72

Pulsatile infusion of gonadotrophin releasing hormone (GnRH): investigative and therapeutic applications

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ABSTRACT

Normal gonadotrophin secretion, and therefore normal ovarian function, depend on delivery to the pituitary of the hypothalamic neuropeptide gonadotrophin releasing hormone (GnRH) in a pulsatile pattern. In the mid-follicular phase of the menstrual cycle, for example, discrete pulses of luteinizing hormone (LH) can be observed at approximately 90 min intervals. Many disorders of ovulation are caused by abnormalities of this natural pulsed signal. We have developed and used a small portable infusion pump to deliver GnRH to women with hypothalamic amenorrhoea; our studies, and those of other groups, have shown that successful ovulation and pregnancy result from such treatment. The results of treatment at St Mary's Hospital show that 16 women with hypogonadotrophic amenorrhoea received a total of 31 cycles of treatment with pulsatile GnRH; 25 (81%) of these cycles were ovulatory and 11 of the 14 women who were trying to conceive became pregnant. There was only one multiple pregnancy (twins).

Keywords: Cyclical phenomena, anovulation, drug delivery, infusion pump, LHRH

INTRODUCTION

While the earliest infusions were first recorded by Majors in 1667[1,2] it is only this century that the technology has evolved to take continuous infusion into everyday therapeutic use. The first portable infusion devices, as opposed to bedside units, were developed for the treatment of diabetes[3] and this has now led to the current commercial availability of general purpose infusion pumps capable of pulsatile infusion of hormones. A selection of pumps currently used for luteinizing hormone releasing hormone (LHRH) therapy is shown in *Figure 1*. These pumps and their performance have been reviewed[4] and the development and operation of the National Institute for Medical Research (NIMR) general purpose infuser (the centre pump in *Figure 1*), which was used in this current study, is described elsewhere[5].

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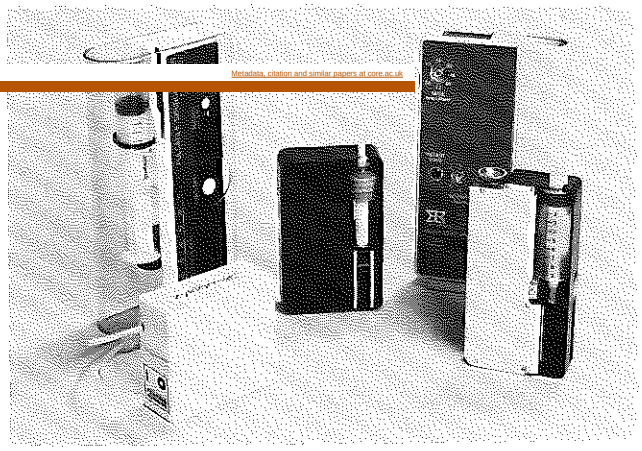

Figure 1 A selection of pulsatile infusion pumps currently used for GnRH therapy. From left to right: the Grasby MS27, the Zykomat, the NIMR General Purpose, the Autosyringe AS6H and the Paxton PU500. All are syringe pumps except the Zyklomat which is peristaltic.

NORMAL AND DISORDERED GONADOTROPHIN SECRETION

Normal gonadotrophin secretion, and therefore normal ovarian function, depend on delivery to the

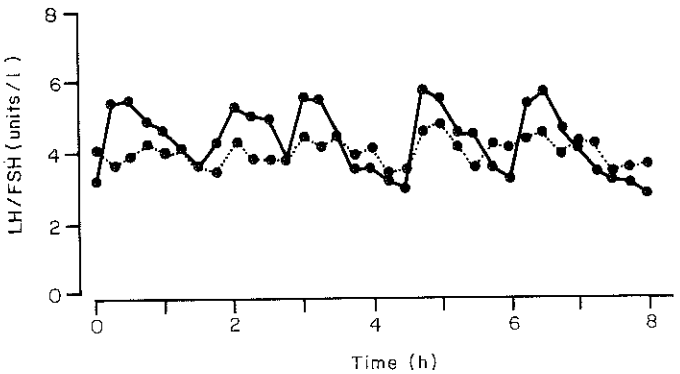

Figure 2 The normal pattern of luteinizing hormone (LH, —) and follicular stimulating hormone (FSH, ·····) secretion during the mid-follicular phase of the menstrual cycle in an ovulatory woman; body mass index (BMI, kg/m^2) = 20.7.

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mixture of symptoms (*Figure 6*). Similarly, there was no significant difference in the timing of the waxing and waning of the various symptoms; on average, significant positive trends started 6–8 days before menstruation, while significant negative trends began at 7–9 days after the onset of bleeding.

Irrespective of the pattern of trends, water retention, negative affect and pain were responsible for the most morbidity and autonomic reactions the least as judged by ESA_{max} and mean daily scores (*Figure 7*). Typically, women found to have PMS trends tended to have lower postmenstrual and higher premenstrual ratings, and thus greater swings in symptoms than those who recorded either Non-PMS trends or No trends.

CONCLUSIONS

The ovarian cycle is an intricate and powerful influence in women's lives. Its accompaniments are numerous, its effects extensive, its appreciation complex. In spite of, or perhaps because of this, our present knowledge is often ignored. The ovarian cycle offers a unique dynamic model that could help our understanding of human biology and pathology, while its manipulation may prove to be a useful therapeutic tool.

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pituitary of the hypothalamic neuropeptide, GnRH, in a pulsatile pattern. In the mid-follicular phase of the normal menstrual cycle, for example, discrete pulses of luteinizing hormone (LH) can be observed at approximately 90 min intervals (*Figure 2*). Many disorders of ovulation are caused by abnormalities of this natural pulsed signal. Amongst the most common of these is anorexia nervosa in which loss of weight leads to a disruption of hypothalamic GnRH control and consequently gonadotrophin secretion.

Treatment of these conditions requires an infusion device that can mimic the normal endogenous pulsatile release of these hormones. The NIMR general purpose pump (*Figure 1*) is a compact syringe driver that is light, unobtrusive and simple to operate. GnRH can be delivered in discrete micro-injections (boluses) of a preset size and time interval. A bolus size of 100 μlitres (100 μg/ml) was used in this study with a time interval of 90 min. The syringe, with its capacity of 5.6 ml, had to be refilled approximately every three days. The infusion site was the subcutaneous tissues of either the arm or waist depending on where the woman preferred to wear the pump.

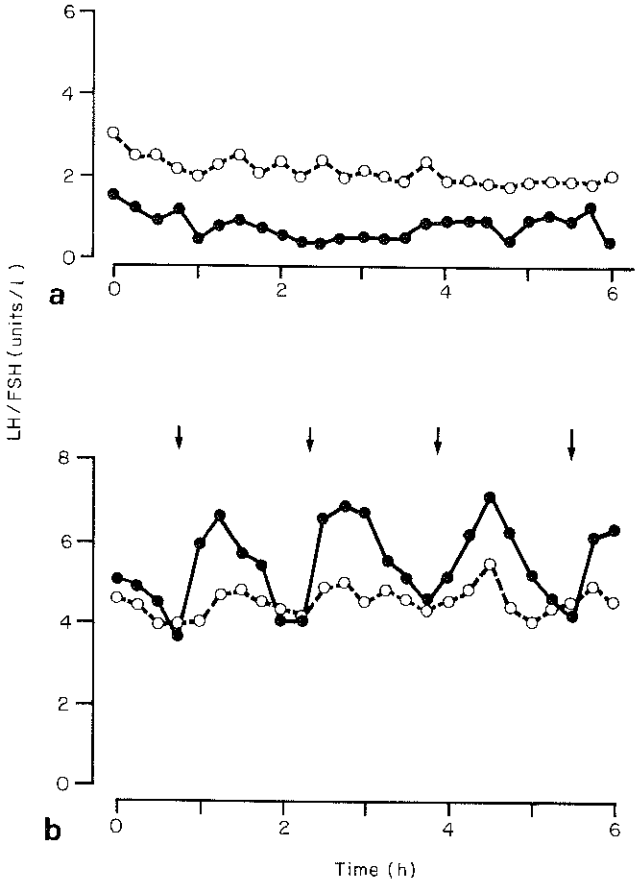

Figure 3 Gonadotrophin deficiency treated with pulsed GnRH: **a**, pre-treatment profile with low LH and no detectable pulses and, **b**, return to normal pattern during treatment with pulses of GnRH (arrowed). ●—●, Luteinizing hormone (LH); ○--○, follicular stimulating hormone (FSH)

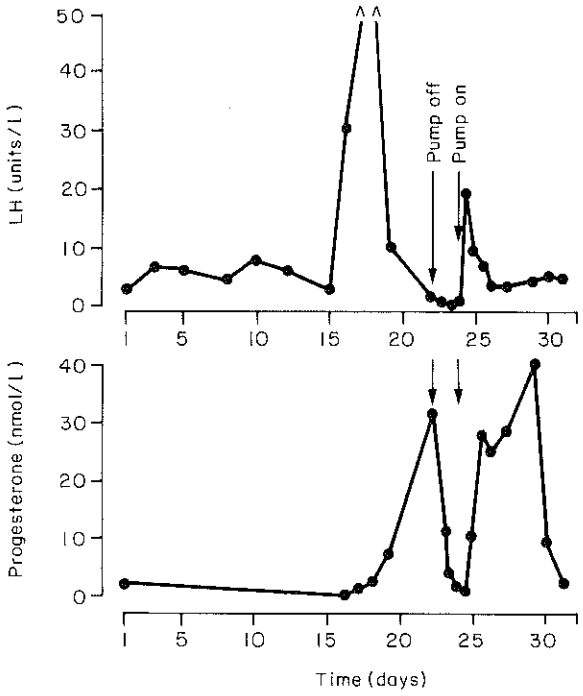

Figure 4 The effect of switching off the pump and removing gonadotrophic support during the luteal phase. Note the immediate fall of LH and progesterone concentrations after withdrawing GnRH and the rapid return of these hormonal levels to normal mid-luteal values after restarting the pump[8]

A CASE OF SEVERE GONADOTROPHIN DEFICIENCY

A 30-year-old woman with severe gonadotrophin deficiency (*Figure 3a*) due to weight loss was treated with pulsatile GnRH from the NIMR pump which restored a normal pattern of gonadotrophin secretion (*Figure 3b*) and resulted in ovulation. As she did not wish to conceive during this cycle (she was still considerably underweight), we took the opportunity to investigate the effect on luteal phase progesterone secretion of withdrawal of gonadotrophic support. The pump was stopped three days after ovulation and the effect is shown in *Figure 4*. LH concentration fell, followed by a fall in serum progesterone to undetectable levels. After 48 h the pump was restarted; LH and progesterone levels rose rapidly to normal mid-luteal levels and the luteal phase was of normal length. The pump was then removed following menstruation. Following weight gain the pump was refitted and subsequent treatment resulted in ovulation and pregnancy.

EFFECT OF TREATMENT WITH PULSATILE GnRH

Our studies[6] and those of other groups[7] have shown that successful ovulation and pregnancy result from such treatment. To date the results of treatment at St Mary's Hospital show that 16 women with hypogonadotrophic amenorrhoea received a total of 31 cycles of treatment with pulsatile GnRH. Twenty five (81%) of these cycles were ovulatory and 11 of the 14 women who were trying to conceive have

become pregnant. There was only one multiple pregnancy (twins).

CONCLUSIONS

These data show that:

1) Ovulation can be induced in women with hypothalamic amenorrhoea by pulsed GnRH.

2) Progesterone secretion by the corpus luteum is dependent on gonadotrophine stimulation even though circulating concentrations of LH are very low at this stage of the cycle.

3) The corpus luteum is capable of recovery after temporary withdrawal of gonadotrophic support.

This study shows clearly that use of the portable infusion pump for delivery of GnRH has implications for understanding the physiology of the menstrual cycle as well as for practical management of infertile patients.

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