PROGESTERONE SECRETION IN THE MIDLUTEAL PHASE AFTER TREATMENT WITH CLOMIPHENE CITRATE

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SUMMARY

The purpose of the study is to find out whether treatment with clomiphene citrate (CC) alters the luteal progesterone (P) production pattern. Five female patients with unovulatory infertility under treatment with 100 mg CC taken on days 2-6 of the cycle, were assigned to the study. Blood samples were drawn at 20 minute intervals from 8.00 to 17.00 hrs, seven days after ovulation to assess P and luteinizing hormone levels. P concentrations showed wide fluctuation during the sampling period. Mean P concentration was significantly higher in the morning than in the afternoon ($p<0.05$). As a conclusion, the diurnal pattern of P production is not disturbed by treatment with CC.

Key Words : Clomiphene Citrate, Luteal Progesterone

INTRODUCTION

Clomiphene citrate (CC) has been in widespread clinical use since 1960 for treating unovulatory infertility (1) and its efficacy is well accepted (2). It has both oestrogenic agonist and antagonist properties, but in vivo it has predominantly anti-oestrogenic effects on the endometrium, cervix and vagina (3,4). In clinical practice CC is given in the first half of the cycle, but only 51% of the oral dose is excreted after five days, and radioactivity from labelled CC appears in the faeces for up to six weeks after administration. Thus CC in low concentrations can still be present in the body during the luteal phase (5,6).

Although CC has been used to treat luteal defects (7), there is experimental (8,9); and clinical (10,11) evidence that it can cause luteal phase deficiency and luteinised unruptured follicle syndrome (12). Ho Yuen (13) demonstrated that CC induced dose-dependent inhibition of progesterone (P) production in human granulosa cells harvested from pre-ovulatory follicles.
CC increases the frequency of LH pulses from the pituitary gland (14,6); but its effect on P pulsatility is unknown. Syrop and Hammond (15) demonstrated a diurnal variation in mid-luteal P secretion in normal women, but pointed out that "whether the same is true in patients receiving clomiphene citrate therapy remains unknown". We therefore studied the effect of CC on the production of mid-luteal LH and P.

MATERIALS AND METHODS

We studied five women with unovulatory infertility who were undergoing standard treatment with CC 100 mg daily on days 2-6 of the cycle. The study was approved by the local ethical committee and each subject gave informed consent. Each woman underwent follicular monitoring by ultrasound from the ninth day of her cycle to confirm ovulation, and pre-ovulatory follicular diameters were measured. Seven days after ovulation the woman was admitted to hospital for the day. Peripheral venous blood samples were obtained at 20 min intervals between 08.00 and 17.00 hrs, using an indwelling venous cannula. Blood samples were allowed to clot and the serum was separated and frozen at -20 °C until assayed for LH and P by radio-immunoassay. Reagents were supplied by Diagnostic Products Corporation (Los Angeles, CA). LH and P assays have a detection limit of approximately 2 mIU/ml and 0.05 mg/ml respectively.

RESULTS

Mean concentrations of LH and P and mean follicular diameter on the day before ovulation are given in Table I for each subject. Subject A, who had two mature pre-ovulatory follicles, had higher mean LH and mean P levels. All subjects had satisfactory P values although mean LH values were low. Fluctuation of P over the clinical sampling period is shown in Table I. The pattern of serum P and LH values is shown graphically in Figure 1. In general, morning values are higher, then decline to lower levels in the afternoon. The difference between morning and afternoon levels is significant on multivariate regression analysis ($F = 10.45$; d.f. 21 & 5; $p < 0.05$).

DISCUSSION

This study is the first to investigate the diurnal pattern of P secretion in women treated with CC. It has

shown that CC does not abolish the diurnal variation in P secretion seen in the normal luteal phase (15). The wide variation in P levels in a single subject is similar to the variation occurring in normal women.
Normal luteal function appears to be dependent on adequate follicular development. Inadequate preovulatory follicular development may be a common pathophysiological mechanism for luteal phase deficiency (16). Several studies have reported decreased gonadotropin concentration in the follicular phase of normal women who had decreased luteal P secretion (17,18), suggesting that preovulatory follicular development is a principal determinant of corpus luteum function. It has also been postulated that luteal phase deficiency could occur from an inadequate LH surge (16).

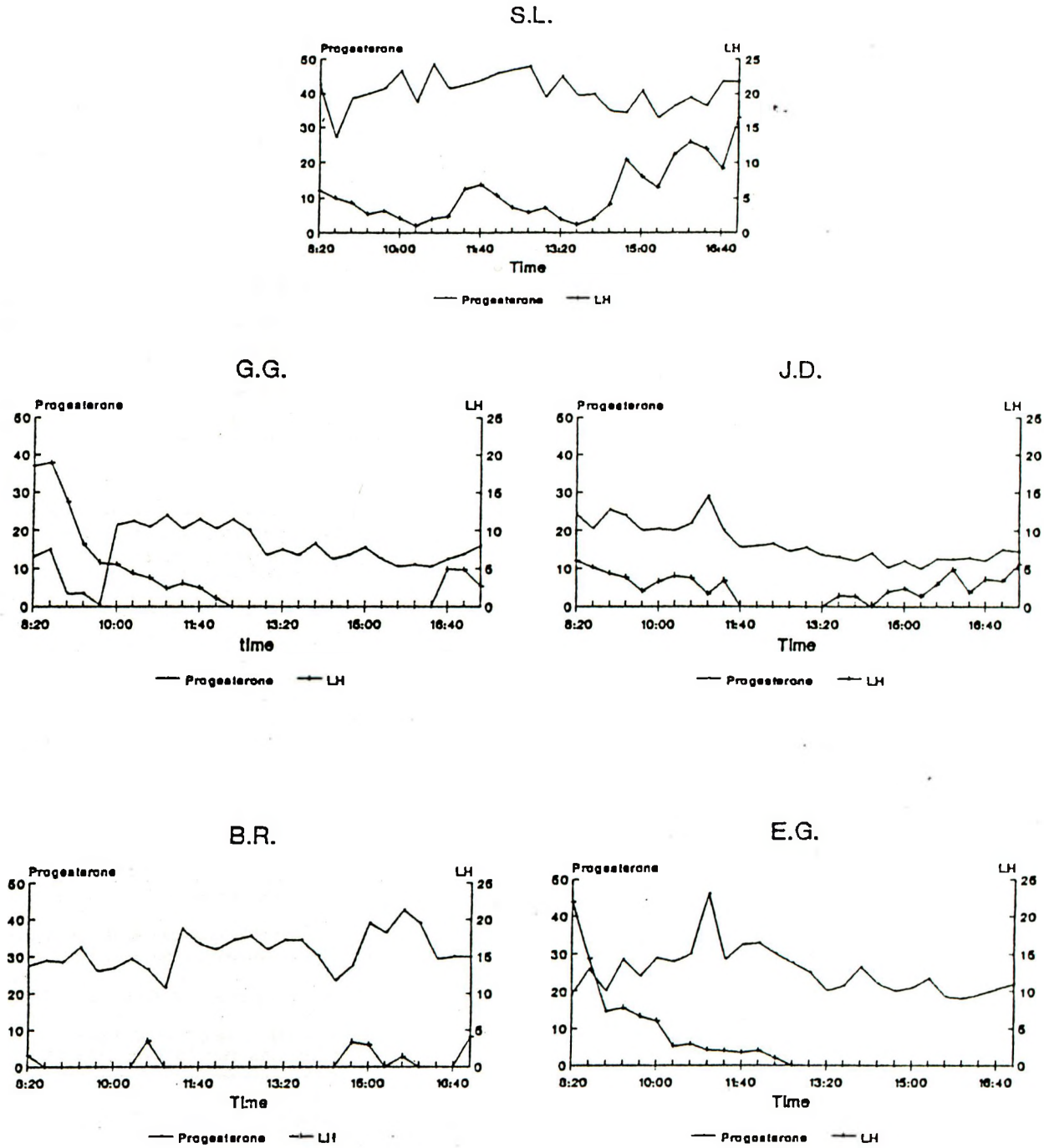

Fig. 1 : The pattern of serum P and LH values

Work by Alila and Hansel (19), corroborated by others, indicates that granulosa cells have different LH receptors from those on theca cells. These receptors are occupied and not internalised. Luteinised granulosa cells have a fixed life-span of ten days, during which they are the major source of luteal P. Theca cells contain LH receptors that remain sensitive to LH pulses throughout the 14 day luteal span: they reach their maximum number by days 5-8 and by day 12 are responsible for most of the P production which is now pulsatile. In the mid-luteal phase there is a correlation between LH pulses and P. LH pulses decrease from the mid-cycle to the end of the luteal phase, probably in relation to decreased GnRH stimulation due to inhibition at the hypothalamus by oestrogen and P. In our study we did not detect a relationship between LH pulses and P.

Table I : Variations in serum progesterone concentration

Subject	Preovulatory Follicular Diameter (cm)	Mean LH	Progesterone Mean (am)	Progesterone Mean (pm)	Progesterone Mean over 9h (& range)	Variation over 9h*
A	2 1.7	5.7	42.2	38.9	40.6 (27-48.5)	53.0 %
B	2.3	3.4	28.7	21.3	25.1 (18-46)	111.5 %
C	1.7	1.4	30.0	32.9	31.5 (21.5 - 42.5)	66.7 %
D	2.4	4.0	16.5	14.3	15.0 (0.5-24)	156.0 %
E	2.0	2.7	20.6	12.8	16.7 (10-29)	113.0 %

LH - Luteinising hormone P - Progesterone
All values of LH and P are serum concentrations in mg/ml.
* Range over 9h divided by the mean P value over 9h.

REFERENCES

1. *Adashi E Y. Clomiphene citrate initiated ovulation: a clinical update. Seminars in reproductive endocrinology. 1986; 4: 255 - 265.*
2. *Hammond MG, Halme JK, Luther LM. Factors affecting the pregnancy rate in clomiphene citrate induction of ovulation. Obstet Gynecol 1983; 62: 196-202.*
3. *Van Campenhaut J, Simard R, Leduc B. Antiestrogen effect of clomiphene in the human being. Fertil Steril 1968; 19: 700-706.*
4. *Pandya G, Cohen MR. The effect of cisisomer of clomiphene citrate on cervical mucus and vaginal cytology. J Reprod Med 1972; 8: 133-138.*
5. *Glass RH. Infertility In: Yen SSC, Jaffe RB. (eds). Reproductive endocrinology: physiology, pathophysiology and clinical management (2nd edn). Philadelphia: W.B. Saunders, 1986; 571-613.*
6. *Glasier AF. Clomiphene citrate. Bailliere's Clinical Obstetrics and Gynecology 1990;4:491-501.*
7. *Hammond MG, Talbert LM. Clomiphene citrate therapy of infertile women with low luteal phase progesterone levels. Obstet Gynecol 1982; 59: 275-279.*
8. *Sgarlatta CS, Mikhail G, Hertelendy F. Clomiphene and Tomoxifen inhibit progesterone synthesis in granulosa cells comparison with estradiol. Endocrinology 1984,114: 2032-2038.*
9. *Asem EK, Hertelendy F. Clomiphene and tomoxifen inhibit the cholesterol side-chain cleavage enzyme activity in hen granulosa cells. J of Repr and Fert 1986; 77: 153 - 155.*
10. *Jones GS, Maffezoli RD, Strott CA, Ross GT, Kaplan G. Pathophysiology of reproductive failure after clomiphene induced ovulation. Am J Obstet Gynecol 1970; 108:847-867.*
11. *Cook C, Schroder JA, Yussman M, Sanfilippo JS. Induction of luteal phase defect with clomiphene citrate. Am J Obstet Gynecol 1984; 149:613-616.*
12. *Randall JM, Templeton A. The effects of clomiphene citrate upon ovulation and endocrinology when administered to patients with unexplained infertility. Hum Repr 1991;6: 659-664.*
13. *Ho Yuen B, Mari N, Duleba AJ, Moon YS. Direct effects of clomiphene citrate on the steroidogenic capability of granulosa cells. Fertil Steril 1988; 49: 626 - 631.*
14. *Kerin JF, Liv JH, Phillipov G, Yen SS, Evidence for a hypothalamic site of action of clomiphene citrate in women. J Clin Endoc Met 1985; 61:265-268.*
15. *Syrop CH, Hammond MG. Diurnal variations in mid luteal progesterone measurements. Fertil Steril 1987;47:67-70.*
16. *Jones GS. The luteal phase defect. Fertil Steril 1976;27: 351 - 356.*
17. *Strott CA, Cargille CM, Ross GT, et al. The short Luteal phase. J Clin Endoc Met 1970;30: 246-251.*
18. *Sherman BM, Korenman SG. Measurement of serum LH, FSH, estradiol and progesterone in disorders of human menstrual cycle. J Clin Endoc Met 1974; 39: 145-149.*
19. *Alila HW, Hansel W. Origin of different cell types in the bovine corpus luteum characterized by specific monoclonal antibodies. Bio Repr 1984; 31: 1015 - 1025.*