LUTEAL FUNCTION IN INFERTILE PATIENTS WITH MILD ELEVATION OF SERUM PROLACTIN

by

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Introduction

Hyperprolactinemia is classically related to the amenorrhoea-galactorrhea syndrome. Though this clinical condition interested the medical profession for many years, it was only recently proved that elevated prolactin plays a major role in the etiology and pathophysiology of this syndrome. The development of a sensitive and accurate radioimmunoassay for this hormone has increased appreciation of the hyperprolactinemic state. In a study conducted at Institute for Research in Reproduction, Parel, hyperprolactinemia was found to be the etiological factor in 14% of 309 cases of secondary amenorrhea. It was found that whenever serum prolactin levels were above 50 ng/ml the patient was invariably amenorrhoeic. In the present study we report the degree of menstrual dysfunction and ovulatory status when the women had mild elevation of serum prolactin.

Material and Methods

Sixteen menstruating women with mild hyperprolactinemia (mean prolactin 28 ng/ml range 20-40 ng/ml) were studied. The normal mean was 10 ng/ml with S.D. ± 4.9 ng/ml. Of the 16 patients, 14 presented with infertility and 2 presented with galactorrhea. Of the 14 infertile patients, 11 had some degree of galactorrhea on examination. The menstrual pattern of the 16 cases is shown in Table I.

TABLE I

Menstrual Pattern in 16 Patients With Mild Hyperprolactinemia

Menstrual Pattern	No.
Irregular cycle	4
Regular short cycle (26 days)	4
Regular long cycle (35 days)	1
Regular normal cycle (28 ± 2 days)	7

These patients were further studied for ovulatory function and adequacy of corpus luteum function on the basis of BBT records, endometrial biopsy and serum progesterone values. Two or more of the mentioned parameters were taken in each patient for assessing ovulation and corpus luteum adequacy.

Serum progesterone was estimated by radioimmunoassay (RIA) using WHO matched assay reagents and WHO method

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manual. Intra and interassay coefficient of variation was 9% and 16% respectively. At least 2 samples of serum prolactin were estimated between 9 and 11 a.m. on two consecutive days. The mean of 2 samples was taken. Serum prolactin levels were determined by RIA using the kit supplied by the National Institute of Arthritis, Metabolism and Digestive Diseases, National Institute of Health, Bethesda, Md. Human prolactin was labelled with 123 I (Radiochemical Centre, Amersham, England) according to the procedure described by Geenwood *et al* (1963) as modified by Midgley (1966). The results were expressed in nanograms per milliter.

Results

Ovulatory status and corpus luteal function (CLF) in 16 patients with mild hyperprolactinemia are shown in Table II.

abnormality was her serum prolactin which was 29 ng/ml. On further work-up for luteal function studies it was found that her cervical mucus score was 10, and it persisted till day 17 of a 26 day cycle. Her BBT charts also showed a short luteal span of 10 days with 2 dips in the temperature records (Fig. 1). Her serum progresterone values were lower than normal (Fig. 1). She was put on Bromocryptine 5 mg daily. Her temperature records and serum progesterone values showed a marked improvement (Fig. 1).

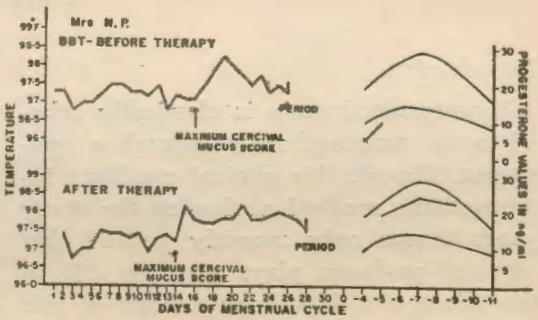


TABLE II

Ovulatory Status (O.S.) and Corpus Luteal Function (C.L.F.) in 16 Patients With Mild Hyperprolactinemia

O.S./C.L.F.	No.	Menstrual Pattern	
Anovulation	5	Regular cycles	1
		Irregular cyclea	4
Inadequate L F	7	Short regular cycles	3
		Normal cycles	3
		Long cycles	1
Adequate L F	4	Regular cycles	3
		Short regular cycles	1

A few typical illustrative cases are described in detail. Mrs. N.P. presented with secondary infertility of 3 years. She was married for 7 years and had one abortion of 3½ months 3 years ago. She menstruated regularly every 26-27 days. A general examination revealed galactorrhea. All routine investigations for infertility were normal. The only indication of

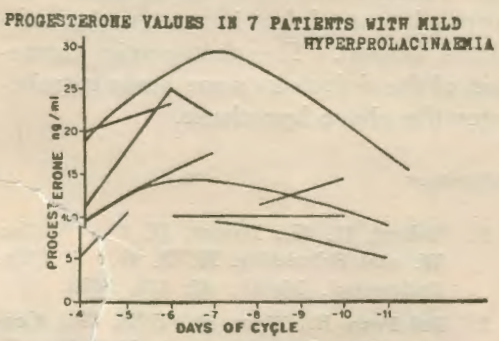
Mrs. N.C. was another case of primary sterility. Her husband had irreversible factor for male infertility so the couple was advised AID. She had galactorrhea, and cycle length of 25-26 days. Serum prolactin was 33 ng/ml. Her BBT records showed typical features of inadequate luteal function. Endometrial biopsy dating and serum progesterone values confirmed

the inadequacy of luteal function. The patient conceived on bromocryptine therapy with AID.

Mrs. S.V. married for 6 years presented with primary sterility and galactorrhea. Serum prolactin was 31 ng/ml. She had oligomenorrhea and BBT record was monophasic. She was given Bromocryptine to which she responded well. All three treatment cycles were ovulatory as judged by biphasic BBT records. The first two showed some evidence of corpus luteum inadequacy. The third cycle was completely normal. She had not conceived while on treatment.

Mrs. C.B. was another patient of primary sterility and galactorrhea. Her serum prolactin was 21 ng/ml. She showed ovulation with adequate luteal function as judged by all three parameters viz. BBT records, EB dating and serum progesterone levels. She was put on Bromocryptine for unexplained infertility but no conception resulted.

Serum progesterone values in 7 of the 16 patients are shown in Fig. 2. It can be



seen from the figure that 3 of the patients had progesterone values below the lower normal range while the other 4 showed serum progesterone within normal limits.

Results in 10 of the 16 cases who were on Bromocryptine are summarized in Table III. No pregnancy occurred in patients who had shown adequate luteal function prior to therapy. Those who had anovulation or inadequate luteal function in the basal period of observation did show ovulation and correction of luteal function. However, conception occurred in only 2 out of 7 patients (Table III).

TABLE III
Result of Therapy in 10 Patients With Mild Hyperprolactinemia

Ovulatory Status	Correction of L F/ Anovulation	Pregnancy
Anovulation—2	2	1
Inadequate L F—5	4	1
Adequate L F—3	-	-

Discussion

There is adequate evidence of the pathological role of elevated prolactin in amenorrhea. A good correlation was shown between the degree of hyperprolactinemia and the severity of gonadal dysfunction (Vaidya *et al*). Recently the pathological role of milder degree of hyperprolactinemia is suspected in infertility/subfertility due to corpus luteum insufficiency (Del Pozo *et al*, 1979; Sappala, 1978). Though a spectrum of gonadal dysfunction is described to correlate with the degree of hyperprolactinemia, its association with corpus luteum inadequacy needs further documentation.

In the present study, only 4 of the 16 patients with mild hyperprolactinemia showed normal ovulation and adequate luteal function while the rest had either anovulation or inadequacy of luteal function. Nine of them indeed reflect the gonadal dysfunction in their menstrual pattern. The correction of corpus luteum in-

sufficiency in 4 of the 5 patients while they were on therapy with a prolactin inhibiting agent Bromocryptine is very suggestive of the pathological role of hyperprolactinemia in corpus luteum defects. Similar therapeutic correction of luteal phase defects have been documented earlier by other investigators. In 6 out of 8 patients reported by Del Pozo *et al* (1979) there was correction of luteal phase defects and 5 conceived. In another series reported by Lenton *et al* (1977) the pregnancy rate was as high as 63% with bromocryptine therapy.

In our series, only 2 patients out of 10 conceived on therapy with bromocryptine. The poor pregnancy rates may have been due to other factors of infertility; 2 couples had a male factor which may have been respnsible for the subfertility. One must also remember the danger of oversuppression of prolactin levels. *In vitro* and *in vivo* studies have shown that an optimal amount of prolactin is required for normal steroidogenesis by the ovary. Very low levels of prolactin suppress progesterone production by the corpus luteum (Bohnet *et al*, 1976; Sappala, 1978). In fact corpus luteum deficiency has been induced by dopamine agonists in euprolactinemic volunteers with regular ovulatory cycles (Schulz *et al*, 1976).

Another cause for poor pregnancy rates may be that some of the cases may not have a persistent hyperprolactinemia and hence bromocryptine may not be a specific therapy. The secretion of prolactin is pulsatile i.e. serum concentrations alter at intervals of a few minutes (McNeilly, 1974; L'Hermite *et al*, 1973). There is also a diurnal variation—the highest levels occur in the early morning hours (Nokin *et al*, 1972). Besides this the stress of venepuncture may alter serum prolactin levels. There are reports, describing changes in serum prolactin concentration during the menstrual cycle (Van Cauwenburge *et al*, 1976; Vekemans, 1977), and still others where there are no such changes (McNeilly, 1974; Tyson *et al*, 1973). In view of all these factors affecting prolactin secretion, one must be very careful in interpreting isolated serum estimations as a mild elevation in a single sample. It may not be a true elevation because of the mentioned physiological variations. In order to establish the diagnosis particularly of mild hyperprolactinemia, one has to do serial estimations of prolactin where blood is collected at 20-30 minutes intervals through an indwelling cannula. This procedure avoids the repeated needle picks and associated stress.

In our previous communication we had shown that hyperprolactinemia more than 50 ng/ml is associated with amenorrhea where the degree of steroidogenesis correlated with the severity of hyperprolactinemia. In the present study we have shown that a mild degree of hyperprolactinemia can cause some degree of gonadal dysfunction like anovulation and corpus luteum defect in mestruating subfertile women. The therapeutic correction of the defects in some cases corroborates the above hypothesis.

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