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Subcutaneous Pulsatile LH-RH Therapy of Secondary Amenorrhoea

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INTRODUCTION

Luteinizing hormone-releasing hormone (LH-RH, LRH) has been clinically available for more than 10 years. Since the identification and synthesis of this hypothalamic hormone, numerous studies have been performed to study its clinical usefulness in reproductive endocrinology. However, LH-RH never came to play an important role in the diagnostic evaluation and treatment of amenorrhoea and infertility during the seventies (2,5).

New insights into the neuroendocrine regulation of the menstrual cycle (3) gave an impetus to further clinical trials with LH-RH for treatment of anovulatory infertility. Intermittent LH-RH stimulation of the pituitary has recently been shown to be important for optimal gonadotrophin secretion (1). Pulsatile injections of small doses of LH-RH at intervals of 1 - 2 hours seem to mimic the physiological stimulation of the pituitary gonadotrophs. The development of small automatically-timed infusion pumps has made this mode of delivery of LH-RH practically possible. The preliminary results with pulsatile low dose LH-RH therapy of hypogonadotrophic hypogonadism are promising.

This paper reviews our experience with subcutaneous LH-RH and LH-RH agonist therapy of secondary amenorrhoea.

CHRONIC INTERMITTENT HIGH DOSE LH-RH THERAPY

In the mid-seventies it was shown that long-term pulsatile subcutaneous (s.c.) self-administration of a high dose (500 μg) of LH-RH every eight hours was effective in inducing both follicular maturation and ovulation in hypogonadotrophic amenorrhoeic women with no evidence of endogenous oestrogen production (4). This is illustrated by Fig. 1, which shows simulation of a normal ovulatory menstrual cycle by chronic intermittent administration of a high s.c. dose of LH-RH in a woman with hypogonadotrophic hypothalamic amenorrhoea. It is interesting to note the quantitative and qualitative changes in the pituitary gonadotrophin responses to LH-RH which occurred during the

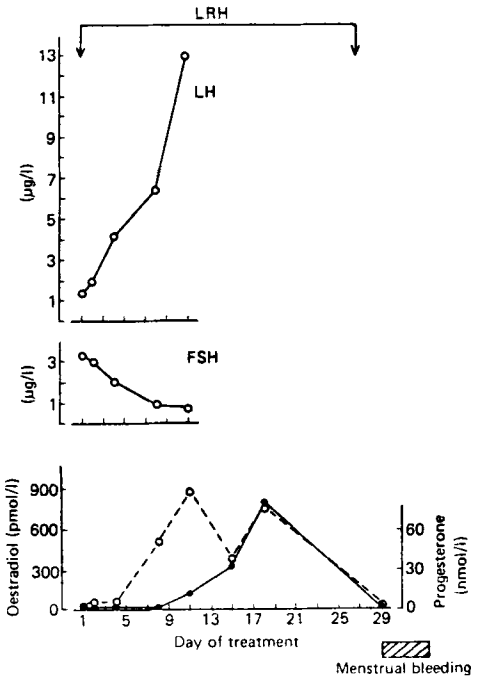

Fig. 1. A normal ovulatory menstrual cycle induced by chronic intermittent high dose LRH treatment (500 µg s.c. every eight hours) of a 33-year-old woman with secondary amenorrhea due to anorexia nervosa. Gonadotrophin responses (above and centre) to LRH and serum levels (below) of oestradiol (o) and progesterone (●) are shown in the figure. The blood samples for the FSH and LH determinations were taken 90 min after subcutaneous administration of the 500 µg LRH dose. Data from Nillius et al. (7).

prolonged pulsatile treatment with an unchanged dose given with the same frequency throughout the LH-RH induced menstrual cycle.

The normal feedback system between the ovaries and the pituitary is operative during LH-RH treatment. When follicular maturation occurs and oestrogen secretion starts to increase, the FSH responsiveness to LH-RH decreases while the LH responsiveness increases (Fig. 1). Theoretically, it should be possible to avoid ovarian hyperstimulation during long-term LH-RH therapy. The intact interrelationship between the ovaries and the pituitary makes it possible to treat anovulatory infertility without the strict daily monitoring which is mandatory during human gonadotrophin therapy (Fig. 2).

Thus, by chronic intermittent high dose LH-RH therapy it was possible to induce normal ovulatory menstrual cycles and pregnancy in hypogonadotrophic amenorrhoeic women without endogenous ovarian activity. However, insufficient luteal function frequently occurred (4). The treatment was also rather cumbersome and never came into clinical routine use.

LH-RH AGONIST THERAPY

Long-acting highly potent agonists of LH-RH were then synthesized to facilitate treatment of infertility caused by hypogonadotrophic hypogonadism.

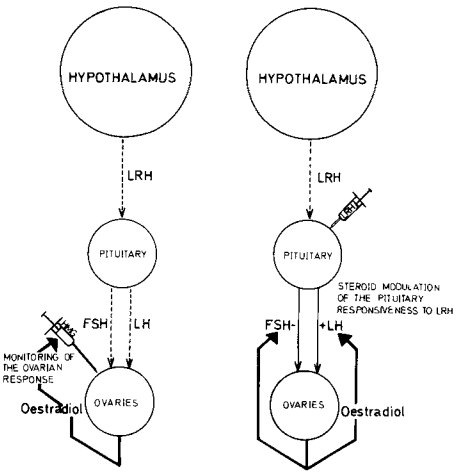

Fig. 2 During induction of follicular growth and maturation by human menopausal gonadotrophins (HMG), monitoring the ovarian response by frequent serum oestradiol determinations is mandatory (left). During chronic intermittent LH-RH therapy, oestradiol from the maturing follicle(s) feeds back at the pituitary level and modulates the responsiveness to LH-RH (right). This feedback system should automatically prevent serious ovarian hyperstimulation during chronic LH-RH therapy.

However, paradoxically the superactive stimulatory analogues of LH-RH seemed to be anti-fertility by nature. We could not induce follicular maturation and ovulation by chronic LH-RH agonist therapy of women with secondary amenorrhoea (8). The superagonists of LH-RH are currently under clinical investigation for potential use as contraceptives. Daily intranasal LH-RH agonist administration has been shown to provide safe and effective contraception in women by desensitizing the pituitary so that ovulation is inhibited (6).

CHRONIC INTERMITTENT LOW DOSE LH-RH THERAPY

The small portable computerized infusion pump Zyklomat® (Ferring) was used for pulsatile delivery of low doses (5 - 20 µg) of LH-RH every 90 min. The s.c. route of administration was preferred for the prolonged treatment of anovulatory infertility. The LH-RH dose was infused during one min every 90 min via an indwelling catheter inserted in the s.c. fat tissue of the lower abdominal wall. The therapy was given with the same frequency until menstruation or pregnancy occurred. Human chorionic gonadotrophin (HCG) was not added to support corpus luteum function. If conception did not occur, the pulsatile LH-RH treatment was given without interruption to induce a new ovulatory cycle (9,10).

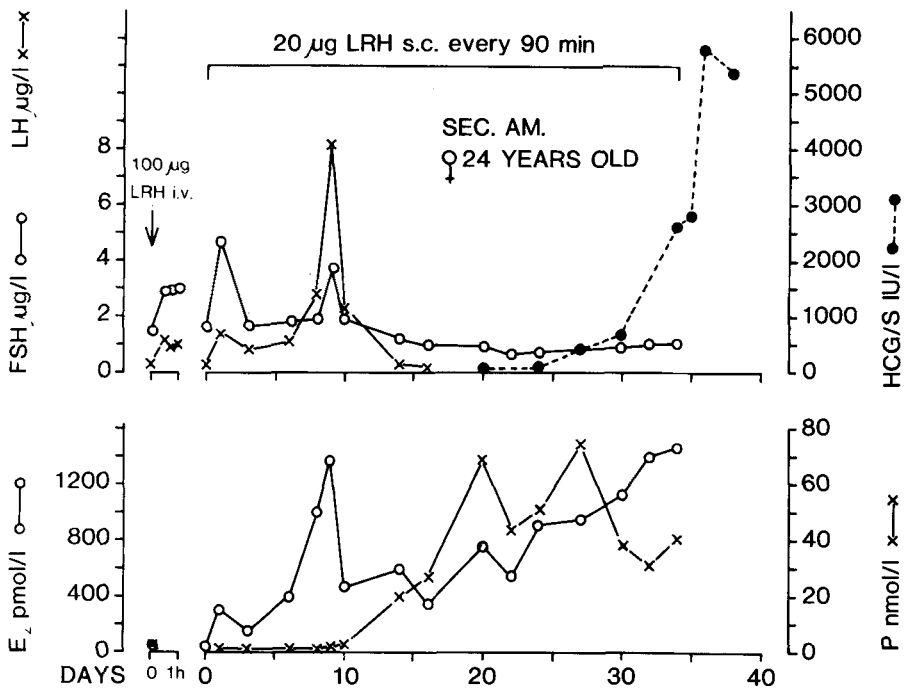

Fig. 3 Serum levels of FSH, LH, HCG, oestradiol (E_2) and progesterone (P) during a normal conceptual cycle induced by s.c. pulsatile low dose LH-RH treatment of a 24-year-old woman with secondary amenorrhoea. FSH and LH response to intravenous (i.v.) LH-RH before treatment are also shown. Reproduced from Skarin et al. (9), with permission.

Seventeen infertile 24-31 year-old amenorrhoeic women, who did not respond to clomiphene citrate, were given 23 treatment courses with a duration of 26 - 187 days (median 70 days). Forty-six ovulatory cycles were induced in 15 of the 17 women. Eleven pregnancies, 10 single and one duplex, occurred. Six healthy children have been born. Three early spontaneous abortions occurred.

Hormone values during a conceptual cycle induced by s.c. pulsatile low dose LH-RH are illustrated in Fig. 3. The pretreatment intravenous LH-RH test showed that the patient had a prepubertal response pattern with a greater FSH than LH release. During the first days of LH-RH therapy, the patient released predominantly FSH which initiated follicular growth. The FSH response to LH-RH decreased during follicular maturation when the oestrogen secretion increased. Oestradiol in serum reached a normal high pre-ovulatory peak which induced an LH surge and ovulation. When pregnancy was diagnosed by HCG, the pulsatile LH-RH treatment was discontinued. One healthy boy was born after an uneventful term pregnancy (9).

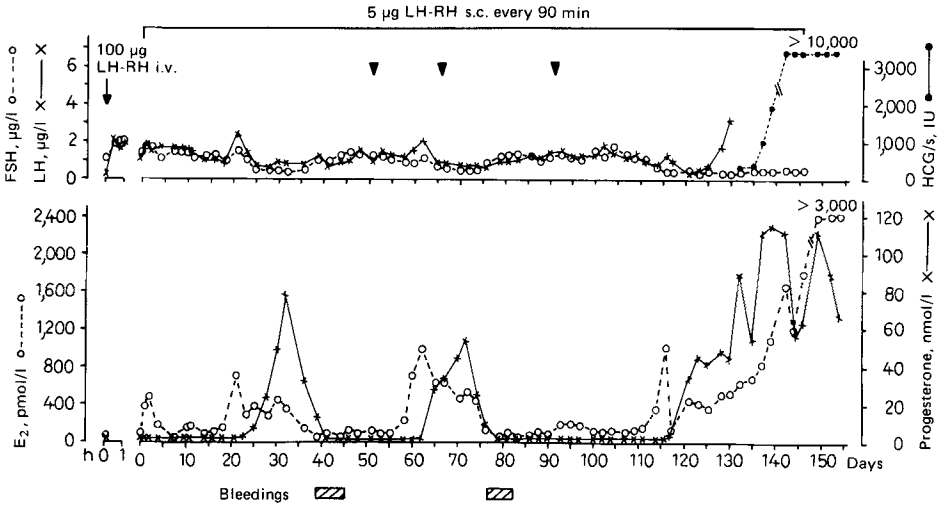

Fig. 4 Serum levels of FSH, LH, HCG, oestradiol and progesterone during three consecutive ovulatory cycles induced by prolonged pulsatile treatment with 5 µg of LH-RH of a 28-year-old woman with 2 years of secondary amenorrhoea. The treatment resulted in a single pregnancy. ▼ change of the s.c. catheter. From Skarin, G., Nillius, S.J. and Wide, L.: Pulsatile subcutaneous low-dose gonadotrophin-releasing hormone treatment of anovulation in fertility. Fertil. Steril. 40:454, 1983. Reproduced by permission of the publisher, The American Fertility Society.

Only 4 of the 46 ovulatory cycles were induced by pulsatile treatment with 5 µg every 90 min. Three of these cycles are illustrated in Fig. 4. The patient, who was treated continously for 146 days, conceived after the third ovulation. She subsequently gave birth to a healthy child at term.

Hormone values during the treatment course resulting in the twin pregnancy are illustrated in Fig. 5. The 30-year-old patient had 7 years of weight loss-related amenorrhoea. She had previously ovulated during five treatment courses with human gonadotrophins but had not conceived. She then received pulsatile low dose LH-RH therapy during 102 days and conceived after the third LH-RH induced ovulation. During the follicular phase of the conceptual cycle a 9-day-long interruption of the LH-RH therapy occurred due to technical problems with the pump. An ultrasonogram in pregnancy week 7 showed three separate amniotic sacs of which two continued to grow. A healthy girl and boy were delivered by caesarean section in pregnancy week 36 (10).

Clinical symptoms of ovarian hyperstimulation did not occur during the prolonged s.c. treatments with 5 - 20 µg of LH-RH every 90 min. However, the patient from Fig. 3 had biochemical and clinical signs (ovarian enlarge-

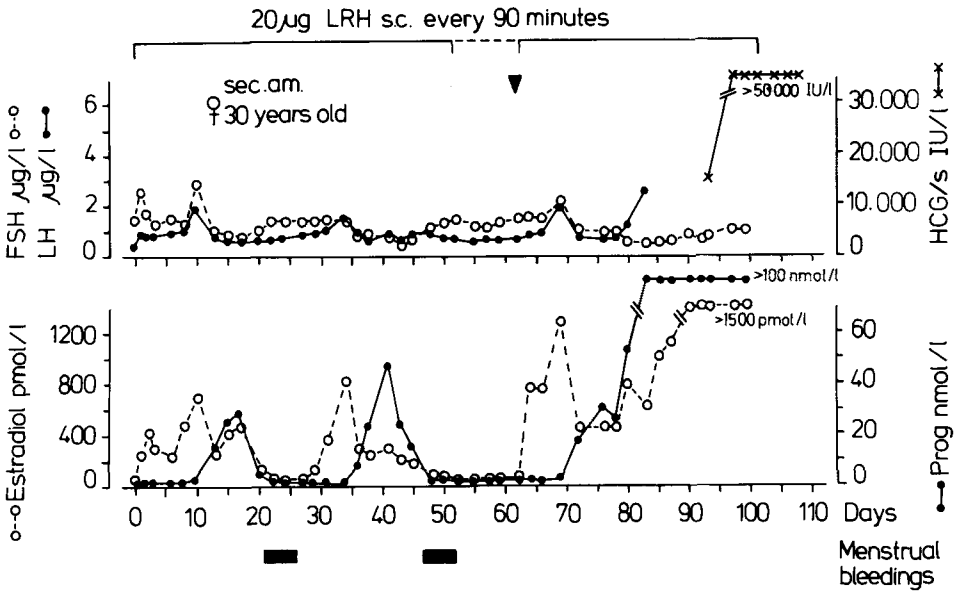

Fig. 5 Serum levels of FSH, LH, HCG, oestradiol and progesterone during three consecutive ovulatory cycles induced by s.c. pulsatile treatment with 20 µg of LH-RH of a 30-year-old woman with 7 years of secondary amenorrhoea. Conception occurred after the third ovulation. Two healthy children were born close to term. ▼ change of the s.c. catheter. From Skarin, G., Nillius, S.J. and Wide, L.: Pulsatile subcutaneous low-dose gonadotrophin-releasing hormone treatment of anovulation in fertility. Fertil. Steril. 40:454, 1983. Reproduced by permission of the publisher, The American Fertility Society.

ment with cyst formation) of hyperstimulation during the first treatment cycle (Fig. 6). The ovarian cysts regressed despite continued LH-RH therapy and a new ovulatory cycle was induced (9).

It was interesting to note that the endogenous ovarian activity improved after the pulsatile LH-RH therapy in 4 of the 12 first treated amenorrhoeic women. The patient from Fig. 3 ovulated and conceived spontaneously 10 months after termination of the LH-RH induced pregnancy. She was then breastfeeding her child and was still amenorrhoeic. A patient who had an early abortion later developed oligomenorrhoea and conceived after treatment with clomiphene. Two of the four amenorrhoeic women who had ovulated but not conceived during the LH-RH treatment also developed oligomenorrhoea and became pregnant after clomiphene therapy (10).

No serious side effects occurred. The long-term pulsatile LH-RH therapy was well accepted by the patients. They could continue their ordinary life at work and at home, including sport activities.

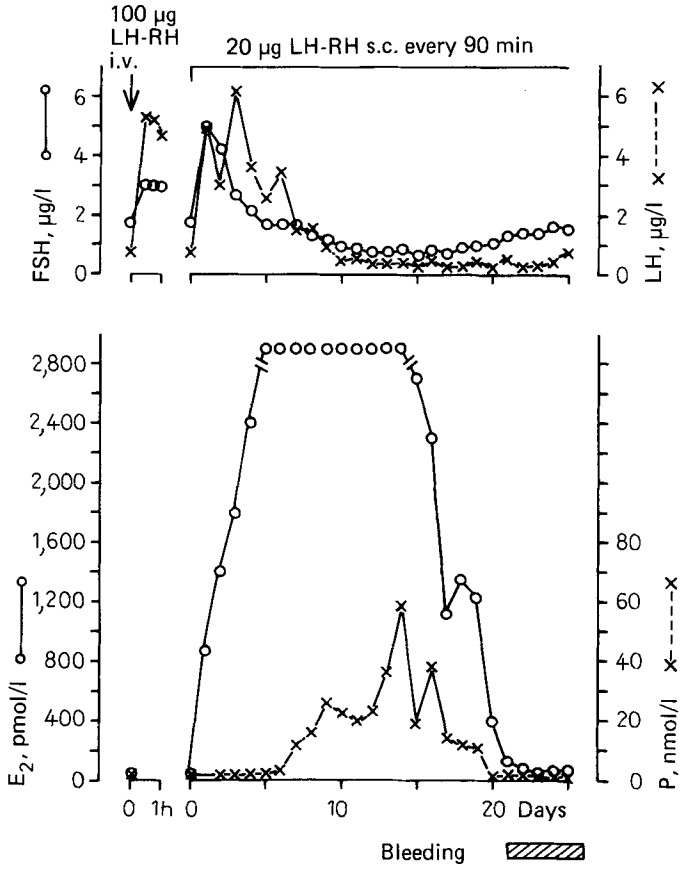

Fig. 6 Serum levels of FSH, LH, oestradiol and progesterone during the first LH-RH induced treatment cycle in the 24-year-old patient from Fig. 3. Ovarian hyperstimulation with very high serum levels of oestradiol occurred but the patient had no clinical symptoms and the ovarian enlargement regressed despite continued LH-RH therapy. Data from Skarin et al. (9).

SUMMARY

A novel promising approach to the treatment of anovulatory infertility has been investigated during the last few years. Pulsatile long-term subcutaneous administration of low doses of LH-RH given by means of small portable computerized infusion pumps has proved to be practical, safe and effective for induction of follicular maturation and ovulation in women with amenorrhoea due to inadequate pituitary gonadotrophin secretion.

ACKNOWLEDGEMENTS

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