

OVULATION INDUCTION WITH PULSATILE GONADOTROPHIN RELEASING HORMONE (GnRH)

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Pulsatile GnRH administration to female rhesus monkeys deprived of endogenous GnRH will restore gonadotrophin secretion whereas continuous exposure or infrequent pulses are ineffective in this regard (1). It appears that GnRH is normally secreted in a pulsatile fashion. To simulate this pattern a commercially available syringe driver (Graseby-Dynamics MS-16) was programmed to deliver 0.2 ml of GnRH solution over 1-3 min each 60, 90 or 120 min.

The following groups of patients were treated :

- a. hypogonadotrophic hypogonadism associated with anosmia
- b. anorexia nervosa
- c. idiopathic anovulation
- d. Stein-Leventhal syndrome

a. This 25 year old woman had 6 menstrual periods following menarche at 19 years. Plasma LH and FSH were in the normal range but Clomiphene, 150 mg/day for 5 days, failed to induce ovulation or menstruation. Human pituitary FSH (HPFSH 290 U/day for 3 days) showed normal ovarian responsiveness. When given HFSH/hCG she developed the hyperstimulation syndrome, nonetheless she conceived but aborted at 19 weeks. Following a second course she conceived but aborted at 13 weeks. When given 80 µg of GnRH/day she ovulated and conceived on the 15th day of treatment. She was subsequently delivered of a normal boy.

b. The first patient, aged 27 years, with anorexia nervosa had recovered from this disorder in that her weight was 50 Kg but amenorrhoea persisted. She failed to respond to Clomiphene, her gonadotrophins were in the normal range. GnRH therapy was instituted at 80 µg/day and at day 25 was increased to 125 µg/day. As determined by plasma LH, FSH, and E<sub>2</sub>, urinary E<sub>3</sub> and basal body temperature measurements she ovulated (and menstruated) for four consecutive months. However conception did not occur and she became amenorrhoeic once the regime was ceased.

The second patient with this disorder was 16 years of age, she weighed 48 Kg and was receiving psychotropic medication. Her menarche had occurred at the age of 13 years but she had been amenorrhoeic for 2 years. She was commenced on 100 µg/day of GnRH and menstruated 30 days later.

c. This woman aged 32 years had been amenorrhoeic for 2 years. Her FSH was 5 U/L, the prolactin was 5 µg/L and she failed to respond to Clomiphene or Medroxy progesterone acetate. When given 60 µg of GnRH/day she had a prompt increase in FSH and LH which then returned to the initial values. At day 23 of treatment the dose was increased to 120 µg/day. The plasma E<sub>2</sub> increased from 0.15 to 3.0 nmol/L and plasma progesterone increased from 0.5 to 43.3 nmol/L on the 40th day of treatment. She menstruated soon after and it was concluded that she had ovulated around day 29.

d. A patient with the Stein-Leventhal syndrome, aged 38 years, had normal levels of gonadotrophins which failed to respond to Clomiphene. When given GnRH at 60 µg/day for 71 days, 180 µg/day for 36 days and 240 µg/day for 38 days there was no increase in E<sub>2</sub> or progesterone, her temperature was unchanged and menstruation did not occur.

Conclusion: Pulsatile GnRH therapy is an effective means of treating anovulatory infertility due to deficient endogenous GnRH secretion. It has the theoretical advantages of reduced pituitary responsiveness in the event of inadvertent overdose of GnRH, furthermore the pituitary is modulated by ovarian steroids. By these means ovarian hyperstimulation and multiple pregnancies should be avoided. Limited experience with the Stein-Leventhal syndrome suggests that this disorder may not respond to GnRH.

Reference: 1. Belchetz P.E., Plant T.M., Nakai Y., Keogh E.J. and Knobil E. Hypophysial responses to continuous and intermittent delivery of hypothalamic gonadotrophin releasing hormone. Science 202 : 631-633, 1978.