Human Gonadotrophin Secretion

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The development of radioimmunologic methods has made it possible to assay follicle stimulating hormone (FSH) and luteinizing hormone (LH) in serum and urine with great sensitivity and great precision, and to study the secretion of these hormones in humans under physiological and pathological conditions.

The mechanisms that regulate gonadotrophin secretion differ in men and women. In addition, different mechanisms operate in women, depending on whether their gonadal function is active or inactive, as after the menopause. We shall therefore discuss separately the factors affecting FSH and LH release in men, and in pre- and postmenopausal women.

GONADOTROPHINS IN MEN

We have reported (Franchimont, 1966, 1968, 1970) that serum FSH levels remain stable during the diurnal cycle whereas serum LH levels drop between 2 and 6 p.m. Burger (1969) and Saxena et al. (1969) found the same drop in LH and showed that it was paralleled by a decline in plasma testosterone. However, the decrease in testosterone lags somewhat behind the fall in LH. Likewise, when LH levels subsequently rise, there is a short delay before plasma testosterone follows suit. LH thus appears to be the causal factor involved in the changes in testosterone concentration.

Influence of Testosterone

The intramuscular injection of 50 mg of testosterone propionate in normal healthy males produces a marked and sustained decrease in LH but causes no statistically significant change in FSH (Franchimont, 1966, 1968, 1970; Peterson et al., 1968). During the hours following injection, LH levels are inversely proportional to plasma testosterone (Burger, 1969). However, a larger dose, such as 100 mg, will decrease FSH levels. Testosterone’s action on LH and its lack of effect on FSH at moderate dose levels is particularly evident under pathologic conditions, such as Klinefelter’s syndrome. In 16 patients with this syndrome, FSH levels were invariably high but LH levels varied widely from normal to very high.

The elevated FSH concentrations are related to the hyalinisation of the...
Stage O: complete hyalinisation
Stage I: Sertoli cells
Stage II: Sertoli cells + spermatogonia
Stage III: Sertoli cells + spermatogonia + rare spermatocytes
Stage IV: Sertoli cells + spermatogonia + many spermatocytes
Stage V: Sertoli cells + spermatogonia + many spermatocytes + rare spermatids
Stage VI: Sertoli cells + spermatogonia + many spermatocytes + spermatids + rare spermatozoa
Stage VII: decrease of all the stages of spermatogenesis
Stage VIII: normal spermatogenesis

Fig. 1. Serum FSH levels in azoospermia and oligospermia as correlated with testicular biopsy findings (Franchimont et al., 1971).
seminiferous tubules and disappearance of the germ cells characteristic of this syndrome. The pituitary reacts to this insufficient germinal development by increasing its secretion of FSH, the gametokinetic hormone.

The variable concentrations of LH seemed to be related to the degree of Leydig cell deficiency, there being a linear relationship between LH levels and plasma testosterone concentrations (Franchimont, 1968, 1970). These findings indicate that testosterone controls LH release but has no effect on that of FSH.

The LH-testosterone feedback mechanism is highly specific, as shown by the administration of mesterolone to normal subjects. Mesterolone, whose formula differs from that of testosterone by the addition of a methyl radical in 1 position and the absence of a double bond in 4 position, has an androgenic potency equal to that of testosterone. When administered by mouth or intramuscular injection at a dose of 200 mg, mesterolone produces no statistically significant change in FSH or LH. At a dose of 400 mg i.m., serum FSH declines but there is no change in LH. Perhaps mesterolone in large doses, like testosterone, stimulates gametogenesis and thereby reduces the secretion of FSH.

Factors Controlling FSH Secretion

FSH secretion is not affected by variations in plasma testosterone. However, a decline or total loss of spermatogenic activity induces a marked rise in FSH without a concomitant increase in LH, provided there is no lesion of the Leydig cells. It is well established that the germ cells are very sensitive to X-rays, whereas the Leydig cells are highly resistant. As a result, after testicular irradiation which destroys spermatogenesis without affecting Leydig cell function, FSH levels rise while LH concentrations remain normal. Similarly, in eight cases of hypogonadism following orchitis due to mumps, FSH levels were found to be elevated in all cases, whereas the LH concentrations were most often normal. Infectious or viral orchitis is known to damage primarily the seminiferous tubules and the germ cells.

In cases of azoospermia and oligospermia due to abnormal spermatogenesis, FSH levels are often higher than in normal adult males. This indicates that the primary lesion occurs during spermatogenesis and that the pituitary gland reacts to the lack of germ cell maturation by increasing its secretion of FSH. Levels of LH are generally normal, as are plasma testosterone concentrations (Franchimont, 1970, 1971). We have recently (Franchimont et al., 1971) studied serum FSH levels in such cases and correlated them with the results of testicular biopsy. The results are shown in Fig. 1.

FSH levels were consistently higher than the normal mean value (4-14 mIU/ml) ± 2 S.D. (S.D. = ± 2.69) in stages 0 through 4. However, in cases
of azoospermia or oligospermia where spermatids were visible on biopsy (stages 5 through 8), the levels of serum FSH proved to be normal. Thus, the transformation of the spermatocyte II into the spermatid must induce or permit formation of a factor controlling the secretion of FSH.

This substance, which diminishes FSH levels, was found to be present in the seminal plasma of normal subjects and patients with oligospermia but not of subjects with azoospermia caused by inhibition of gametogenesis. The seminal plasma from these three types of subjects was administered in four subcutaneous injections (1 or 0.1 ml) to castrated male rats at 18-hour intervals. That from normal or oligospermic patients decreased the rat serum FSH while that from subjects with azoospermia failed to reduce serum FSH. The active substance in the sperm has not yet been identified.

Howard et al. (1950) and Johnsen (1970) have advanced the hypothesis that the testis and perhaps the Sertoli cells may produce an oestrogen-like substance which regulates the secretion of FSH. It is true that the oral administration of oestrogen to male subjects causes a rapid and marked decrease in both FSH and LH (Peterson et al., 1968; Swerdloff and Odell, 1968). Nevertheless, it should be recalled that under normal conditions both oestradiol and oestrone levels are identical in men and postmenopausal women (Lipsett, 1970a) and that in the latter group these oestrogens do not block the secretion of FSH, which is very high. In addition, the circulating oestradiol in males is probably not of testicular origin, whereas oestrone does appear to be secreted by the testis (Lipsett, 1970b). It is thus unlikely that oestrogens play any physiological role in the regulation of FSH in men.

A more reasonable explanation might be that there is a steroid secreted by the Sertoli cells. Lacy and Pettitt (1970) have shown that the Sertoli cells produce androgens, particularly testosterone and derivatives of pregnane and pregnene. The residual bodies provide a substrate for the synthesis of these steroids. These lipid-rich bodies undergo phagocytosis by the Sertoli cells and are eliminated during the transformation of the spermatids into spermatozoa. They are then transformed within the Sertoli cells into cholesterol, which serves as the departure point for the synthesis of the androgens and the derivatives of pregnane and pregnene. Johnsen had already speculated in 1964 that the feedback-active substance might originate in the residual bodies during the stage of spermatid development and might act either immediately or after phagocytosis of these bodies by the Sertoli cells.

The steroid secreted by the Sertoli cells seems to be essential during the mitotic stages of spermatogenesis (Lacy and Pettitt, 1970). The early phases of spermatogenesis can take place in tissue culture in the absence of hormone; Steinberger and co-workers (1970) have shown that in the testes of several
mammalian species, the initiation and progression of spermatogenesis up to late pachytene primary spermatocytes can occur in the absence of hormone. However, the later stages of reductional mitosis and spermatid formation require the presence of FSH.

In man in particular, FSH may play an important role in spermatid maturation (Steinberger et al., 1970). FSH might act partly or wholly by stimulating the steroid secretion of the Sertoli cells (Lacy and Pettitt, 1970), and the steroid secreted might then, in turn, regulate the secretion of FSH. However, it is not yet known whether the substance secreted by the Sertoli cells is in fact a steroid or, if it is, what type of steroid it might be. Our initial experiments indicate that the derivatives of pregnane and pregnene have no effect on serum FSH in male subjects or castrated rats.

**Influence of Clomiphene**

In men, clomiphene evokes the release of FSH and LH, as illustrated in Fig. 2. Ten normal male subjects given 200 mg of clomiphene by mouth daily for 7 days began to show a significant rise of serum FSH and LH on day 4.

This increase in serum FSH and LH as determined by radioimmunoassay has also been found by Bardin et al. (1967), Odell et al. (1967), Peterson et al. (1968) and Faiman et al. (1968), all of whom reported a clear-cut response after administering 200 mg clomiphene for a minimum of three days.

The finding that the rise in LH precedes the rise in plasma testosterone by at least two days (Bardin et al., 1967; Burger, 1969) demonstrates that clomiphene acts on the hypothalamic-hypophyseal structures responsible for the release of gonadotrophins. The exocrine and endocrine functions of the testis are, in turn, stimulated by the liberated gonadotrophins.

The mode of action of clomiphene remains mysterious. However, one fact seems clear: the compound acts at the hypothalamic level where it apparently blocks the androgen-sensitive receptors and abolishes their inhibition of gonadotrophin release. Evidence for this view comes from the finding that pre-treatment with high doses of androgens blocks the gonadotrophic response to clomiphene (Bardin et al., 1967).

Administration of clomiphene can thus serve as a dynamic test for evaluating the integrity of the hypothalamic–hypophyseal–gonadal axis and for gauging the secretory function of the pituitary.

**Gonadotrophin Function in various Disease States in Men**

1. **Baseline Levels in various Types of Hypogonadism.** In hypogonadism due to testicular lesions, there is often an extensive or complete loss of germ cell
production. This is the case after testicular irradiation, infectious or viral orchitis, and in Klinefelter's syndrome. In contrast, the Leydig cells, which are far more resistant than the germ cells, are spared to a greater extent and
the endocrine function of the testis is only partially depressed. In addition, the adrenals secrete androgens and can thus compensate somewhat for the insufficiency of testicular endocrine secretion. As a result, cases of hypogonadism due to a primary testicular lesion are invariably marked by elevated FSH levels due to the germ cell damage but the LH levels may be either normal or high depending on the secretion of androgens, and testosterone in particular (Franchimont, 1971).

In patients with organic pituitary lesions, FSH and LH are sometimes undetectable but may often be measurable, in which case they are generally low but occasionally normal. LH secretion is more readily depressed than FSH secretion. The persistence of low or normal levels of FSH or LH is probably due to secretion by remnants of normal pituitary tissue. The hypogonadism in these cases may be accounted for by the insufficiency of one or both gonadotrophins or perhaps by an imbalance in the FSH/LH ratio.

2. FSH and LH in Hypothalamic Lesions. When there is a lesion at the hypothalamic level, the pituitary may preserve an autonomous ability to secrete gonadotrophins but the regulatory feedback mechanisms are lacking. Thus, in patients with hypogonadism and hyposmia due to agenesis of the olfactory lobe, the hypogonadism is probably due to hypoplasia of the anterior hypothalamus and of the zones regulating gonadotrophin secretion. This is a genetic disease transmitted by a dominant gene on the X chromosome. In our study with Bricaire et al. (1971) of three such patients, serum FSH levels were abnormally low in all cases, whereas LH values were normal in two, and high in the third case. The administration of 200 mg of clomiphene daily for six days failed to raise either FSH or LH.

Cases of delayed puberty seem to correspond to an insufficient secretion of gonadotrophic hormones, in particular FSH. In all patients over 16 years of age with delayed puberty, FSH and LH levels were either undetectable, decidedly low, or at the lower limit of normal.

The mechanisms regulating gonadotrophin secretion were found to be immature in all cases studied, as shown by the absence of response to clomiphene which failed to evoke a rise in FSH. However, its effects on LH varied, depending on how longstanding was the disorder. No response could be elicited in two subjects aged 18 and 25 whereas a release of LH was produced in two 16 year olds (Franchimont, 1971).

This response pattern is identical to that observed in boys in the prepubertal stage when FSH and LH concentrations are low and do not rise in response to clomiphene. In contrast, when the child enters puberty, as shown by testicular growth and the appearance of pubic and scrotal hair, FSH and LH levels rise with clomiphene administration (Franchimont et al., 1971).
GONADOTROPHINS IN POSTMENOPAUSAL WOMEN

In postmenopausal women, FSH levels are ordinarily higher than during the normal menstrual cycle and represent a response to the loss of ovarian germinal function. The concentration of LH is most often equal to or greater than the peak observed at midcycle in normally menstruating women. In some cases, LH concentrations are of the same order as those found during the pre-ovulatory and luteal phases (Fig. 3). This postmenopausal variability in LH

Fig. 3. Serum FSH and LH in postmenopausal women, as compared with gonadotrophin levels during the menstrual cycle.
levels is due to the fact that the endocrine functions of the ovary are not abolished by the menopause and that the adrenals also supply the body with oestrogen. The high FSH and LH levels persist and are the rule even 25 years or more after the menopause. Pituitary involution must therefore be suspected in postmenopausal women who have low serum gonadotrophin concentrations.

Since the high FSH and LH levels after the menopause are relatively stable from day to day, the influence of various gonadal steroids on gonadotrophin release can easily be studied.

Influence of Oestrogen
In postmenopausal women, the effect of oestrogen on gonadotrophin levels depends on the compound used and the dose. For example, ethinyl oestradiol administered in low doses (20 µg by mouth daily) for 21 days causes a decrease in FSH during the first few days of treatment and a slight and delayed decrease in serum LH. When oestrogen treatment is stopped, FSH gradually recovers to pre-treatment levels while LH displays a very marked rebound effect (Franchimont, 1971).

At a dose level of 50 µg/day, ethinyl oestradiol lowers both FSH and LH. At the same dose level, the oral administration of either mestranol or 1-hydroxy-ethinyl-oestradiol-1,3-diacetate for more than 15 days likewise depresses serum FSH and LH.

If the 17β-hydroxy group is replaced by another group, as in 17-dioxanyl-oestradiol, FSH and LH remain unchanged even in response to 200 µg/day for 15 days. This dose level has a peripheral oestrogenic effect as shown by cornification of the vaginal smear. When treatment is stopped, LH levels rise. These studies apparently indicate that the presence of the hydroxy group in the 17β position is necessary for oestrogen to inhibit FSH and LH release.

Oestrogen in low doses inhibits primarily the secretion of FSH and exerts only a slight, delayed effect on LH. At higher dose levels, there is a concomitant decrease in both FSH and LH. We have never observed a stimulation of LH release during oestrogen treatment. However, the withdrawal of oestrogen is followed by a rise in LH, most likely when circulating oestrogen levels decline. This rebound is also obtained with oestrogens, such as 17-dioxanyl oestradiol, which do not inhibit the secretion of gonadotrophins. Two possible hypotheses would be consistent with this finding: (a) there may be two regulatory centres, one sensitive to increases in oestrogen concentration and the other to decreases, or (b) there may be only one oestrogen-sensitive centre in the hypothalamus that is more readily stimulated by a decrease than inhibited by a rise in circulating oestrogen.
Influence of Progesterone and Other Progestogens

Progesterone (25 mg i.m.) does not modify serum FSH or LH during the first 24 hours in postmenopausal women (Franchimont, 1968). Norethisterone acetate in small doses (0.3 mg/day by mouth) causes no change in FSH levels but lowers serum LH (Franchimont et al., 1970). When injected intramuscularly in larger doses (200 mg), norethisterone enanthate produces a marked drop in serum LH within 24 hours, often to undetectable values. Recovery to pre-treatment levels takes up to two months. FSH levels also decline, but the decrease is less marked, less rapid, and less sustained. The hormone never falls to undetectable levels and returns to pre-treatment concentrations at the end of the first month after injection. At this point, FSH begins to rise significantly. Norethisterone thus blocks both of the gonadotrophins but acts preferentially on LH release. A similar response pattern for FSH and LH is obtained by administering medroxyprogesterone (150 mg i.m.). More than six weeks after injection there is an FSH rebound.

Norethisterone's action on the gonadotrophins accounts for its anti-ovulatory effects when administered intramuscularly to eugonadal women.

Gonadotrophins in Premenopausal Women

FSH and LH during the Menstrual Cycle

Study of 25 normal menstrual cycles disclosed a peak of FSH and LH coinciding with the lowest cutaneous temperature. For comparisons of the control cycles with one another, day 0 was taken to be the day on which serum LH was at its highest peak. The preceding days correspond to the preovulatory phase and the following days to the luteal phase. Figure 4 shows the mean curve calculated from 25 individual cycles. In addition to the FSH and LH peaks at midcycle, both gonadotrophins were higher during the preovulatory period than during the luteal phase. FSH concentrations in particular were very elevated during the first few days of the cycle. However, these levels were still lower than the midcycle FSH peak. The levels of LH have been shown (Ross et al., 1970) to rise gradually during the follicular phase. Rarely, some normal women seem to have an increase in LH during the luteal phase.

Various workers have established that the preovulatory oestrogen peak precedes the burst of LH (Fig. 5) (Burger et al., 1968; Goebelsmann et al., 1969; Catt, 1969). This chronological order makes it highly probable that it is the oestrogen which induces the release of LH at midcycle. The sequential analyses of Catt (1969) and ourselves seem to show that the factor triggering LH release is the decline in plasma oestradiol. The relationship is apparently inversely proportional, with the decrease in oestradiol prompting an increase...
We have, moreover, shown in postmenopausal women that LH is discharged after the withdrawal of exogenous oestrogen, when oestrogen concentration falls.

The stimulatory action of oestrogen on LH levels is also apparent from an analysis of young women suffering from functional amenorrhoea without any detectable organic basis. Franchimont et al. (1972) administered 20 mg of Premarin intravenously to 15 such patients. In 6 cases there was no change in LH. We have, moreover, shown in postmenopausal women that LH is discharged after the withdrawal of exogenous oestrogen, when oestrogen concentration falls.

![FSH and LH levels during the menstrual cycle](image-url)
LH but in 9 cases there was a significant rise in LH occurring after 8 hours (2 cases) or between 24 to 32 hours (5 cases) or delayed to more than 48 hours (2 cases). FSH concentrations, in contrast, fell in 12 of the 15 cases and showed no rebound effect. Similar findings have been reported by Van de Wiele et al. (1970). It can thus be asserted that it is the preovulatory peak of oestrogens that triggers the LH burst. While the corpus luteum is functional there is ordinarily no change in FSH and LH levels, which suggests that luteal function is autonomous. Occasionally, a slight rise in LH is detected. This might be related to the reported decrease in oestrogen secretion during the luteal phase (Ruffie et al., 1971; Franchimont, 1971).

Progesterone does not appear to exert any influence over the burst of LH and FSH at the time of ovulation. Plasma progesterone is barely detectable during the first phase of the cycle and progesterone concentration only begins to increase 0 to 4 days after the burst of LH, reaching a peak three to four days later to maintain maximal values for several days before dropping rapidly until, a few hours before menstruation, it falls to the levels recorded at the beginning of the cycle (see Fig. 5) (Neill et al., 1967; Cargille et al., 1969; Strott et al., 1969; Ross et al., 1970).

Some purely speculative suggestions may be offered as to the role of FSH and LH during the normal menstrual cycle.

The high concentrations of FSH during the follicular phase are undoubtedly related to the development of the ovarian follicle. FSH is known to induce maturation of the ovum but it also provokes development of the membrana granulosa. The midcycle burst of FSH might serve various functions. First, it may stimulate the end of growth of the follicle, which develops slowly over the first 10 days of the cycle and then grows rapidly 12 to 24 hours prior to ovulation (Hartman, 1962). In addition, it might terminate the ovum’s reductional mitosis and trigger the second mitosis, both of these processes occurring in humans after the ovocyte has been discharged from the follicle (Edwards, 1969). Lastly, the FSH burst may also induce a new proliferation of the cells of the granulosa which are to form the corpus luteum.

LH is secreted in increasing amounts during the preovulatory phase. It induces the endocrine secretion of the cells of the theca interna, which respond by producing 17β-oestradiol and its precursors, including 17α-hydroxyprogesterone. This secretion of oestrogen blocks the pituitary secretion of FSH, whose serum levels decline until midcycle. In contrast, the oestrogens do not affect LH. The preovulatory oestrogen peak, acting via a positive or negative feedback mechanism, triggers the burst of LH, which is also thought to participate in the formation of the corpus luteum by inducing the development of vascularisation and the growth of cells derived from the theca interna.
Moreover, LH may induce secretion by the endocrine cells of the corpus luteum. These cells are of two types. The first, which are in the majority, are derived from the cells of the membrana granulosa. Since they are devoid of enzymes capable of hydrolysing progesterone and cleaving the C21 steroids into C18 steroids, they produce only progesterone. Cells of the second type derive from the theca interna and produce oestrogens.

Once the secretion of oestrogens and progesterone has been induced by LH,
the corpus luteum appears to function autonomously. If the corpus luteum continues to secrete oestrogens and progesterone throughout the luteal phase, pituitary secretion of FSH and LH is blocked. If, however, the level of oestrogen diminishes, there may be a release of LH. At the end of the luteal phase, just prior to the onset of menstruation, oestrogen secretion by the corpus luteum drops to almost nothing and the secretion of FSH and LH can again increase.

Influence of Hormonal Contraceptives
Nonsequential oral contraceptives, containing a mixture of oestrogen and progestogen, suppress the early rise in FSH during the follicular phase and eliminate the peak of FSH and LH at midcycle (Ross et al., 1967; Franchimont, 1971). FSH and LH baseline levels also have a tendency to drop during the follicular and luteal phases due to a reduction in gonadotrophin release by the pituitary (Kohler et al., 1968). Occasionally, a luteal rise in FSH and LH is seen during the 48-hour period following withdrawal of nonsequential contraceptives.

Sequential contraceptives block only the rise in FSH at the beginning of the follicular phase and at midcycle. In contrast, oestrogen administered alone permits and even stimulates the release of LH (Swerdloff and Odell, 1969).

The action of progestogens administered alone as contraceptives seems to depend on the chemical nature of the gestagen. For example, norethisterone acetate (0.3 mg/day by mouth) suppresses the normal midcycle bursts of FSH and LH (Franchimont et al., 1970). This blockade of the cyclic release of the gonadotrophins occurs during all succeeding cycles of treatment. Norgestrel in doses of 30 μg/day by mouth causes menstrual irregularities and modifies the chronological sequence of FSH and LH secretion. However, abnormally high or low midcycle peaks of FSH and LH occur during the treatment cycle (Franchimont and Cession, 1972).

The intramuscular injection of medroxyprogesterone (150 mg) on day 7 of the cycle sometimes suppresses the FSH and LH peaks at the middle of the cycle (Franchimont et al., 1970).

Gonadotrophin Function in various Disease States in Young Women
In 16 patients with organic pituitary lesions we found low values of FSH in 10 cases and abnormally low LH values in 12 cases. The persistence of detectable gonadotrophic concentrations in organic pituitary disease is well known (Faiman and Ryan, 1967; Demura et al., 1967; Saxena et al., 1969, etc.) and is due to the fact that some healthy pituitary tissue remains.

In contrast, 18 of 19 patients with Turner’s syndrome had FSH levels that were appreciably higher than those normally seen during the menstrual
cycle. Only one patient had an FSH concentration compatible with normal gonadal function. This almost invariable finding of an elevated concentration of FSH is well accounted for by the deficit of ovarian follicles in this syndrome. The LH levels showed greater scatter, being much higher than normal in six cases and within the range of normality in 13 cases; the high values may represent the pituitary’s response to insufficient oestrogen secretion (Franchimont 1971). These LH values may be related to the amount of circulating oestradiol and oestrone, derivatives of Δ4-androstenedione which is secreted by the adrenal cortex and transformed in various tissues of the body.

In cases of amenorrhoea, gonadotrophin secretion can be evaluated only by repeated and, if possible, daily determinations of FSH and LH for a 28-day period and by the clomiphene test. These repeated assays make it possible to determine the absolute value of FSH and LH concentrations, their day-to-day ratio, their cyclic changes, and the synchronisation of these changes. High levels of FSH and LH showing only slight fluctuations from one day to the next are seen in gonadal dysgenesis and in premature menopause. In the Stein-Leventhal syndrome, serum LH is elevated and marked by wide fluctuations whereas serum FSH is normal or even low and shows no significant variations (Yen et al., 1970).

In cases of amenorrhoea and oligomenorrhoea characterised by normal FSH and LH levels which vary from day to day but without any evidence of cyclic release, the hypothalamic regulation of gonadotrophin secretion may be presumed to be disturbed even though there is no detectable organic lesion. This secretion pattern is also seen in anorexia nervosa of short duration, in psychogenic amenorrhoea and in galactorrhoea without tumour (Dignam et al., 1969). In most of these cases, the administration of clomiphene evokes a release of FSH and LH and in some cases restores the secretory gonadotrophin sequence, thus leading to ovulation.

Lastly, FSH and LH levels are sometimes found to be normal but stable, reflecting autonomous pituitary secretion with a loss of hypothalamic control. In such cases, clomiphene fails to produce a release of FSH and LH.

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