS are overweight. Insulin resistance is seen in 10-15% of slim and 20-40% of obese women with PCOS and all women with PCOS are at increased risk of developing type 2 diabetes and cardiovascular events. Risk factors for PCOS include family history and/or type 2 diabetes.

There is no satisfactory biochemical diagnostic test for PCOS. PCOS is a syndrome and no single diagnostic test can be used to make the diagnosis. It is also a diagnosis of exclusion: other conditions that cause menstrual irregularities and androgen excess should be ruled out. Clinical and biochemical features of related disorders are detailed in table 1.

Diagnostic criteria:

Once other causes have been excluded, the diagnosis of PCOS requires the presence of at least two out of the three following criteria (Rotterdam consensus):

1. Oligo- or amenorrhoea
2. Clinical (particularly hirsutism) **and/or** biochemical hyperandrogenism (increased testosterone)
3. Polycystic ovaries on ultrasound (ovary containing 12 or more peripheral follicles measuring 2 -9 mm)

3. Purpose and scope

This policy gives guidance on the biochemical investigation of PCOS in adult females. It is intended for use by healthcare professionals across both primary and secondary care.

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4. Definitions

PCOS – polycystic ovary syndrome

SHBG – sex hormone binding globulin

TSH – thyroid stimulating hormone

FSH – follicle stimulating hormone

USS – Ultrasound scan

BMI – Body mass index

BP – Blood pressure

5. Duties

All staff involved in the investigation and management of adult females with suspected PCOS, whether clinical or laboratory must adhere to this policy.

6. Investigating polycystic ovarian syndrome in adult females

Clinical history and examination:

Full medical and family history, including menstrual history and fertility requirements.

Examination and check for presence of hirsutism, acne, male-pattern hair loss. Record BMI and BP.

Ultrasound:

To assess ovarian morphology and endometrial appearance

Baseline blood tests:

Baseline biochemical investigations aim to 1) establish hyperandrogenism and 2) exclude other causes of hirsutism and menstrual disturbance. In women with amenorrhoea, the specimen may be taken at any time; otherwise an early follicular phase sample is recommended. Patients should not be taking the oral contraceptive pill or other oestrogen therapy.

- **Testosterone**

Testosterone concentration is commonly slightly increased in women with PCOS and has been reported to be the most frequently increased androgen in PCOS. Higher concentrations (typically >5 nmol/L) of testosterone may suggest an androgen-secreting tumour.

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Testosterone is structurally similar to some other steroids and positive interference in immunoassay methods at the low concentrations seen in females can occur with some drugs (e.g. norethisterone). The immunoassay in use in EKHUFT demonstrates good specificity. However, if the testosterone concentration is >3.5 nmol/L when analysed by immunoassay, the laboratory will send the sample to a referral laboratory to confirm the result and exclude assay interference using a mass spectrometry method.

If the testosterone concentration is >5 nmol/L (confirmed by mass spectrometry), and pregnancy has been excluded, the patient should be referred (within 2 weeks) to endocrinology, especially if hirsuitism/other virilising features are of recent onset.

Consider measuring the following, particularly if the patient presents with menstrual disturbances:

- **Thyroid function tests –** to exclude hypothyroidism
- **LH and FSH –** to exclude premature ovarian insufficiency
- **Oestradiol -** hyperestrogenaemia (or high normal) in the context of disordered LH:FSH ratio is often supportive of PCOS
- **Prolactin –** to exclude hyperprolactinaemia
- **SHBG -** this is normal to low in women with PCOS and provides a surrogate measurement of the degree of hyperinsulinaemia, independently of sex steroids. SHBG is only indicated in symptomatic patients, who have an equivocal testosterone concentration (1 – 2 nmol/L). If testosterone is < 1.0 nmol/L or > 2.0 nmol/L, measurement of SHBG is not indicated. It is only available to secondary care.

Testosterone circulates bound to SHBG in addition to albumin, with the unbound (free) fraction being biologically active. Measurement of SHBG has been suggested to enable a calculated estimate of the free testosterone fraction (free androgen index, FAI). However, SHBG concentration itself is subject to influence from many other factors (e.g. BMI, insulin resistance, thyroid function). Commonly used equations for calculating FAI have not been validated for use with current assays used in EKHUFT. Furthermore, the equations assume that there is no interindividual variability in SHBG-binding affinity and that albumin concentrations and albumin-binding affinity for testosterone are constant.

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If the patient is obese, has a strong family history of type 2 diabetes/gestational diabetes or ischaemic heart disease, or are over the age of 40 years suggest measurement of:

- **HbA1c**
- **Lipid profile**

Second line blood tests:

Exclusion of other causes of hyperandrogenaemia is dependent on clinical symptoms and presentation (see table 1). Referral to endocrinology may be appropriate in these cases.

17-hydroxyprogesterone (17-OHP) – to exclude non-classic (late onset) congenital adrenal hyperplasia, particularly if the testosterone concentration > 5.0 mmol/L and/or rapidly progressive virilisation. If late onset congenital adrenal hyperplasia is suspected, 17-OHP must be measured in a morning sample (collected before 8am), or after synacthen stimulation.

Androstendione and dehydroepiandrosterone sulfate (DHEAS) are not indicated in the diagnosis or monitoring of PCOS, but may be useful in differential diagnosis when total testosterone is significantly elevated.

If the testosterone is significantly elevated (testosterone > 5 nmol/L) and there is clinical suspicion of a virilising neoplasm then androstenedione and DHEAS may aid differentiation of the source. Androstendione may be elevated in adrenal or ovarian cancer, whilst DHEAS may be elevated in adrenal cancer.

Cortisol (post dexamethasone) and/or urine free cortisol (24-hour collection) may be measured if there are clinical features of Cushing's syndrome (see Cushing's syndrome - Guidelines for investigation (BIO NO 300)).

7. Investigation of long-term health consequences of PCOS

Once a patient is diagnosed with PCOS, further investigations may be required. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events. It is therefore suggested that the patient has HbA1c and lipids measured, particularly if they are obese, have a strong family history of type 2 diabetes/gestational diabetes or ischaemic heart disease, or are over the age of 40 years.

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Condition	Presence of hyperandrogenism	Oligo- or amenorrhoea	Clinical features	Biochemical features
Non-classical congenital adrenal hyperplasia (CAH) (21-hydroxylase deficiency)	Yes	Not often	Family history of infertility, hirsuitism, common in Ashkenazi Jews	Elevated (morning sample before 8 am) 17-hydroxyprogesterone or after synacthen stimulation
Cushing's syndrome	Yes	Yes	Hypertension, striae, easy bruising	Elevated 24-hour urinary cortisol or failure to suppress to overnight dexamethasone
Hyperprolactinaemia	None or mild	Yes	Galactorrhoea	Elevated serum prolactin
Primary hypothyroidism	None or mild	May be present	Goitre may be present	Elevated serum TSH
Acromegaly	None or mild	Often	Enlarged feet and hands, enlarged, thickened nose, changes in the jaw, deepening of the voice	Increased serum IGF-1
Premature ovarian insufficiency	None	Yes	May be associated with other auto-immune endocrinopathies	Elevated serum FSH/LH
Simple obesity	Often	Not often	Exclusion	None
Virilising adrenal or ovarian neoplasm	Yes	Yes	Clitoromegaly, extreme hirsuitism, male pattern hair loss	Significantly elevated serum androgens. Androstendione may be elevated in adrenal or ovarian cancer. DHEAS may be elevated in adrenal cancer))
Drug related condition	Often	Variable	Drug history: use of androgens, valproic acid, ciclosporin, spironolactone	Possible elevated serum testosterone

Table 1. Exclusion of related disorders

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8. Key Stakeholders, Consultation, Approval and Ratification Process

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

This document has been prepared in consultation with Dr Stonny Joseph (and endocrinology colleagues)
Consultation has been through e-mail communication between clinical biochemistry staff and medical consultants. Email correspondence is stored on the shared drive.

9. Review and Revision arrangements

Three years from implementation date, by author.

10. Dissemination and Implementation

The guidance will be hosted on the Health Professionals/Pathology area of TrustNet, and will be proactively implemented through the Care Group by appropriate clinical leads and by proactive dissemination to primary care partners.

11. Document control including archiving arrangements

Archive of this document will be via Q-Pulse.

12. Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

13. References

1. The Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, 2004. Revised 2003. Consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*, 19(1), pp.41-47.
2. Royal College of Obstetrics and Gynaecologists Guideline No 33, 2007. Long term consequences of Polycystic Ovary Syndrome
3. Azziz, R. et al., 2006. Position statement: Criteria for defining Polycystic Ovary Syndrome as a predominantly Hyperandrogenic syndrome. An androgen excess society guideline. *JCEM*, 91(11) pp.4237-4245
4. Wild, R.A. et al., 2010. Assessment of Cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: A consensus statement by the androgen excess and polycystic ovary (AE-PCOS) society. *JCEM*, 95(5), pp2038-2049
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6. Teede, H.J *et al*., 2018. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 110(3):364-379
7. NICE CKS Polycystic ovary syndrome (revised 2018) https://cks.nice.org.uk/polycystic-ovary-syndrome#!topicSummary
8. O'Reilly, M.W *et. al.,* 2014. Hyperandrogenemia predicts metabolic phenotype in polycystic ovary syndrome: the utility of serum androstendione. J Clin Endorinol Metab, 99(3):1027-1036
9. Karakas, S. E. 2017. New biomarkers for diagnosis and management of polycystic ovary syndrome. Clinica Chimica Acta 471; 248-253

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	

Details of person completing the EHRIA	
Name	Dr Sally Stock
Job Title	Consultant Clinical Scientist
Department/Specialty	Pathology/Clinical Biochemistry
Telephone Number	723 6025

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
Does it relate to our role as a service provider and/or an employer?
Service provider.

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2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Dr Sally Stock, Consultant Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Edmund Lamb, Clinical Director of Pathology

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

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Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

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Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Diagnosis of Polycystic Ovary Syndrome in adult females		
Version Number:	1.0		
Approval Date:		**Dissemination lead:**	Dr Sally Stock
Previous document already being used?	No		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	n/a		
Proposed instructions regarding previous document:	n/a		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	Trustnet	electronic	
Primary care	Trustnet	electronic	
Clinical Biochemistry staff	Q Pulse	electronic	

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	**By Whom?**	**Format (i.e. paper or electronic)**	**Date Disseminated:**

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