0021-972X/80/5101-0173$02.00/0
Journal of Clinical Endocrinology and Metabolism
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Vol. 51, No. 1
Printed in U.S.A.

SIMULATION OF THE NORMAL MENSTRUAL CYCLE IN KALLMAN'S SYNDROME BY PULSATILE ADMINISTRATION OF LUTEINIZING HORMONE-RELEASING HORMONE (LHRH)

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ABSTRACT: The administration of small doses of LHRH at 2-hourly intervals over a 27 day period to a 24-year old patient with Kallman's syndrome resulted in ovulation as indicated by: (1) a biphasic temperature response, (2) anatomical changes in the ovaries demonstrated by ultrasound, and (3) the pattern of circulating gonadotropin and gonadal steroid concentrations.

In theory, luteinizing hormone releasing hormone (LHRH) possesses unique advantages over other agents for the induction of ovulation in a variety of anovulatory disorders. It affords the potential to: (a) utilize endogenous gonadotropins, (b) incorporate physiologic feedback mechanisms to assure release of the precise amounts of FSH and LH required to ripen and ovulate a single follicle, and (c) avoid ovarian hyperstimulation with the attendant requirement for dose monitoring. In practice, realization of these assets has proved elusive. Apart from a small group of patients with anorexia nervosa who were treated with thrice daily doses of 500 µg of LHRH (1), few have ovulated or conceived. Diagnostic ambiguities and inadequate monitoring have likely contributed to these disappointing results. However, the cardinal reason for failure appears to have been an unphysiologic mode of administration of LHRH. The observation that endogenous gonadotropins are discharged episodically in human beings (2-6) and that 60-90 min LHRH pulses reverse the hypogonadotropic state and induce apparent ovulation in arcuate-nucleus lesioned and prepubertal rhesus monkeys (7-9) and in hypothalamic amenorrhea (10-11), suggested that pulsatile administration of LHRH might induce follicular maturation and ovulation. Accordingly, we have initiated a program to evaluate the effectiveness of this mode of treatment, utilizing the Auto-Syringe, an automatically timed infusion pump, to administer LHRH in a pulsatile manner. We here report the induction of ovulation in a 24-year old woman with Kallman's syndrome, the entity selected for the initial trials.

Case History:

M.F. is an anosmic 24-year old woman with primary amenorrhea. She experienced a normal growth spurt and limited breast development at age 12. Axillary and pubic hair appeared at age 14, but menstruation did not ensue. No history of a similar occurrence in other family members could be elicited. On physical examination, the patient's height was 170.5 cm, span 174 cm and weight 69 kg. Breast development had attained Tanner stage II, and pelvic examination disclosed a tiny uterus and atrophic vagina. The serum LH was 1.2 mIU/ml, the FSH 4.0 mIU/ml LER 907, and the serum estradiol was < 20 pg/ml. The karyotype was XX and tomograms of the sella turcica were normal. The bone age was 16 years. Both the initial levels of TSH, prolactin, ACTH and growth hormone and those attained after stimulation with 200 µg TRF and 0.15 u/kg insulin were within normal limits. She was treated with conjugated estrogens 2.5 mg/day for 12 months until maximum breast growth had been achieved. Estrogen treatment was then suspended 30 days prior to the initiation of the therapeutic trial with LHRH.

Submitted January 30, 1980

Protocol:

The patient was admitted to the Clinical Research Center of the Massachusetts General Hospital, and blood was drawn at 20 minute intervals for 12 hours to establish accurate baseline levels of serum FSH, LH and estradiol. She was then given LHRH (25 ng/kg subcutaneously) at 2 hourly intervals for 27 days. The medication was administered via an automatically-timed infusion syringe (Auto-Syringe). Previous experience with this device indicated its suitability for out-patient delivery of insulin to diabetics (12) and LHRH to hypogonadotropic males (13). Isotopic calibration of this device demonstrated its capability to deliver the correct dosage (± 2%). The patient was examined daily to determine ovarian size and cervical mucus characteristics. Blood samples were drawn daily at 8 a.m., immediately before a bolus of LHRH. Ultrasonic examination of the ovaries was performed before treatment, and on day 13 of LHRH therapy.

Materials and Methods:

Serum LH, FSH, estradiol and progesterone levels were determined by radioimmunoassay methods previously reported (14). All samples for any given hormone were analyzed in a single assay. Under these assay conditions 1 mg LER 907 = 60 IU LH and 20 IU FSH of the 2nd IRP-hMG. Employing 200 λ of serum,

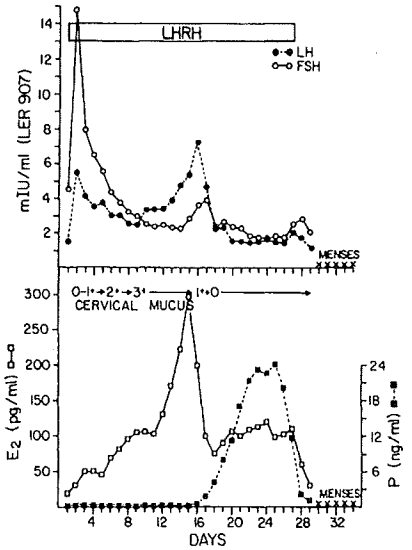

Figure 1. Serum FSH (o), LH (•), estradiol (□) and progesterone (■) correlated with cervical mucus characteristics in a 24-year old woman with Kallman's syndrome during 27-days of pulsatile LHRH therapy. Ultrasound examination on day 13 revealed a single follicle in the right ovary.

the sensitivity of the assay for LH was .3 mIU/ml while that for FSH was 1.0 mIU/ml. Intra-assay variability was < 10%. The range of normal mid-cycle peaks of LH and FSH in this assay are 10.7 - 36.6 and 2.6 - 11.0 respectively. Ultrasonic evaluation of ovarian size throughout the cycle was performed as previously reported (15).

Results:

The patient's baseline serum LH was 1.6 ± .06 (SE) mIU/ml LER 907, the serum FSH was 4.6 ± .08 mIU/ml, and the estradiol was < 20 pg/ml. Initially the ovaries were too small to be identified by a diligent ultrasound examination. Figure 1 depicts the patient's 8 a.m. levels of gonadotropins, gonadal steroids, and cervical mucus characteristics. Following 12 pulses of LHRH, her serum FSH and LH rose to peaks of 15.0 and 5.4 respectively, the estradiol increased from an undetectable level to 23 pg/ml. Subsequently, both gonadotropins declined, the serum FSH reaching a nadir of 2.3 on day 14, and LH a nadir of 2.5 on day 9 of therapy. Both gonadotropins then rose, reaching secondary peaks of LH (7.2) and FSH (3.9) on days 16 and 17, respectively. While these values were obtained just before an LHRH pulse and are thus nadir values for these days, both were within or near normal mid-cycle levels. Following these "mid-cycle surges", the gonadotropins declined until the 27th and last day of LHRH treatment, when the serum FSH rose to 2.5 and the LH to 2.0. The serum FSH level continued to rise for an additional day, but thereafter the levels of both FSH and LH declined.

During LHRH therapy, the estradiol rose steadily from undetectable levels to a peak of 300 on day 15. The estradiol peak preceded the LH peak by 1 day and the FSH peak by 2 days. After a decline to 72 on day 18, the estradiol level remained on a plateau above 100 for 8 days until LHRH treatment was terminated; it then declined precipitously from 112 to 60 pg/ml within 24 hours. The serum progesterone level remained below .20 ng/ml until day 16 (the day of the LH surge), when it increased to .54. The serum progesterone level then rose progressively attaining a peak of 24 nine days after the LH surge. During the last 24 hours of LHRH treatment, progesterone levels declined sharply from 20 to 11.7 and continued to fall after LHRH administration was terminated.

The cervical mucus exhibited delicate arborization at the outset, presumably a reflection of the previous estrogen treatment. Thereafter, both ferning and spinnbarkeit increased in synchrony with circulating estradiol levels until day 18. A marked change in the mucus then took place, with a decrease in volume and disappearance of the fern pattern that persisted until menses occurred. The basal body temperature rose on day 16 and remained elevated until the menstrual flow began. On day 13, both ovaries were detectable by ultrasound and a single cystic area was visualized in the right ovary.

Discussion:

Published evidence implying an LHRH defect in Kallman's syndrome include the demonstration of pathologic changes in the hypothalamus (16), responsiveness to Clomiphene stimulation in a subset of hyposmic male patients (17), and increases in LH and FSH responsiveness during the acute and chronic administration of LHRH (18-21). Thus, patients with anovulation attributable to this hypothalamic disorder seemed ideally suited for definition of a more physiologic "replacement" schedule of LHRH. The goals were to restore pulsatile gonadotropin secretion, to initiate gonadal function, and to demonstrate feedback modulation of gonadotropin release by gonadal secretions. If all of these criteria were met, the ripening and ovulation of an ovarian follicle should ensue. Selection of the LHRH dosage was based upon the findings of others (22) and upon our own experience with short-term LHRH administration to women with Kallman's syndrome and long-term administration to hypogonadotropic men (23). Timing was selected to imitate the endogenous LH pulses that occur at intervals of 60-120 minutes in normal men and women during the follicular phase of the menstrual cycle (2-5).

It appears that repetitive administration of these small doses of LHRH were successful in achieving all of the above-mentioned goals. Pulsatile release of LH and FSH (data not shown) was observed with an initial FSH-predominant pattern of secretion. Follicular maturation followed, as attested to by rising estradiol levels and ultrasonic appearance of the ovaries. Corpus luteum function appears to have been relatively normal judging by the peak progesterone levels and luteolysis had begun in a "physiologic" manner prior to the cessation of LHRH treatment. This observation contrasts with the deficient luteal phase reported to occur during the thrice daily administration of larger doses of LHRH to patients with anorexia nervosa (24).

The occurrence of ovulation in this patient is necessarily presumptive, since definitive confirmation (pregnancy, retrieval of an ovum, or direct visualization of a fresh corpus luteum) was not feasible.

It is of special interest that all of these changes occurred with a fixed input of hypothalamic releasing factor. This observation is consistent with the view of the hypothalamic role as merely a "permissive" one in these physiologic events (8,9). It is important to note, however, that such successes of hypothalamic replacement do not preclude an important modulatory role for the hypothalamus during the normal menstrual cycle. Replacement experiments may still employ a supraphysiologic program of LHRH to achieve the goals of folliculogenesis, ovulation, and corpus luteum function. The normal hypothalamus might achieve these same changes with subtler modulations of dosage and frequency of LHRH discharge. Further studies are needed to define more precisely the role of the hypothalamus in the normal menstrual cycle.

Such studies provide an opportunity to gain additional insight into the physiologic control of the menstrual cycle. On a practical level, the possibility of harnessing endogenous feedback mechanisms to control the amount of FSH secreted during ovulation induction promises an advance in safety and efficacy over existing methods. Use of a portable and automatically-timed pump such as the Auto-Syringe should permit such a program to be mounted on an outpatient basis. Investigation of the susceptibility of other anovulatory disorders to pulsatile LHRH treatment is required, and is in progress in our laboratory.

Acknowledgements:

We gratefully recognize the invaluable assistance of Judith Donnelly, Carolyn Albers and Nancy Delaney.

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