

## Disorders of gonadotrophin secretion

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In recent years, particularly since the advent of radio-immunoassay, the regulation of pituitary gonadotrophin secretion has been extensively studied in man and in animals (Greep *et al.*, 1976). I shall not comprehensively catalogue the different diseases and syndrome complexes associated with disordered gonadotrophin secretion. These are systematically covered in several textbooks and reviews (London, 1975; James *et al.*, 1976). Instead I shall consider the more practical situation of a pathologist or other clinician faced with the result of a serum gonadotrophin measurement and discuss the factors that need to be borne in mind when interpreting that result. This will lead me to some conclusions about the optimal use of these assays in clinical practice.

### Factors relevant to serum gonadotrophin levels

#### AGE

Secretion of the pituitary gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) varies considerably at different stages of a person's life-span. Although little is known about the regulation at these stages clearly the effect of any abnormality may vary according to the age of the individual.

#### Fetal life

Immunoreactive LH and FSH are detectable in both pituitary and serum of human fetuses from about 60 days' gestation (Kaplan *et al.*, 1976). The amounts of both hormones seem to be greater in females than in males. A peak concentration in serum is reached at about 120 days gestation. The same is true of pituitary concentration ( $\mu\text{g}$  hormone/g tissue) but the total content of the pituitary rises throughout gestation. Little is known about either the neuroendocrine control of the fetal pituitary or possible abnormalities. In the male it has been proposed that prenatal deficiency of LH, which normally stimulates the interstitial cells of the testis to produce testosterone, causes hypospadias, cryptorchidism, and hypogonadism and may be the result of anencephaly, con-

genital hypopituitarism, congenital gonadotrophin deficiency, or Prader-Labhart-Willi syndrome. Probably some abnormalities arising during reproductive life will also prove to be the result of disorders of gonadotrophin secretion in the fetus.

#### Perinatal development

Although there are still discrepancies in the reported data (Forest, 1975), there is a peak of LH and FSH secretion in the first few weeks of postnatal life. In the case of LH the plasma level remains at two to three times higher than that of prepubertal children until the age of 1 year. As in the prenatal period, marked changes in gonadotrophin secretion occur whose significance is not understood. In the rat sexual differences in the central regulation of the anterior pituitary and subsequent sexual behaviour are determined in the early postnatal period. Such information in the human is totally lacking but possibly disorders of gonadotrophin secretion in early postnatal life may be associated with later disruptions of reproductive life.

#### Prepubertal development

Gonadotrophin secretion and its control between birth and puberty is not well understood. Excessive secretion may result in precocious puberty. This is more common in girls than boys (70:30). In girls there is generally no demonstrable underlying lesion (80% of cases)—the so-called idiopathic or constitutional precocious puberty. In 70% of boys with this condition there is an underlying lesion of the central nervous system (for example, a glioma, a pinealoma or basal meningitis).

#### Puberty

The process of sexual maturation in the human is complex (Odell and Swerdloff, 1976). Before puberty the hypothalamic-pituitary-gonadal relationship is dominated by tight central control of gonadotrophin secretion. During puberty this control is relaxed and both LH and FSH rise slowly, producing maturation of the gonads. FSH rises before LH, just as the FSH response to exogenous gonadotrophin-releasing hormone (GnRH) also appears before that of LH.

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This natural sequence of events can be observed during treatment of anorexia nervosa in which condition hypothalamic-pituitary function reverts to a prepubertal pattern. On regaining weight the patient goes, hormonally, through puberty again.

The onset of puberty is variable and the age at which it can be said to be pathologically delayed or absent is arbitrary. Delay or absence can be caused by a primary gonadal failure as well as by gonadotrophin failure. Failure of gonadotrophin secretion at puberty can be caused by pituitary lesions or by a failure of secretion of hypothalamic GnRH. In either event gonadotrophin deficiency may be isolated or part of a more extensive failure of pituitary function.

#### Postpubertal gonadotrophin secretion

After puberty secretion of the gonadotrophins continues subject to the negative feedback control by the sex hormones and to the menstrual rhythm. At the menopause lack of feedback causes high levels in women, whereas in men there is only a slow and smaller rise as gonadal function wanes (Baker *et al.*, 1976). Similarly, a rise will follow removal of the gonads or their premature failure (premature menopause).

#### DAY-TO-DAY VARIATIONS

No consistent day-to-day variations in LH and FSH are seen in adult men, but women have an obvious cyclical pattern of secretion. This needs to be borne in mind when interpreting an assay result. Elucidation of possible abnormalities in this pattern requires repeated blood sampling. Korenman and Sherman (1976) have identified five variations from the typical cycle: (1) long follicular phase, seen in younger women; (2) short follicular phase, seen in older women; (3) inadequate luteal phase; (4) short luteal phase; and (5) anovulatory cycles, seen during menarche and menopause.

Clearly it is impracticable in every case of abnormality to carry out either the sampling or the hormone assays required to make a diagnosis. In amenorrhoea FSH assays (and to a lesser extent LH assays) are of value in differentiating primary ovarian failure from hypopituitarism and other causes of secondary amenorrhoea. A logical and cost-effective approach to the investigation of secondary amenorrhoea has been proposed (Jacobs *et al.*, 1975). It is based on the principle that investigations should be restricted to those that have a direct bearing on the treatment of the patient—for example, gonadotrophins need only be measured in patients who do not respond to progestogen.\* The

integrity of feedback action by gonadal steroids on LH release can be tested with oestradiol or clomiphene, which blocks the normal feedback (see below). Sequential sampling will show whether there has been an LH response (Shaw *et al.*, 1975).

#### HOUR-TO-HOUR VARIATIONS

Gonadotrophin secretion by the pituitary has two components—namely, a steady basal secretion with superimposed spikes or pulses (Yen *et al.*, 1976). There is much evidence to suggest that these pulses occur in response to pulses of secretion of GnRH. The raised LH and FSH levels after gonadectomy are maintained by an increase in the size rather than the frequency of the spikes. The size of the pulses decreases in anorexia nervosa. This spiking (occurring every one to two hours) means that the analysis of single blood samples does not necessarily reflect the secretion rate of LH and FSH. During puberty there is a sleep-related increase in pulsatile LH release which disappears after puberty (Boyar *et al.*, 1972).

#### ENDOGENOUS HORMONES

Gonadotrophin secretion is modified by the sex hormones, and plasma levels of LH and FSH can best be interpreted in the light of concurrently obtained analyses of plasma steroid levels.

#### DYNAMIC TESTS

Dynamic tests are often used diagnostically when investigating disordered gonadotrophin secretion, though their usefulness is not well established. As already mentioned, suppression by exogenous sex steroids may be applied to the study of the negative feedback—for example, to identify ectopic hormone production which cannot be suppressed.

Stimulation tests are much more widely used. GnRH, available as the synthetic decapeptide, stimulates LH and FSH release by a direct action on the pituitary, but numerous studies have led to the conclusion that its application as a diagnostic test is of little value. In general, the response to GnRH is directly related to the basal prestimulation level.

Clomiphene has also been widely used as a stimulant. It is presumed to act via its anti-oestrogenic effect to reduce negative feedback on the hypothalamus.

#### DIFFERENTIAL LH OR FSH DEFICIENCY

In most physiological and pathological states changes in the secretion of LH and FSH are parallel. In some cases, however, they diverge. There is a rare condition, the fertile eunuch syndrome, in which there is normal FSH secretion (which stimulates the seminiferous tubules) and a failure of LH secretion (which stimulates the interstitial cells to secrete testosterone).

\*Vaginal bleeding on withdrawing a progestogen indicates an oestrogenised endometrium—Ed.

Conversely, in conditions where gametogenesis is deficient without an associated defect in sex hormone production there is an isolated ('monotropic') increase in FSH levels with normal LH levels. This is evident in men in the common conditions of oligospermia and azospermia with normal Leydig cell function. In the polycystic ovary syndrome there is a raised basal level of LH with a reduction of FSH (Baird, 1976).

#### NON-SPECIFICITY OF LH AND FSH ASSAY

Apparently raised circulating levels of LH and/or FSH may be the result of non-specific cross-reaction in immunoassays. Two other glycoproteins, human chorionic gonadotrophin (hCG) and human thyroid stimulating hormone (hTSH), have a similar structure to LH and FSH. Pregnancy is a clear instance where high levels of hCG may give falsely high immunoassay results for LH and FSH. The  $\alpha$ -subunit, which is similar in all the glycoprotein hormones, may also be secreted—notably in postmenopausal women and after GnRH; this may cross-react in the assay.

As a general concept it is becoming apparent that there may not be such a thing as 'LH' in serum, at least as a single discrete molecular species. There may be larger molecular forms (prehormones), which have been found for both LH and FSH in the pituitary, or free subunits or breakdown products that retain some immunoreactivity (for example, after desialylation). Moreover, the glycoprotein molecules themselves are not homogenous, since microheterogeneity has been identified at the N-terminus of the  $\alpha$ -subunit and the C-terminus of the  $\beta$ -subunit of human LH.

Ectopic production of gonadotrophins may occur. Trophoblastic tumours secrete hCG and variable quantities of its subunits. In addition, gonadotrophin secretion, particularly that of hCG, may be associated with a variety of tumours of non-endocrine origin—for example, lung. Some non-malignant chronic inflammatory conditions of the gastrointestinal tract may also involve secretion of detectable amounts of hCG. Vaitukaitis *et al.* (1976) have summarised recent knowledge on gonadotrophin subunits and their secretion.

The final possible type of non-gonadotrophin material in serum that registers in immunoassay is 'assay garbage'. There are many assays being operated whose lack of specificity and poor optimisation result in erroneous levels of LH and FSH being recorded.

#### QUALITY OF GONADOTROPHIN ASSAYS

The most frequent cause of an abnormal serum LH or FSH result is a bad assay. Gonadotrophin assays

have for many years been bedevilled by a lack of purified reference materials and, partly because of that, a lack of specific antisera. In the UK the picture is now brighter. A set of reagents, a standardised assay protocol, and an external quality control scheme are available to all laboratories in the public sector. Thus high quality gonadotrophin assays will eventually be available and clinicians will be able to rely on the authenticity of the results—and get the same results when they move to another hospital.

#### Conclusions

(1) Gonadotrophin secretion varies considerably from hour to hour, from day to day, and at different stages of life. This has to be considered when interpreting assay results.

(2) Gonadotrophin secretion is regulated by interaction between the central nervous system and gonadal steroid secretion. Exogenous dynamic tests can be used to study this.

(3) Secretion of LH and FSH does not always run in parallel.

(4) Assays for LH and FSH are often not specific.

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