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Induction of Ovulation with Pulsatile LH-RH in Infertile Women

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ABSTRACT

In five women who had demonstrated repeatedly ovulatory cycles with insufficient luteal phases ovulation was supported by continuous intermittent administration of LH-RH, 5 µg per 90 min, intravenously by means of a portable pump. All 18 induced cycles were ovulatory. The production of progesterone rose by 75% to 51 nM/l during the midluteal phase. The duration of the luteal phase increased with 49% to 14 days.

One patient became pregnant , but aborted spontaneously 20 days postovulatory.

The only major side effect seen was an occasional superficial trombophlebitis.

INTRODUCTION

Ovulation induction within the framework of the infertility management has been applied already many years. Till recently this was mainly performed by using clomiphene citrate, human menopausal gonadotropin, human chorion gonadotropin and bromocriptine.

After the first publications by the groups of Nillius (6), Leyendekker (5) and Knobil (4) about the succesful application of gonadotropin releasing hormone (LH-RH), this too could be added to that list of drugs.

Earlier studies done at our institute as well as data from the literature indicates that the induction of ovulation by means of continuous, intermittent, intravenous administration of LH-RH in hypogonadotropic, hypoestrogenic, normoprolactinemic women with an intact pituitary ovarian axis has become a practical possibility with excellent results.

In order to establish whether or not other types of infertility caused by hormonal dysfunction can be treated efficiently by menas of GnRH we investigated to what extent the inadequate luteal phase in normoprolactinemic, normo-androgenic women may improve by this therapy.

METHODS AND MATERIAL

The Zyklomat pump* is a portable gadget (2.8x6.5x7.0 cm) consisting of a peristaltic pump, a computerized timing device and a sterile, disposable, plastic reservoir. Every 90 min for the duration of one min it is activated and delivers 50 µg of a LH-RH solution via a chronic, indwelling catheter (O.D. 0.965 mm; I.D. 0.58 mm) into the median cubital vein.

LH-RH (LH-RH Ferring*) was dissolved in physiological saline to a concentration of 0.1 µg/µl. The determinations of LH, FSH, 17ß-estradiol (E_2) and progesterone (Prog.) were performed by means of a specific radio immuno assay as reported by Roumen et al. (7). Frequent blood samples were taken at random throughout the course of the treatment. The blood sampling was not synchronized with the LH-RH infusion. Pregnancy was assessed by measurement of human chorion gonadotropin (HCG) ß-subunit in serum and by ultrasound examination of the internal genital organs in adition to regular physical examination. The patient population consisted of five normoprolactinemic, normo-androgenic women, who have shown repeatedly to have luteal phases of eleven days or less with low progesterone levels. No histologic dating of the endometrium was performed. Table I summarizes the group.

TABLE I:

Serum progesterone concentration (mid luteal) and duration of the luteal phase of five women with endogenous luteal phase defect prior to and during LH-RH treatment

	PRIOR TO TREATMENT	DURING TREATMENT	PRIOR TO TREATMENT	DURING TREATMENT	
PAT.	MID LUTEAL PROGESTERONE nM/l		LUTEAL PHASE days		n
1	29.1 + 9.5*	51.8 + 11.2*	10.3 + 1.0*	15.5 + 1.7*	6
2	26.8 + 8.6	43.3 + 10.1	10.0 + 0.8	14.8 + 1.2	4
3	24.8 + 15.7	80.7 + 26.6	10.0 + 0.7	15.2 + 2.1	3
4	21.0 + 8.3	37.5 + 7.8	8.8 + 1.5	13.1 + 0.8	3
5	23.7 + 10.4	42.6 + 9.3	9.0 + 1.4	13.3 + 1.7	2
MEAN	25.1	51.2	9.6	14.4	

* MEAN + S.D. n = number of induced GnRH cycles.

*Ferring GmbH, Kiel, F.R.G.

RESULTS

Eighteen ovulatory cycles were induced. In comparison to their pretreatment levels periovulatory estradiol concentration increased by 62% to 1145 pM/l. The production of progesterone rose by more than 75% to 51 nM/l during the mid luteal phase. The duration of the luteal phase increased with 49% to 14 days (Table I).

One patient became pregnant, but aborted spontaneously 20 days after ovulation.

DISCUSSION

After the isolation in 1971 of LH-RH (1,9) and following it's artificial synthesis, clinical trials were started in attemps to obtain ovulation and pregnancy in women with anovulatory infertility.

Studies by Knobil and coworkers (4) in rhesus monkeys with hypothalamic lesions indicated clearly the importance of intermittent LH-RH release.

Follicular development leading to ovulation and normal corpus luteum function has been considered to depend upon the appropriate sequential dose response of the follicle to gonadotropin stimulation resulting in proliferation of granulosa cells, in differentiation of those into luteal cells, and in gonadotropin dependent luteal steroidogenesis.

Although Hsueh and collaborators (3) have provided evidence of a direct inhibitory effect of LH-RH on ovarian cell functions in vitro, this has not been detected so far to occur in vivo.

We observed an enhanced proliferation of granulosa cells as judged from the periovulatory serum estradiol levels and the conditions of the cervical mucus.

Although our results in term of pregnancy rate is disappointing we did increase significantly both the duration as well as the production of progesterone during the luteal phase.

By improving the hormonal responsiveness and steroidogenic capacity of the granulosa cells in the way we did one may conclude indirectly that the cause of the luteal phase defect in these women is an inappropriate stimulation of the pituitary gland by the hypothalamus.

The importance of lowering the pulse frequency or even the necessity to continue the LH-RH infusion at all during the luteal phase remains partly unsettled. As shown by Knobil (4) more than one pulse per hour during the follicular phase in the rhesus monkey diminishes the secretion of both LH and FSH, while one pulse every three hours resulted in an impaired LH/FSH ratio. On theoretical grounds one may speculate that, because of the normal,

endogenous difference in pulse frequency between the follicular and luteal phase (2) stage dependent pulse frequency of the infused LH-RH would improve the outcome.

Both the report by Sawder et al. (8), the review article by Schoemaker et al. (10) as well as our results do not indicate that such an adoption is obligatory in the treatment of women with hypogonadotropic amenorrhea or inadequate luteal phase.

Despite the continuation of the LH-RH administration postovulatory in our patients, FSH declines to low levels during the luteal phase. This is less pronounced for LH. In women who conceived FSH decreased even further to very low values as occurs after spontaneous conceptions. Therefore, this demonstrates that despite the LH-RH delivery, the pituitary gland becomes partially resistant to LH-RH during the luteal phase and even more so during pregnancy. An important question which remains to be clarified is the necessity to continue the LH-RH infusion during the luteal phase.

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