

**BLOOD SCIENCES  
DEPARTMENT OF CLINICAL BIOCHEMISTRY**

Title of Document: Biochemical Investigation of Suspected Endocrine Problems in Females  
Q Pulse Reference N<sup>o</sup>: BS/CB/DCB/EN/19  
Authoriser: Fiona Davidson

Version N<sup>o</sup>: 5  
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**BIOCHEMICAL INVESTIGATION OF COMMON ENDOCRINE PROBLEMS IN  
FEMALES**

This document described tests that may be useful in the investigation of common endocrine problems in females (infertility, menopause and the monitoring of HRT).

**Definitions**

It is estimated that infertility affects 1 in 7 heterosexual couples in the UK. A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. An earlier referral is suggested when older than 36 years old, or where there is a known clinical cause for infertility.

The main causes of infertility in the UK are (percent figures indicate approximate prevalence):

- unexplained infertility (no identified male or female cause) (25%)
- ovulatory disorders (25%)
- tubal damage (20%)
- factors in the male causing infertility (30%)
- uterine or peritoneal disorders (10%).

In about 40% of cases disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play a role.

**Related documents**

BS/CB/DCB/EN/20 Biochemical Investigation of Suspected Endocrine Problems in Males

**Background**

The aim is to determine whether biochemical investigations can elucidate the cause of the presentation.

The normal menstrual cycle involves fluctuating levels of luteinising hormone (LH), follicle stimulating hormone (FSH), oestrogen and progesterone. LH stimulates the secretion of steroids (oestrogen, progesterone, testosterone) and FSH follicle growth and development. At a critical point in the cycle (usually day 14-16), ovulation occurs and progesterone/oestrogen levels increase, reaching a peak 5-7 days later (ie day 21).

It is therefore important that hormone levels are taken at the right stage in the female cycle otherwise interpretation may be difficult.

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## **Ovulatory disorders**

WHO classification:

Type 1: Hypothalamic-pituitary disorders (Hypogonadotrophic hypogonadism).

Common causes include weight loss or over-exercise but other causes include hyperprolactinaemia, chronic disease, opiates, diabetes, tumours, infiltrative diseases, trauma, surgery, infections and pituitary apoplexy.

Type 2: Ovarian dysfunction (Normal gonadotrophins)

Includes polycystic ovarian dysfunction

Type 3: Ovarian Failure (Hypergonadotrophic hypogonadism).

Turners may cause congenital primary ovarian failure and acquired causes include endometriosis, ovarian surgery, autoimmune disease and chemotherapy or radiotherapy.

## **Specific Investigations**

Regular cycles - mid-luteal progesterone to assess ovulation, day 21 if the cycles are 28 days in length, otherwise the sample should be collected 7 days prior to next expected menses.

Irregular cycles - progesterone to assess ovulation, initially on day 21 then repeated weekly thereafter until the next menstrual cycle starts.

- Oestradiol may be useful to distinguish between primary and secondary ovarian failure in patients with low/low normal LH/FSH and in the assessment of oestrogen status in patients prescribed depot Provera.

Testosterone - One of the Rotterdam criteria for PCOS is either clinical or biochemical evidence of hyperandrogenism. A raised testosterone may be of use in the investigation of suspected polycystic ovary syndrome or in women showing signs of hirsutism/virilisation. See special notes for testosterone.

Thyroid - NICE advocate testing should only be carried out in females showing signs of thyroid dysfunction. However, there is some evidence that patients with subclinical disease may be prone to infertility problems.

Prolactin -NICE advocate testing only in females with an ovulatory disorder, galactorrhoea or suspected pituitary tumour; this test may, however be more widely useful.

LH/FSH ratio - this has been defined as greater than 2-3 and has been suggested to indicate PCOS. However, it is positive in only 50% of cases and LH levels tend to be reduced in obesity, making it less sensitive in this group of patients and is not included in the Rotterdam criteria.

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### **Special Notes for Testosterone**

1. Any female patient with a raised testosterone should have the result repeated (along with an SHBG).
2. If the result is still raised, consider the further investigations listed in the 'further investigations' section.
3. If the result is  $\geq 4$  nmol/L it should be confirmed by a more specific method. Norethisterone, for example, is known to cross-react with the Roche assay and cause elevated results. The sample should be sent for confirmatory testosterone analysis by tandem mass spectroscopy (Winpath code TSTM) to Dr Julian Barth, SAS Steroid Hormone Centre, PO Box 323, United Leeds Hospitals, Leeds, LS1 3EX. This is because of potential falsely elevated results due to lack of specificity in the assay.

### **Further Investigations**

- Sex Hormone Binding Globulin to assess free androgen status (Calculate Free Androgen Index but interpret with caution since this is only a guide to free androgen levels).

The following are more specialist investigations which are commonly only undertaken after at least a consultation with an endocrinologist:-

- 17 hydroxy progesterone (possibly after a short synacthen test). This will allow identification of late onset 21 hydroxylase deficiency, which is a rare but treatable cause of hirsutism.
- DHEAS and Androstenedione measurement may have a role where hirsutism is marked or virilisation is present. Elevation of the former suggests an adrenal origin of the increase in androgens; the latter an ovarian origin.
- Consider an overnight dexamethasone suppression test, if there are any other features of Cushing's Syndrome.

Chromosome studies in primary amenorrhoea, especially in patients of short stature (< 5'2", 159 cm).

### **Reference ranges for laboratory tests used in the investigation of infertility**

Testosterone 0.2 - 1.7 nmol/L (samples left unseparated overnight can give falsely high values)

Prolactin up to 700 mU/L

These reference ranges may not be appropriate for patients undergoing ovulation induction or those receiving other medication.

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**FEMALES - POST PUBERTY**

| Stages of Cycle       | FSH (IU/L)      | LH (IU/L) | Progesterone (nmol/L) | Oestradiol (pmol/L) |
|-----------------------|-----------------|-----------|-----------------------|---------------------|
| <b>Follicular</b>     | 1 - 9           | 3.2 - 8.0 | less than 8           | 46-607              |
| <b>Luteal</b>         | 1 - 9           | 2.4 - 7.2 | greater than 30       | 161-774             |
| <b>Postmenopausal</b> | greater than 30 |           |                       |                     |

**Ovarian reserve testing**

The following measures may be used to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- Anti-Mullerian hormone of less than or equal to 5.4 pmol/l for a low response and greater than or equal to 25.0 pmol/l for a high response.
- FSH greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response.  
 Total antral follicle count of less than or equal to 4 for a low response and greater than 16 for a high response.

**Do not use** inhibin B or oestradiol to predict any outcome of fertility treatment

**Menopausal Symptoms**

FSH only. In women over 45 years symptoms are likely to indicate the menopause and routine investigations are not required.

In younger women, or in those patients where hypopituitarism is suspected FSH should be measured. Since considerable variation in levels is often seen during progress through the menopause, and FSH levels change during the menstrual cycle, two measurements of FSH should be taken 4-6 weeks apart. A result >30U/L that is confirmed on a second sample is consistent with the menopause, but does not exclude the possibility of future ovulatory cycles, and as such FSH cannot be used to indicate that contraception is no longer necessary.

**References**

- NICE Guideline (CG156) Feb 2013 Fertility problems: assessment and treatment  
 NICE Guideline (NG23) Nov 2015 Menopause: diagnosis and management