SERUM PROLACTIN ASSAY IN LUTEAL PHASE INSUFFICIENCY

by

VINITA SALVI AND DURU SHAH

SUMMARY

Thirty-two patients with luteal phase insufficiency had a serum prolactin assay done. All 3 hyperprolactinemic patients conceived on Bromoergocryptine therapy. Of the 29 euprolactinemic patients, 12 conceived; six with progesterone supplementation and 6 with clomiphene citrate plus progesterone supplementation.

Introduction

The spontaneous occurrence of the inadequate luteal phase has been considered an explanation for infertility in 3-10% of all barren marriages (DiZerega and Hodgen, 1981). Moreover, in those women who are over 35 years of age or with a history of habitual abortions or hyperprolactinemia manifest an even higher incidence of luteal phase defects (DiZerega and Hodgen, 1981).

To further elucidate the relationship between hyperprolactinemia and luteal phase defects, we studied 32 patients with luteal phase insufficiency.

In vivo (Fluckiger and del Pozo, 1978) and *in vitro* (McNatty *et al*, 1974) work has shown an association between hyperprolactinemia and decreased secretion of progesterone by the corpus luteum. Therefore, all the patients in the current study, had a serum prolactin assay done as well.

Material and Methods

Thirty-two women with luteal phase inadequacy were selected for the study. All the patients were spontaneously menstruating infertile women in whom all other factors for infertility had been ruled out.

For purpose of inclusion in the study, each patient had to satisfy at least 2 of the following 3 criteria of a luteal phase insufficiency:

(i) a post-ovulatory basal body temperature rise persisting for less than 12 days duration.

(ii) 2 endometrial biopsies on the 11-13th postovulatory day which show a lag in maturation of 2 or more days by the criteria of Noys *et al* (1950).

(iii) a Serum Progesterone assay on the 5th-7th post-ovulatory day with a level less than 10 ng/ml.

All the patients had a routine serum prolactin assay done as well.

The euprolactinemic patients were treated with either:

(a) Progesterone supplementation therapy i.e. Injection Hydroxyprogesterone caproate 250 mg i.m. every 3rd day after ovulation.

(b) Clomiphene citrate 50 mg O.D. days 5-9.

(c) Clomiphene citrate + Progesterone supplementation therapy i.e. (a) + (b).

Accepted for publication on 3-7-86.

The hyperprolactinemic patients were treated with Bromoergocryptine 2.5 mg twice daily.

Results

Table I shows that 3 of the 32 patients had hyperprolactinemia; of the 3, 2 had associated galactorrhoea as well.

All the 3 patients who were hyperprolactinemic conceived on a therapy of Bromoergocryptine 2.5 mg twice daily (Table III).

Discussion

It has been suggested that the basic cause for a short luteal phase lies in the events that occur prior to ovulation (Munlenstedt *et al*, 1979). A deficiency of FSH in the perimenstrual and the early follicular phase probably results in an inadequate induction of granulosa cell receptors. This in turn causes an inadequate corpus luteum with a diminished secretion of progesterone therapy resulting in a secretory endometrium which shows a distinct lag in maturation.

Correction of the inadequate luteal phase

TABLE I
Serum Prolactin Assay in Luteal Phase Defects

32 patients

Hyperprolactinemic	Euprolactinemic
3	29

Serum prolactin:

(i) 35 ng/ml
(ii) 29 ng/ml
(iii) 33 ng/ml

As seen in Table II, 12 of the 29 euprolactinemic patients (41.4%) conceived. None of the patients who were treated with progesterone alone conceived. However, 6 of the 12 patients who were treated with Clomiphene citrate and 6 of the 9 patients who were treated with Clomiphene citrate plus progesterone conceived.

TABLE II
Luteal Phase Defects
(Euprolactinemic patients—29)

Therapy	No.	Pregnancies	Preg. Rate
Progesterone*	8	0	
Clomiphene citrate**	12	6	50.0
Clomiphene citrate + Progesterone	9	6	66.7
	29		

* Hydroxyprogesterone caproate 250 mg i.m. every 3rd day from ovulation.
** 50 mg O.D. days 5-9.

TABLE III

Hyperprolactinemia with Luteal Phase Defects

No. of patients	..	3 (9%)
Treatment given	..	Bromoergocryptine 2.5 mg twice daily
Pregnancies	..	3
Pregnancy rate	..	100%

requires either supplemental addition of exogenous progesterone or stimulation of increased endogenous FSH secretion.

Clomiphene citrate is useful because it stimulates endogenous FSH production during the follicular phase of the cycle (Daly *et al*, 1983). Clomiphene has been found to be the most practical therapeutic modality available for this defect in the absence of hyperprolactinemia. In the current study, 50% of the patients treated with Clomiphene alone conceived, while 66.7% of the patients treated by Clomiphene with progesterone supplementation conceived.

However, clomiphene citrate may have a variable effect on the endometrium (Daly *et al*, 1983). Because of its anti-oestrogenic effect, Clomiphene may inhibit induction of progesterone receptors by oestrogen, resulting in an inadequate endometrium. Thus, while the ovarian cycle is corrected, the endometrial cycle may be variably affected and not improved at all. Further, in patients on Clomiphene citrate, luteal phase estradiol levels are frequently elevated above normal and this may further inhibit the decidualisation process. Either of these two mechanisms may explain the failure to achieve a pregnancy on clomiphene therapy.

The mechanism of a luteal phase defect associated with hyperprolactinemia is slightly different and occurs due to a direct prolactin induced inhibition of steroidogenesis by the pre-ovulatory follicle (Seppala *et al*, 1976; DiZerega and Hodgen, 1981). In patients with hyperprolactinemia, McNatty *et al* (1974) have demonstrated high levels of prolactin (PRL) in the antral fluid of the follicle, which cause suppression of the estradiol levels in the follicle. These decreased levels of estradiol do not sustain optimal proliferation of granulosa cells in the dominant follicle which is expressed clinically as a deficient luteal function.

Secondly, a luteal phase defect may also be due to an indirect prolactin induced inhibition of the hypothalamopituitary gonadotrophin secretion (DiZerega and Hodgen, 1981).

Bromoergocryptine, a drug that lowers peripheral PRL, is thus utilised as a form of therapy of luteal phase insufficiency with hyperprolactinemia (Fredriccson *et al*, 1977).

On reviewing a few studies on luteal phase defects (Table IV), it is seen that when Saunders *et al* (1979) and Muhlenstedt *et al* (1979) treated euprolactinemic patients with bromoergocryptine the results were extremely poor. However, when the euprolactinemic patients were treated with either progesterone supplementation or augmentation of the FSH by Clomiphene as by Daly *et al* (1983) and in the current study the results are significantly better. Daly's (1983) results are superior to those of the current study since he utilised other therapies e.g. gonadotrophins in patients who failed to conceive on progesterone or clomiphene.

TABLE IV
Review of Studies on Luteal Phase Defects

Author	Luteal phase defects (Euprolactinemic)		Luteal phase defects (Hyperprolactinemic)	
	No. of patients	Pregnancies	No. of patients	Pregnancies with BCP
Saunders *et al* (1979)	15	2 (with BCP) (13%)	—	—
Muhlenstedt *et al* (1979)	11	2 (with BCP) (18%)	7	4 (57%)
Del Pozo *et al* (1979)	—	—	8	4 (50%)
Daly *et al* (1983)	36	28 (78%)	7	5 (71%)
Current study (1986)	29	12 (41%)	3	3 (100%)

BCP = Bromoergocryptine

Table IV also demonstrates that though the indidence of luteal phase defects with hyperprolactinemia is relatively low, its treatment with bromocryptine yields significant rewards.

Thus, the mechanism of euprolactinemic luteal phase defects is different from those associated with hyperprolactinemia. Clomiphene citrate and progesterone supplementation benefit euprolactinemic patients while the hyperprolactinemic patients are best treated with bromo-ergocryptine.

References

1. Daly, D. C., Walters, C. A., Soto-Albors, C. E. and Riddick, D. H.: Fertil., **40**: 305, 1983.
2. del Pozo, E., Wyss, H., Tolis, G., Alcaniz, J., Campana, A. and Naftolin, F.: Obstet. Gynec., **53**: 282, 1979.
3. DiZerega, G. S. and Hodgen, G. D.: Fertil. Steril. **35**: 489, 1981.
4. Fluckiger, E. and del Pozo, E.: Influence on the Endocrine System. Handbook of Experimental Pharmac. Edited by B. Berde, H. O. Schild, Berlin: Springer Verlag, 1978, pp. 615-690.
5. Fredriccson, B., Bjork, G. and Carlstrom, K.: Lancet, **1**: 1210, 1977.
6. McNatty, K. P., Sawers, R. S. and McNeilly, A. S.: Nature (Lond.), **250**: 653, 1974.
7. Muhlenstedt, D., Bohnet, H. G., Hanker, J. P. and Schneider, H. P. G.: Int. J. Fertil. **23**: 213, 1979.
8. Noyes, R. W., Hertig, A. T. and Rock, J.: Fertil. Steril., **1**: 3, 1950.
9. Saunders D. M., Hunter, C., Hanse, H. R. and Wilson, G. R.: Obstet. Gynec., **53**: 287, 1979.
10. Seppala, M., Hirvonen, E. and Ranta, T.: Lancet, **1**: 229, 1976.