

INDUCTION OF OVULATION WITH CLOMIPHENE CITRATE FOLLOWED BY LH-RH IN WOMEN

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Abstract

Maia H Jr, Barbosa IC, Maia H, Hirsch C, Tironi E, Coutinho EM (Maternidade Climerio de Oliveira, Federal University of Bahia, Salvador, Bahia, Brazil). Induction of ovulation with clomiphene citrate followed by LH-RH in women.

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Luteinizing hormone-releasing hormone (LH-RH) was used to induce ovulation following clomiphene priming to stimulate follicular growth. Ovulation was assumed to have occurred following LH-RH injection when progesterone levels started to rise within 48 h following treatment and LH pretreatment levels were below 8 mIU/ml. Ovulation occurred in eight of 10 patients following the administration of LH-RH and six pregnancies were achieved in the first 4 months of treatment.

Key words: Luteinizing hormone; Ovulation; Clomiphene; Stimulate follicular growth; LH-RH injection; Progesterone levels; Pregnancy; Polycystic ovarian disease; Menstrual cycle disorders; Ovum extrusion

Introduction

Clomiphene citrate has been extensively used for inducing ovulation in patients with

polycystic ovarian disease. Clinically, these women present a variety of menstrual cycle disorders, with distinct ovarian estrogen production and normal follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin levels. Additional treatment schedules using either clomiphene and estrogens or clomiphene and human chorionic gonadotropin (HCG) have been proposed for patients who did not respond to clomiphene therapy alone. HCG has been used as a substitute for LH to induce follicular rupture and ovum extrusion. More recently, the synthesis of hypothalamic decapeptide that releases LH and FSH from the pituitary gland has provided a more physiologic approach for inducing or timing follicular rupture in patients who did not respond to clomiphene citrate therapy alone. Luteinizing hormone-releasing hormone (LH-RH) has been successfully used to provoke ovulation in patients previously treated with epimestrol to induce complete follicular maturation [23]. Attempts to use LH-RH alone to induce follicular growth and rupture, on the other hand, have not been successful. Daily administration of LH-RH or one of its potent analogs blocks ovulation or causes severe luteal phase insufficiency in normally menstruating women [1,4]. This shows that chronic administration of LH-RH exerts a paradoxical antifertility effect instead of increasing fertility. In our work, clomiphene citrate followed by LH-RH was used to induce ovulation in patients with polycystic ovarian disease (PCO).

Materials and methods

Ten patients with anovulation and menstrual irregularities were studied. Prolactin levels were within the normal range in all patients. Withdrawal bleeding was induced with 5 mg of medroxyprogesterone for 5 days in all cases. Thyroid function was normal and 17 kS and 17 OH urinary levels were not elevated. Anovulation was confirmed by measurement of plasma progesterone by radioimmunoassay, by basal body temperature records and observation of cervical mucus change.

Clomiphene citrate was used in the dose of 100 mg/day for 5 days starting on day 4 of the menstrual cycle. LH-RH was used in the dose of 100 μ g subcutaneously for 1–3 days when estradiol levels were above 200 pg/ml, as measured by radioimmunoassay. When cervical mucus production was scanty following clomiphene citrate (two patients), 2.5 mg

of estradiol benzoate was injected on day 14 of the cycle. LH-RH was injected subcutaneously 2 h before and during the 2 days following estradiol administration. In two patients, the response to LH-RH was monitored during clomiphene therapy.

The occurrence of ovulation was assessed by the rise in plasma progesterone, basal body temperature records and changes in cervical mucus score. The couples were instructed to have intercourse within 24 h following LH-RH injection.

In six patients, no ovulation had previously occurred on clomiphene therapy alone. In the remaining four, LH-RH was used to time the day of ovulation.

Ovulation was assessed to have occurred following LH-RH when the basal LH levels were below 8 mIU/ml, estradiol levels were above 200 pg/ml and progesterone rose to levels above 3 ng/ml within 2 days following LH-RH administration. LH, FSH, progesterone

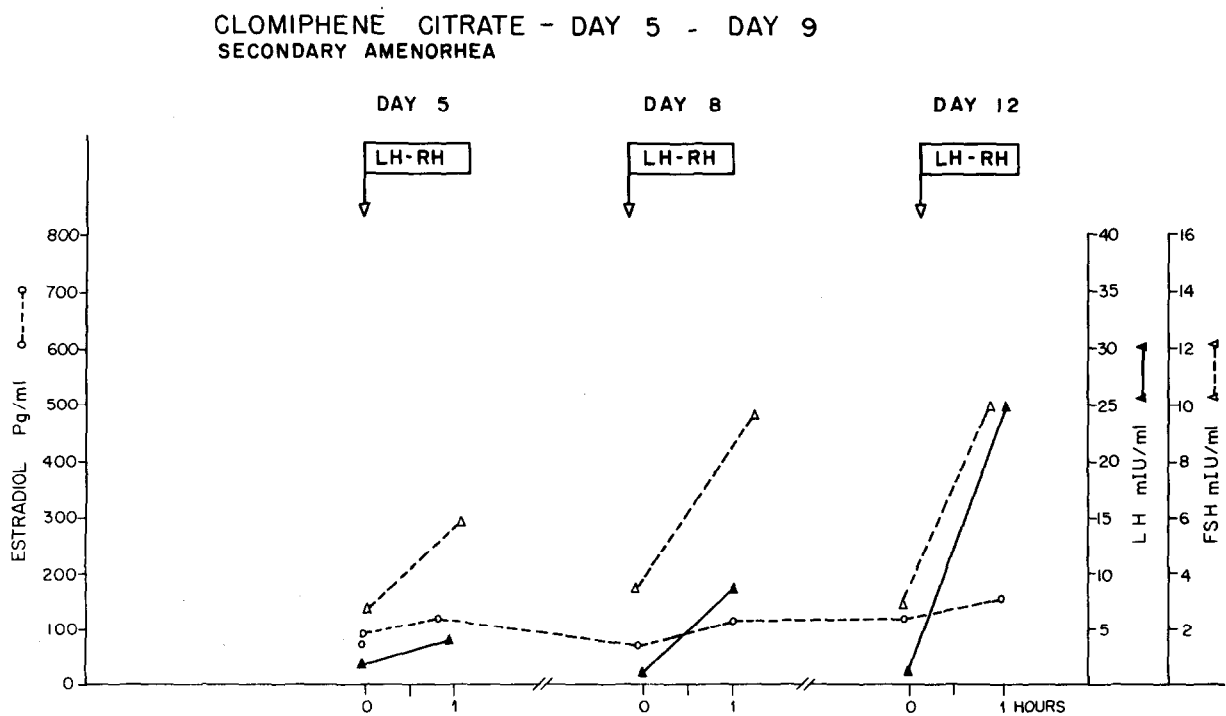


Fig. 1. Effect of clomiphene citrate on the response of the pituitary gland to LH-RH. Note the increase in pituitary responsiveness to LH-RH following clomiphene citrate treatment.

and estradiol levels were measured by radio-immunoassay, according to the procedures recommended by the matched reagent program. The occurrence of pregnancy was confirmed by HCG determination in the urine or by ultrasound scan of the uterus using the full bladder technique.

Results

Clomiphene citrate administered from day 5 to day 9 of the cycle induced a progressive increase in the response of the pituitary gland to LH-RH. LH-RH responses were minimal on day 5 of the cycle, and they started to increase within 48 h following the beginning of clomiphene therapy. This increase in sensitivity was not caused by changes in estradiol levels, since they remained constant during the first 7 days of treatment (Fig. 1).

In two patients in whom a strong anti-estrogen effect on the cervix was noticed, 2.5 mg of estradiol benzoate was administered on day 14 of the cycle, when estradiol levels were 500 pg/ml and progesterone 0.4 ng/ml. These patients had been previously treated with LH-RH 24 h before (Fig. 2). LH-RH induced a marked rise in LH levels and ovulation was not suppressed, as inferred by plasma progesterone levels of 5 ng/ml on day 22 despite the administration of estrogen. Cervical mucus production was greatly increased following estradiol benzoate administration, and post-coital tests were normal in these patients. LH-RH responses were exaggerated following estrogen treatment.

In six patients in whom clomiphene therapy did not result in ovulation as inferred from progesterone levels below 3 ng/ml, the administration of LH-RH (100 µg administered subcu-

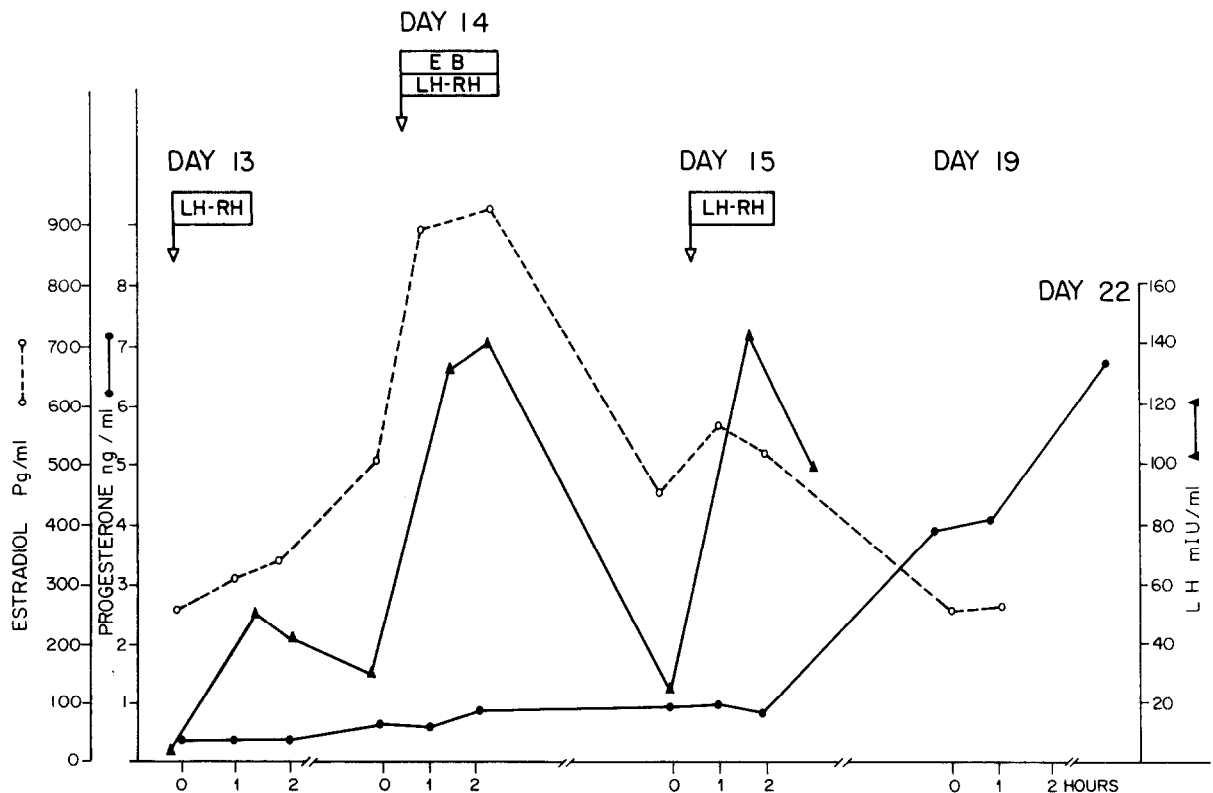


Fig. 2. Effect of estradiol benzoate on the response of pituitary gland to LH-RH. Note that ovulation following LH-RH treatment was not suppressed by estradiol injection on day 14.

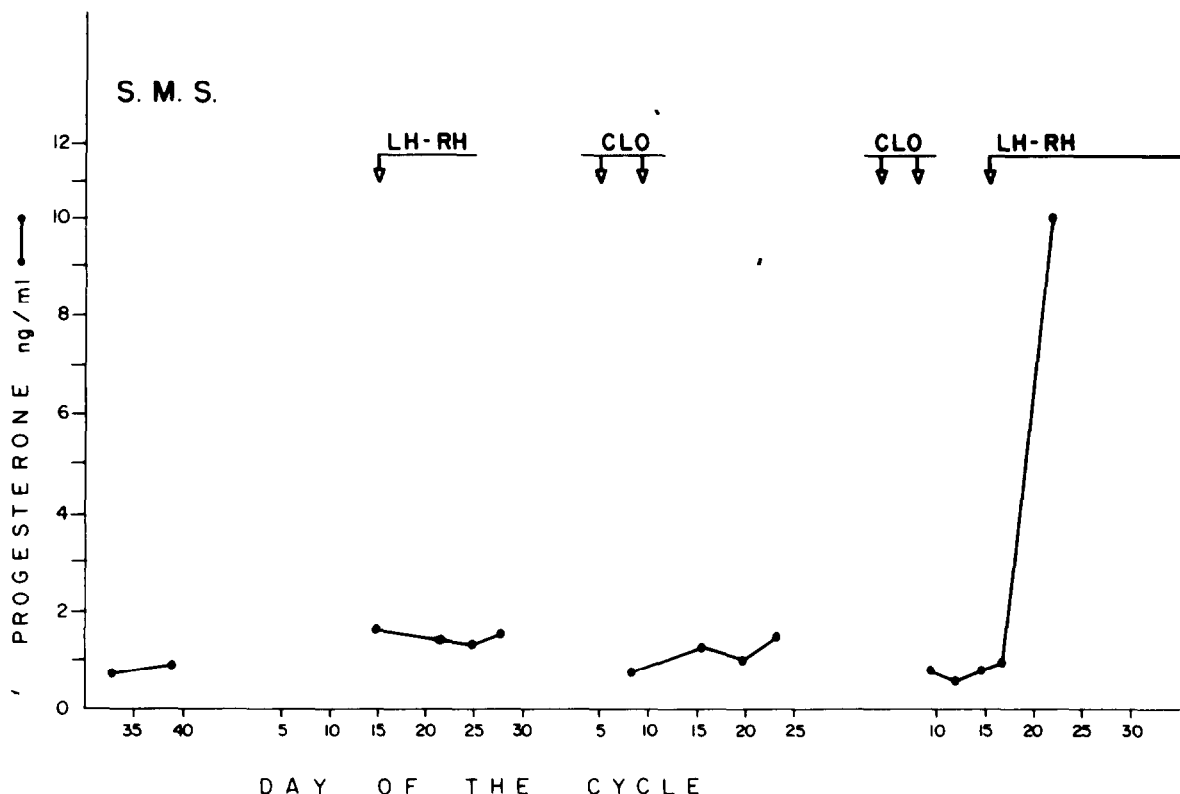


Fig. 3. Induction of ovulation with clomiphene followed by LH-RH in a patient with polycystic ovarian disease. Note that neither clomiphene nor LH-RH when given alone were able to induce ovulation.

taneously) for 2 days succeeded in inducing ovulation in four of these patients. LH-RH was used at 6–8 days following the discontinuation of clomiphene, when estradiol levels were above 200 pg/ml. Three pregnancies occurred in the first four cycles of treatment. Figure 3 illustrates one of these cases. The patient had polycystic ovaries and failed to respond to clomiphene or LH-RH when these agents were used alone. However, when LH-RH was given following clomiphene priming, ovulation occurred and corpus luteum function was normal. Pregnancy occurred in the second cycle of clomiphene and LH-RH treatment. No multiple pregnancies were observed.

In four patients, LH-RH was given following clomiphene to time the moment of ovulation. Ovulation occurred in all subjects as inferred from the rise of progesterone levels or the shift in basal body temperature within 48 h following the last LH-RH injection

(Fig. 5). Spontaneous LH surge had not occurred in any one of the patients when LH-RH was given. Three pregnancies occurred following 4 months of treatment.

Discussion

The present study shows that LH-RH will induce ovulation in patients previously treated with clomiphene citrate to stimulate follicular growth. LH-RH administration will increase the ovulatory responses following clomiphene therapy. Our findings that pituitary responses to LH-RH are greatly increased by clomiphene citrate provide a physiologic basis for the clinical effectiveness of LH-RH and clomiphene therapy.

In this respect, the use of LH-RH is more physiologic than HCG, which is a luteotrophic hormone produced by the developing tropho-

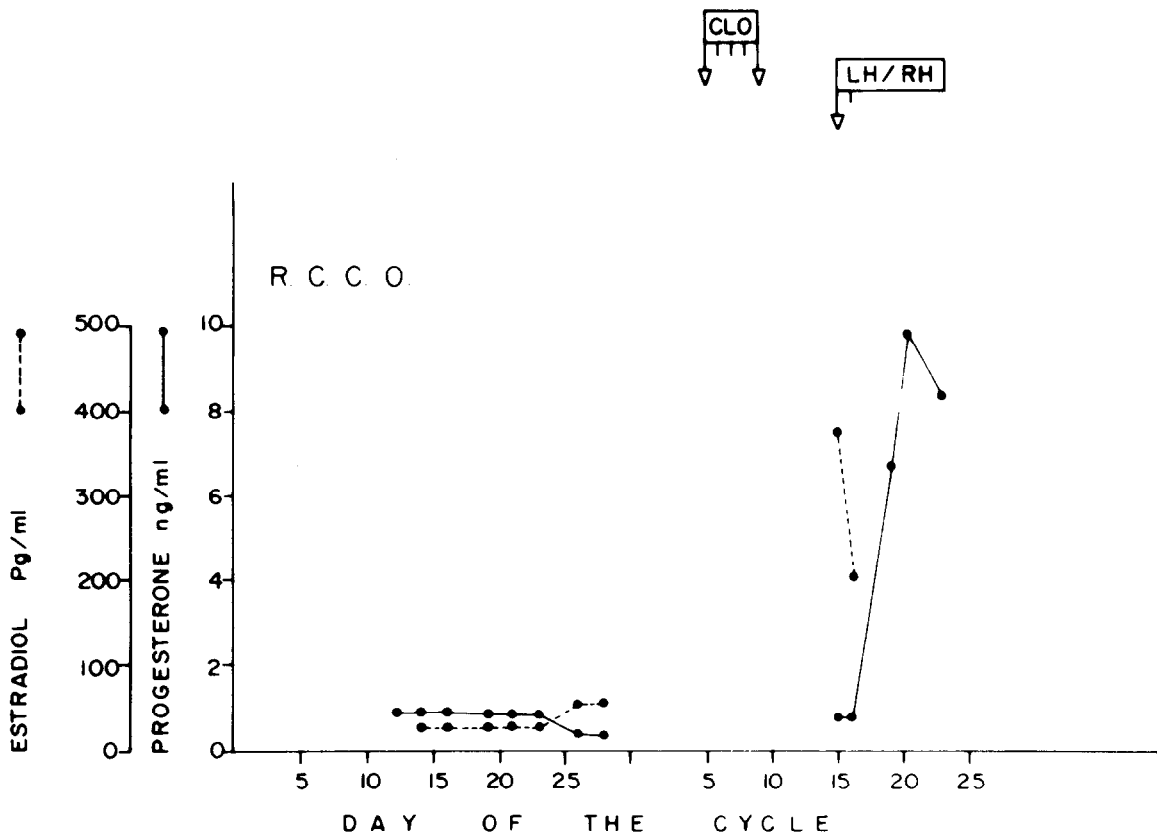


Fig. 4. Induction of ovulation with clomiphene and LH-RH in patient with polycystic ovarian disease. LH-RH was given when estradiol levels were above 300 pg/ml. Note the rise in progesterone following LH-RH injection.

blastic tissue. Our findings that the injection of estradiol benzoate on day 14 following clomiphene priming does not prevent LH release and ovulation indicate that a single administration of estradiol at midcycle can be an alternative form of treatment for correcting the anti-estrogenic effects of clomiphene on the cervix. In these patients, cervical mucus production was greatly increased within 24 h following estradiol injection and ovulation was not suppressed. In all patients who ovulated following LH-RH injection, estradiol levels were above 200 pg/ml.

This result suggests that a mature follicle is a prerequisite for LH-RH to act. This is in agreement with earlier observation of the effect of LH-RH in patients previously treated

with epimestrol to induce follicular growth [2,3]. The timing of administration of LH-RH is therefore very important. In normally menstruating women, repeated administrations of LH-RH before follicular development is completed results in ovulation blockade or in the development of an insufficient corpus luteum [1,4]. This explains the failure of previous attempts to induce follicular growth and ovulation with repeated administration of LH-RH alone in patients with anovulation and secondary amenorrhea. LH-RH is effective in inducing ovulation only when complete follicular maturation was achieved with the use of other agents, such as clomiphene, epimestrol and human menopausal gonadotropin [2,3,5].

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