BIOCHEMICAL INVESTIGATION OF COMMON ENDOCRINE PROBLEMS IN FEMALES

This document describes 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 stimulates 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 (i.e. day 21).

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

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.

Special Notes for Testosterone

1. Any female patient with a raised testosterone should also have FSH, LH and SHBG added if not already measured.

2. If testosterone is >4 nmol/L a repeat sample should be requested (with LH, FSH and SHBG) to confirm the result. If the result is confirmed, the repeat sample should be analysed by a more specific method. The sample should be sent for confirmatory testosterone analysis by tandem mass spectroscopy, to exclude any interference or falsely elevated results. Winpath code is TSTM and the sample is sent to the SAS Steroid Hormone Centre, PO Box 323, United Leeds Hospitals, Leeds, LS1 3EX.

3. If testosterone is ≥6 nmol/L, then the first sample should be sent for confirmatory testosterone analysis by tandem mass spectrometry (as above) to avoid any delays in waiting for a repeat sample.

4. Note current REMEDY guidelines advise a routine referral if testosterone confirmed to be >4 nmol/L and an urgent referral if testosterone is ≥6 nmol/L.

Further Investigations

- Sex Hormone Binding Globulin (SHBG) to assess free androgen status (calculates 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-hydroxyprogesterone (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 <2.7 nmol/L (note samples left unseparated overnight can give falsely high values).

Prolactin <700 mU/L

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

FEMALE HORMONE RANGES - POST PUBERTY

Stages of Cycle	FSH (IU/L)	LH (IU/L)	Progesterone (nmol/L)	Oestradiol (pmol/L)
Follicular	3.9 - 8.8	2.1 - 10.9	<4	80 - 420
Mid-cycle	4.5 - 22.5	19.2 - 103	N/A	120 - 1900
Luteal	1.8 - 5.1	1.2 - 12.9	>12*	130 - 900
Post-menopause	>30	N/A	N/A	<110

***Note:** When measured 7 days before onset of menses, progesterone >30 nmol/L confirms ovulation. A result of 12-30 nmol/L should be repeated with careful timing. Repeat results >12 nmol/L (in the presence of regular cycles) is consistent with normal ovulation.

Ovarian reserve testing

NICE Guideline (CG156) states the following measures may be used to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- Total antral follicle count of less than or equal to 4 for a low response and greater than 16 for a high response.
- 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.

Inhibin B or oestradiol should NOT be used to predict any outcome of fertility treatment.

Menopausal Symptoms

FSH only. In women over 45 years FSH should not be used to diagnose menopause, and instead should be based on clinical symptoms (NICE NG23).

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