

The luteinizing hormone–releasing hormone pulse generator in men: Abnormalities and clinical management

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Most men with hypogonadotropic eunuchoidism have absent luteinizing hormone and presumably absent luteinizing hormone–releasing hormone pulses. Pulsatile luteinizing hormone–releasing hormone therapy is effective in restoring normal gonadotropin secretion and testicular function and inducing fertility in men with hypogonadotropic eunuchoidism. Furthermore, pulsatile (versus continuous) luteinizing hormone–releasing stimulation of the pituitary gland is an absolute requirement for normal gonadotropin secretion. Men with idiopathic oligozoospermia and selective elevation of follicle-stimulating hormone levels have slow luteinizing hormone and presumably luteinizing hormone–releasing pulse frequency. In these men, pulsatile luteinizing hormone–releasing treatment is effective in decreasing serum follicle-stimulating hormone levels, but it is unclear whether spermatogenesis and fertility are improved. (AM J OBSTET GYNECOL 1990;163:1743-52.)

Key words: Hypogonadotropic eunuchoidism, luteinizing hormone, luteinizing hormone–releasing hormone, idiopathic oligozoospermia, follicle-stimulating hormone

Secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) by the anterior pituitary gland is controlled by LH-releasing hormone (LHRH) secretion from the hypothalamus. LHRH is released episodically into the hypophyseal portal system and stimulates the pulsatile secretion of LH and FSH into the peripheral circulation, which in turn regulate gonadal function.

Because of its short circulating half-life,¹ LHRH is found in highest concentrations in the hypophyseal portal circulation and is difficult to detect in peripheral blood, making direct clinical assessment of pulsatile LHRH secretion impossible. Studies in experimental animals have confirmed that the pattern of pulsatile LH secretion into peripheral blood is a very good index of episodic LHRH release from the hypothalamus.^{2,3} Therefore we and others have used frequent blood-sampling studies to characterize LH pulse patterns carefully as indexes of hypothalamic LHRH pulse–generator activity in humans.^{4,5}

Two major disorders of LHRH pulse generation

have been identified by comparing the patterns of pulsatile LH secretion in these disorders with those of normal men: (1) hypogonadotropic eunuchoidism or idiopathic hypogonadotropic hypogonadism and (2) idiopathic oligozoospermia with selectively elevated serum FSH levels.

LHRH pulse generator in hypogonadotropic eunuchoidism

Hypogonadotropic eunuchoidism is a heterogeneous disorder characterized by failure to undergo normal pubertal development (usually by 18 years of age), low serum testosterone levels, low or normal serum gonadotropin concentrations, and otherwise normal anterior pituitary functioning.^{6,8}

The clinical presentation of hypogonadotropic eunuchoidism is variable because of differences in the onset and severity of the disorder. The hypogonadotropic hypogonadism is often associated with anosmia or hyposomia (Kallmann's syndrome) and other midline morphologic and functional defects such as cleft lip and palate.^{6,8} The mode of inheritance of hypogonadotropic eunuchoidism is variable.^{6,7} The underlying pathophysiology of the hypogonadotropic hypogonadism is presumed to be relative deficiency of LHRH secretion.

To characterize the abnormalities in the LHRH pulse generator in men with hypogonadotropic eunuchoidism, frequent blood-sampling studies (e.g., every 10 minutes for 24 hours) have been performed to define the secretory patterns of hypogonadotropic eunuchoidism, which reflect those of LHRH.^{5,9} Compared with

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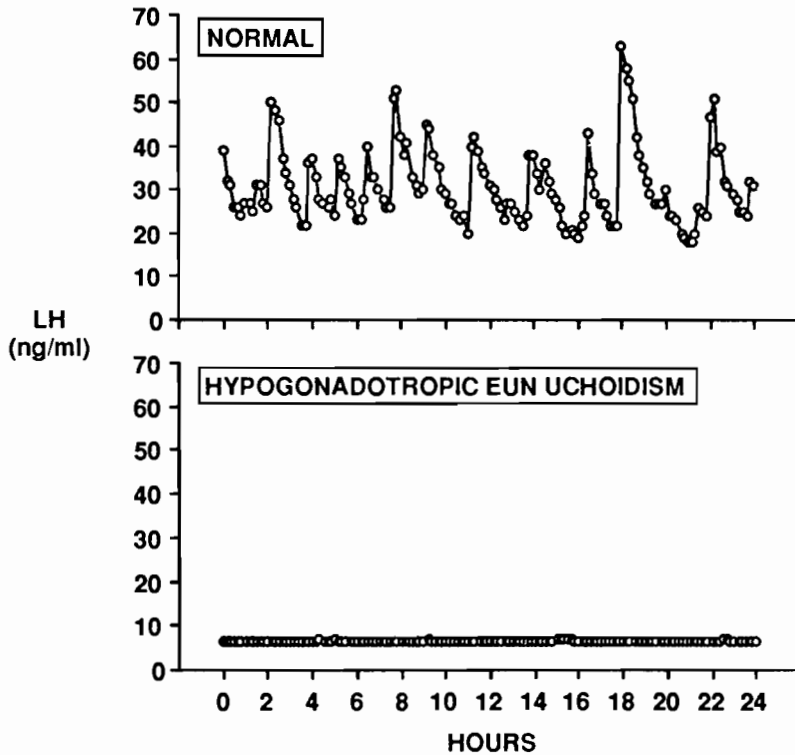


Fig. 1. LH pulse patterns in a normal man (*top*) and a man with hypogonadotropic eunuchoidism (*bottom*), as determined on frequent blood sampling studies performed every 10 minutes for 24 hours. Note the absence of spontaneous LH pulses in the man with hypogonadotropic eunuchoidism.

normal men who demonstrate LH pulses every 100 to 120 minutes, the vast majority (more than 90%) of men with hypogonadotropic eunuchoidism have no detectable LH pulses during frequent blood sampling (i.e., an apulsatile pattern^{5, 9}) (Fig. 1), suggesting absent or severely reduced LHRH pulse generation. In other men with hypogonadotropic eunuchoidism, decreases in LH pulse amplitude or frequency have been reported,^{5, 9} suggesting disordered LHRH pulse generation.

LHRH pulse generator in oligozoospermia with selective elevation of FSH levels

Approximately 5% to 6% of men in the reproductive age group are infertile. The majority of infertile men have disordered spermatogenesis of unknown cause (i.e., idiopathic oligozoospermia). Approximately 20% of men with oligozoospermia have elevated serum FSH and normal serum LH and testosterone levels.¹⁰

Several mechanisms have been proposed to explain the selective elevations in FSH relative to LH levels in these men, including increased pituitary stimulation by a separate FSH-releasing factor and decreased testicular production of negative feedback factors, such as inhibin¹¹ and/or sex steroids.¹² We and others have

found evidence for an alternative hypothesis to explain selective elevation of FSH levels (i.e., that the frequency of LHRH stimulation of the pituitary gland is capable of differentially regulating FSH and LH levels).^{13, 14}

Men with selectively increased FSH levels often demonstrate a reduced LH pulse frequency compared with normal men (Fig. 2). We performed frequent blood sampling every 10 minutes for 24 hours to characterize LH pulse patterns in a group of five men with elevated FSH and normal LH and testosterone levels and seven age-matched normal men. Men with selective elevations in FSH levels had fewer LH pulses per 24 hours (10.6 ± 0.5 , mean \pm SEM) than had normal men (12.9 ± 0.6 ; $p < 0.01$), with no significant differences in LH pulse amplitude and total and free testosterone and estradiol levels.¹³ Other investigators have also found a reduced LH pulse frequency in men with selective elevations in FSH levels compared with normal men.¹⁴ These findings suggest that the frequency of LHRH pulse generation is reduced in men with idiopathic oligozoospermia and selective elevation in FSH levels.

The spermatogenic defect in men with idiopathic oligozoospermia has been attributed to a primary testicular disorder. However, there is generally no history of known causes of testicular damage, and biopsy speci-

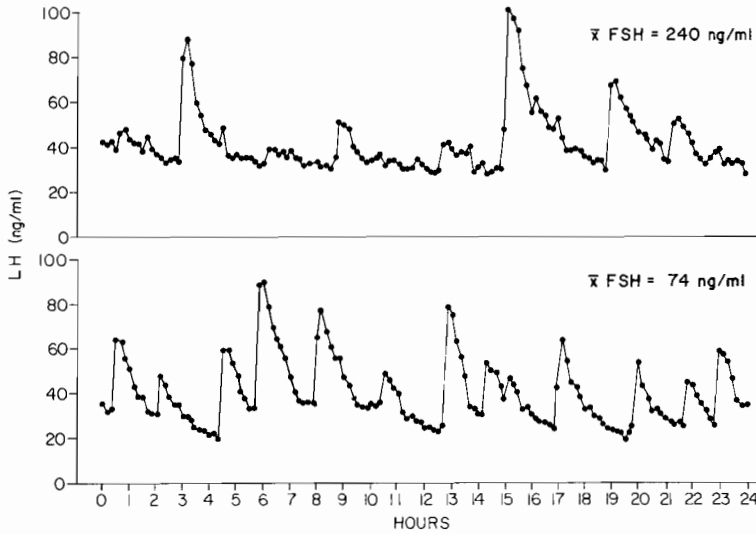


Fig. 2. LH pulse patterns in a man with idiopathic oligozoospermia and selective elevation of serum FSH levels (*top*) and a normal man (*bottom*), as determined on frequent blood-sampling studies performed every 10 minutes for 24 hours. Note the decreased frequency of spontaneous LH pulses in the man with oligozoospermia and selective elevations of FSH levels.

mens of testes do not demonstrate pathologic correlates of injury, such as inflammation or fibrosis.¹⁰ Therefore it is possible that some men with idiopathic oligozoospermia may have a primary hypothalamic rather than testicular disorder, resulting in decreased LHRH pulse frequency, selective elevations in FSH levels, and disordered spermatogenesis as a result of the altered hormonal milieu. We and others are beginning to test this hypothesis by determining the effect of long-term pulsatile LHRH administration at increased pulse frequencies on sperm production in men with idiopathic oligozoospermia and selective elevations in FSH levels (see below).

Treatment of hypogonadotropic eunuchoidism

Most men with hypogonadotropic eunuchoidism have deficient hypothalamic LHRH pulse generation, resulting in absent pulsatile gonadotropin secretion and lack of spontaneous pubertal development. Depending on the clinical situation, hypogonadotropic eunuchoidism may be treated with testosterone, gonadotropins, or "physiologic" pulsatile LHRH replacement.

If pubertal development and normal sexual functioning are desired but induction of fertility is not an issue, treatment of hypogonadotropic eunuchoidism is most practically accomplished with testosterone therapy. A long-acting 17 β -hydroxyl ester of testosterone, such as testosterone enanthate or cypionate, 100 to 200 mg intramuscularly every 10 days to 2 weeks, results in significant virilization by 4 to 6 months of treatment.¹⁵ The development of longer-acting analogs of testosterone may reduce the requirement for injections to every 3 to 4 months.

When stimulation of sperm production and induction of fertility are desired, gonadotropin or pulsatile LHRH therapy is required. Gonadotropin therapy is usually initiated with a preparation containing LH-like activity alone, such as human chorionic gonadotropin (hCG), 1000 to 3000 units subcutaneously or intramuscularly two to three times weekly for 6 months, to stimulate testicular steroidogenesis and induce virilization.¹⁶⁻¹⁹ In some men, treatment with hCG alone may also induce spermatogenesis. However, in most men with hypogonadotropic eunuchoidism a preparation with FSH activity, such as human menopausal gonadotropin, 37.5 to 150 units subcutaneously or intramuscularly two to three times weekly, must be coadministered with hCG for another 6 months to 1 year to stimulate sperm production and induce fertility.¹⁶⁻¹⁹ Prior testosterone therapy does not alter subsequent testicular responsiveness to gonadotropin therapy.^{18, 20}

With the availability of LHRH for clinical use and portable, automatic infusion pumps, long-term, physiologic LHRH-replacement therapy for hypogonadotropic eunuchoidism has become a practical therapeutic option for men with hypogonadotropic eunuchoidism. In general, low doses (5 to 20 μ g) of subcutaneous LHRH are administered at a frequency similar to that in normal men (i.e., every 2 hours).^{5, 21} Pulsatile LHRH administration in men with hypogonadotropic eunuchoidism results in a rapid restoration of pituitary gonadotropin secretion by several weeks of treatment (Fig. 3) and normalization of testosterone secretion during the initial 3 months of therapy.²² Continued pulsatile LHRH treatment for several months or years can stimulate sperm production and induce fer-

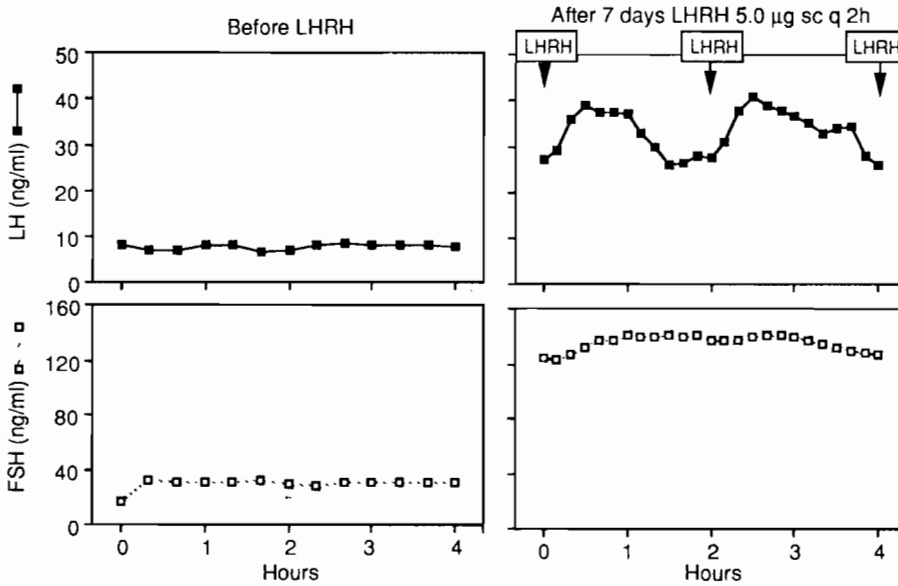


Fig. 3. Mean serum LH (top) and FSH (bottom) levels during frequent blood sampling every 20 minutes for 4 hours in four men with hypogonadotropic eunuchoidism before (left) and after 7 days of pulsatile LHRH therapy (5 μg subcutaneously every 2 hours). LH and FSH levels are low and there are no spontaneous LH pulsations before LHRH therapy. After 7 days of pulsatile LHRH treatment, both LH and FSH levels increase into the normal adult male range (8 to 60 ng/ml and 30 to 230 mg/ml, respectively), and discrete LH pulses follow each LHRH bolus, mimicking a normal physiologic LH pulse pattern.

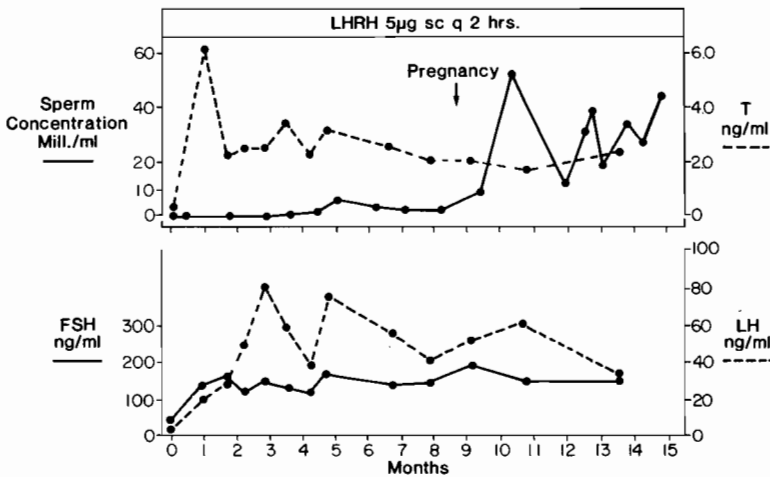


Fig. 4. Testicular (top) and gonadotropin (bottom) responses to long-term pulsatile LHRH therapy (5 μg every 2 hours for 15 months) in a man with hypogonadotropic eunuchoidism. Pulsatile LHRH treatment increases LH, FSH, and testosterone (T) levels into the normal adult male range by 1 month and stimulates sperm production by 9 months, resulting in fertility. (From Matsumoto AM, Bremner WJ. *Bailliere's Clin Endocrinol Metab* 1987;1:71.)

tility in men with hypogonadotropic eunuchoidism (Fig. 4).^{21,22} The ability of exogenous pulsatile LHRH administration to restore pituitary gonadotropin and testicular function is consistent with the hypothesis that hypogonadotropic eunuchoidism is caused by a deficiency in LHRH pulse generation.

Previous studies in hypothalamic-lesioned, LHRH-deficient monkeys have demonstrated that a pulsatile mode of LHRH administration is absolutely necessary for normal pituitary gonadotropin secretion, whereas continuous administration failed to maintain normal gonadotropin levels.²³ In humans continuous

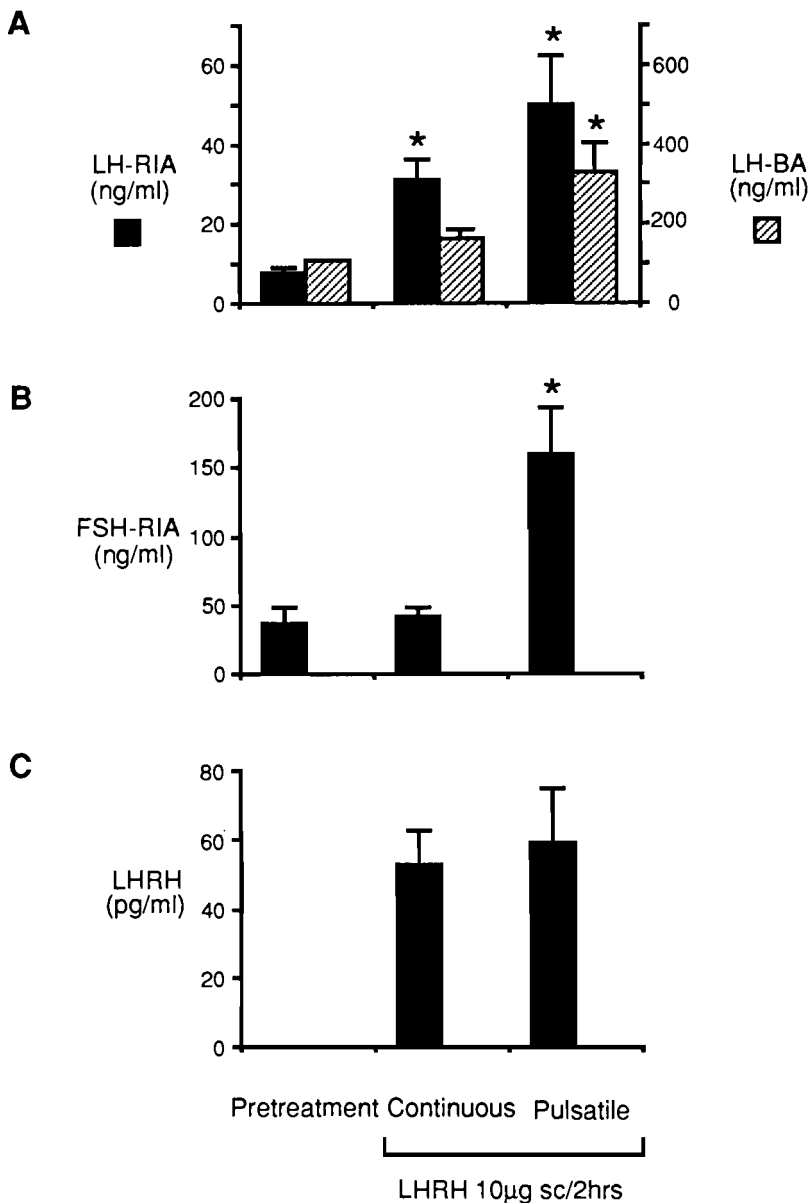


Fig. 5. Mean (\pm SEM) serum LH by radioimmunoassay (RIA) and bioassay (BA), FSH, RIA, and LHRH levels in four men with hypogonadotropic eunuchoidism before (pretreatment) and at the end of 1 week each of continuous and pulsatile LHRH infusions (10 μ g every 2 hours). Compared with pretreatment values, serum LH-RIA levels (solid bars, A) increased significantly during both continuous and pulsatile LHRH treatment. However, compared with pretreatment levels, LH-BA (hatched bars, A) and FSH-RIA (B) were not significantly different during the continuous regimen but did increase significantly during pulsatile LHRH administration. LHRH concentrations (C) were similar during the continuous and pulsatile regimens. * $p < 0.05$, compared with pretreatment values. (From Matsumoto AM, Gross KM, Bremner WJ. The physiological significance of pulsatile LHRH secretion in man: gonadotropin responses to physiological doses of pulsatile versus continuous LHRH administration. *Int J Androl* [in press]. Copyright 1990 by Scriptor Publisher ApS, Copenhagen.)

administration of markedly supraphysiologic LHRH doses^{24, 25} or treatment with very potent, long-acting LHRH agonistic analogs²⁶ initially stimulates and then suppresses LH and FSH secretion. However, it was not known whether continuous administration of lower, more physiologic doses of LHRH (i.e., dosages known

to be effective in restoring testicular function when given in a pulsatile manner) could stimulate normal pituitary gonadotropin secretion in humans.

To assess the physiologic significance of pulsatile LHRH stimulation of the pituitary gland, we compared the gonadotropin responses to a physiologic dose of

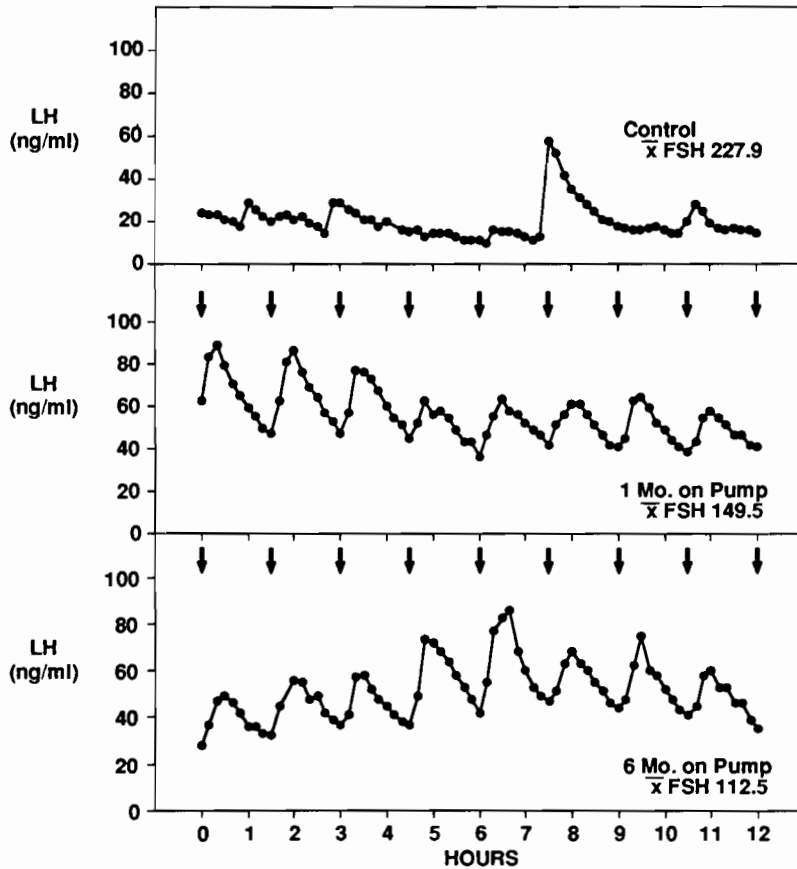


Fig. 6. Serum LH levels during frequent blood sampling every 10 minutes for 12 hours in a man with idiopathic oligozoospermia and selective elevation of FSH levels before (control) and 1 and 6 months after pulsatile LHRH therapy ($5 \mu\text{g}$ every 90 minutes). Arrows indicate the timing of LHRH pulses delivered by an automatic, portable infusion pump. Note that long-term pulsatile LHRH treatment increased the LH pulse frequency and mean LH levels while decreasing mean FSH levels.

LHRH administered in pulsatile versus continuous pattern in four men with hypogonadotropic eunuchoidism.²⁷ These men stopped hormone treatment for 5 to 6 weeks before being studied (pretreatment) and then were treated with LHRH, $5 \mu\text{g}$ subcutaneously every 2 hours for 1 week, to prime pituitary responsiveness. After this period of LHRH priming, each man received the same physiologic dose ($10 \mu\text{g}$) subcutaneously every 2 hours in a pulsatile fashion for 1 week and as a continuous infusion for 1 week, in varying order. Frequent blood sampling for LH, FSH, and LHRH was performed every 20 minutes for 4 hours during the pretreatment period and at the end of each LHRH regimen. We found that pulsatile LHRH administration in a physiologic dose stimulated normal pituitary LH and FSH secretion (Fig. 5). In contrast, continuous LHRH infusion of the same physiologic LHRH dose increased immunoreactive LH levels but did not stimulate bioactive LH levels or FSH levels above pretreatment values (Fig. 5). Serum LHRH (Fig. 5), testosterone, and estradiol levels were comparable during the pulsatile and

continuous infusions. These results demonstrate that a pulsatile versus continuous LHRH signal is an absolute requirement for normal pituitary gonadotropin secretion in men. Therefore, they suggest that low-dose continuous LHRH administration is unlikely to stimulate normal testicular function.

Treatment of men with oligozoospermia who demonstrate selective elevations of FSH levels

Infertile men with idiopathic oligozoospermia and high serum FSH levels are considered to have irreversible seminiferous tubular damage. Many therapeutic modalities have been tried but have been uniformly unsuccessful in improving sperm production and fertility in these men. However, compared with normal men, men with idiopathic oligozoospermia and selective elevation of FSH levels demonstrate a decreased frequency of spontaneous LH pulses. This raises the possibility that some of these men may have a primary abnormality of hypothalamic LHRH pulse generation. We hypothesized that the disordered spermatogenesis

in these men may be a consequence of the altered hormonal milieu induced by the abnormally slow LHRH pulse frequency, and LHRH administration at more rapid pulse frequencies may reduce FSH levels and improve sperm production.

As an initial test of this hypothesis, we have shown that short-term administration of LHRH at increasing pulse frequencies results in a progressive decrease in serum FSH levels into the normal range, without significant changes in serum LH, testosterone, and estradiol levels.²⁸ Similar findings have been reported by others.²⁹

The effects of LHRH on LH and FSH levels in our study are consistent with previous work in animals³⁰⁻³² and men,^{13, 28, 29, 33} which has shown that increasing the LHRH pulse frequency leads to more rapid LH pulses but lower mean FSH levels. Conversely, slowing the LHRH pulse frequency led to slower LH pulses and higher FSH levels. This finding of a differential effect of LHRH pulse frequency on LH and FSH levels has been extended by more recent work in animals demonstrating selective control of gonadotropin subunit gene expression by the frequency of pulsatile LHRH stimulation.³⁴

To test further the hypothesis that reduced LHRH pulse frequency may cause or contribute to the spermatogenic defect in men with idiopathic oligoazoospermia and selective elevation of FSH levels, we tested the effects of more prolonged (6 to 12 months) administration of pulsatile LHRH at a relatively rapid pulse frequency.

In this preliminary study we studied seven men with idiopathic oligoazoospermia (with mean sperm concentrations on three to six specimens during 3 months of less than 20 million/ml), elevated FSH levels (normal range 30 to 230 ng/ml), and normal LH and testosterone levels (8 to 60 ng/ml and 2.8 to 10.0 ng/ml, respectively). All subjects were infertile for more than 1 year but were otherwise healthy as determined by history and physical examination. None had known primary testicular disease and testis size ranged from 15 to 25 ml.

After a 3-month control period during which no hormones were administered, subjects began a 6-month treatment period throughout which they received LHRH, 5 µg subcutaneously every 90 minutes, into the abdominal wall by a portable automatic infusion pump (Zyklomat; Ferring Laboratories, Suffern, N.Y.). In two men pulsatile LHRH treatment at the same dosage was continued for 12 months. At the end of the treatment period, LHRH was discontinued and subjects were followed up for an additional 3 months (recovery period).

Throughout the entire study, seminal fluid analyses^{35, 36} were performed every 2 weeks on semen samples obtained by masturbation after 48 hours of abstinence

from ejaculation. Frequent blood sampling for LH and FSH levels by radioimmunoassay^{4, 36} was performed every 10 minutes for 12 hours at the end of the control period, after 1 and 6 months of treatment, and at the end of the recovery period; testosterone and estradiol levels were measured by radioimmunoassay³⁷ in single samples at the beginning of the frequent sampling studies (7:00 to 9:00 AM).

During the control period, all subjects demonstrated a slow spontaneous LH pulse frequency typical of this group of patients.¹³ After 1 and 6 months of LHRH treatment, 5 µg every 90 minutes, LH pulse frequency increased and the LH patterns in all men were directly related to the activity of the LHRH pump (Fig. 6). After exogenous LHRH was discontinued, LH pulse frequency reverted to the typically slower frequency exhibited in the control period.

Compared with control levels (41 ± 4 ng/ml), LH levels increased significantly after 1 and 6 months of LHRH treatment (70 ± 7 and 70 ± 13 ng/ml, respectively; both $p < 0.05$). Three months after discontinuation of LHRH, LH levels decreased to 35 ± 5 ng/ml and were comparable to control values. During the control period, FSH levels (311 ± 25 ng/ml) were considerably higher than the upper limit of the normal range for men. FSH levels decreased after 1 and 6 months of LHRH treatment to 236 ± 30 and 264 ± 52 ng/ml, respectively (borderline significance, $p < 0.09$), and rose to near control values (300 ± 42 ng/ml) in the recovery period.

Testosterone levels increased from 3.9 ± 0.2 ng/ml during the control period to 4.6 ± 0.7 and 5.4 ± 0.7 ng/ml after 1 and 6 months of LHRH treatment, respectively. Three months after LHRH therapy was completed, testosterone levels decreased to 3.3 ± 0.3 ng/ml. During the control period, estradiol levels were 26 ± 4 pg/ml, rose to 47 ± 5 pg/ml and 52 ± 9 pg/ml after 1 and 5 months of LHRH treatment, respectively, and then decreased to 35 ± 9 pg/ml at the end of the recovery period.

Before the LHRH treatment, five of seven men had azoospermia. No sperm appeared in the ejaculates of the subjects with azoospermia at any time during the study period. One man with control sperm counts of 0.6 to 7.0 million/ml remained severely oligospermic and infertile during LHRH therapy. The final subject had less severe oligospermia at baseline (sperm counts 2.0 to 26.2 million/ml). Although sustained improvement in his sperm counts during pulsatile LHRH treatment (2.8 to 37.4 million/ml) could not be established, this man impregnated his wife after 3 months of LHRH therapy. In two men, continuing LHRH therapy for as long as 12 months did not improve sperm production.

Our preliminary results demonstrate that the long-term administration of exogenous LHRH to men with

idiopathic oligozoospermia with a more rapid physiologic pulse frequency can reliably increase their LH pulse frequency and decrease their mean serum FSH levels, but we were unable in these studies to demonstrate an improvement in sperm production.

Recently Bals-Pratsch et al.³⁸ reported results of long-term pulsatile LHRH therapy in nine men with idiopathic oligozoospermia with elevated serum FSH levels that were similar to our findings. Six men with severe oligospermia (sperm counts <5 million/ml) and three men with azoospermia received the same LHRH dosage regimen that we used in our study (i.e., 5 µg subcutaneously every 90 minutes) by a portable infusion pump for 24 weeks. Despite lowering serum FSH levels, pulsatile LHRH treatment did not result in any improvement of sperm count or other seminal fluid parameters.

However, other groups have reported a stimulatory effect of long-term pulsatile LHRH treatment in men with oligospermia with elevated FSH levels. Wagner and von zur Mühlen³⁹ found that in some men with severe oligospermia (sperm counts <10 million/ml) and elevated serum FSH levels, pulsatile LHRH therapy (4 µg every 129 minutes) for 6 to 12 months increased progressively motile sperm density.

Recently Aulitzky et al.⁴⁰ determined the effect of long-term pulsatile LHRH treatment in men with varying degrees of oligospermia, elevated serum FSH levels, and slow spontaneous LH pulse frequency. Subjects were grouped according to the severity of their spermatogenic defect, based on the SPT score (number of type A_d spermatogonia per tubule square) and sperm density. Group 1, with the least testicular damage, had SPT scores of 1.0 or greater and sperm densities of 1 to 20 (8.84 ± 4.0) million/ml, group 2 had SPT scores of 0.25 to 1.0 and sperm densities of 1 to 20 (3.38 ± 1.75) million/ml, and group 3, with the most severe spermatogenic dysfunction, had SPT scores less than 0.25 and sperm densities of less than 1 (0.65 ± 0.31) million/ml. Administration of pulsatile LHRH (4 µg every 120 minutes) for a period of 6 months significantly increased sperm density (with three pregnancies) and serum LH levels and decreased serum FSH levels in men with less severe degrees of spermatogenic damage (i.e., groups 1 and 2). In contrast, men with severe testicular damage (group 3) failed to show significant changes in sperm density or FSH levels.

These results of Aulitzky et al. suggest that some men with idiopathic oligospermia and selective elevations in FSH levels may benefit from pulsatile LHRH treatment. Furthermore, they suggest that baseline assessment of the severity of the spermatogenic disorder (e.g., by SPT scores) may be useful in selecting patients who are more likely to respond to therapy. These find-

ings may also help to explain why we and Bals-Pratsch et al.,³⁸ who studied men with severe spermatogenic dysfunction, failed to show a stimulatory effect of pulsatile LHRH therapy on sperm production.

None of the studies investigating pulsatile LHRH treatment of men with idiopathic oligozoospermia included placebo-treated control subjects. Because sperm counts exhibit marked within-individual fluctuations in men with oligospermia, such controls are essential in determining whether pulsatile LHRH therapy indeed has a stimulatory effect on spermatogenesis. Because no other therapeutic options exist, the use of pulsatile LHRH therapy for men with idiopathic oligospermia and selective elevations of FSH levels deserves to be evaluated critically in formal double-blind, placebo-controlled clinical trials. Pulsatile LHRH treatment is the only promising new therapeutic modality on the horizon for this common and, at the present time, untreatable disorder.

In summary, using frequent measurement of blood LH levels to reflect episodic LHRH release, two major disorders of the LHRH pulse generator have been characterized in men: (1) men with hypogonadotropic eunuchoidism, most of whom lack detectable LH pulses and presumably have LHRH deficiency, and (2) men with idiopathic oligozoospermia with selective elevations in serum FSH levels many of whom demonstrate decreased spontaneous LH pulse frequency, presumably as a result of slowed LHRH pulse generation.

In men with hypogonadotropic eunuchoidism long-term low-dose (physiologic) pulsatile LHRH administration is effective in restoring normal pituitary gonadotropin and testicular steroid and sperm production. In contrast, continuous administration of a physiologic LHRH dosage, although increasing immunoreactive LH levels, does not stimulate bioactive LH levels or FSH levels. Therefore a pulsatile LHRH stimulus pattern is an absolute requirement for normal pituitary gonadotropin secretion in men, and long-term low-dose continuous LHRH treatment is unlikely to stimulate normal testicular function.

In men with idiopathic oligozoospermia and selective elevation of FSH levels, long-term pulsatile LHRH administration is effective in decreasing serum FSH levels. However, the efficacy of LHRH treatment in stimulating spermatogenesis and improving fertility in these men is unclear. Because this therapeutic modality holds promise as a useful treatment for a common, presently untreatable disorder, it deserves further formal clinical investigation.

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