HYPERPROLACTINEMIA : A COMMON ENDOCRINE THREAD IN INFERTILITY

JAYESH J. SHETH ● FRENNY J. SHETH

SUMMARY

One hundred and ninetyeight (198) women with primary or secondary sterility were investigated for prolactin (PRL) estimation. An overall incidence of hyperprolactinemia was found to be 24.7% in our study. Fortyfour per cent, 31.25%, 30%, 27.7% and 17.64% of women with raised PRL had galactorrhoea, secondary amenorrhoea, polycystic ovarian diseases (PCOD), oligomenorrhoea and primary sterility respectively. Serum progesterone (P) along with PRL estimations were carried out in 19 primary sterility cases on day 7 after ovulation. Five of them (29.41%) had transient hyperprolactinemia i.e. their follicular phase PRL was normal and midluteal PRL was elevated. From the present study we conclude that all females with primary or secondary sterility irrespective of their menstrual function should be screened for hyperprolactinemia and those with transient or stress spikes of hyperprolactenemia might be considered for bromocryptine therapy.

INTRODUCTION :

Prolactin is unique among the anterior pituitary hormones in at least two respects : It is the only one under tonic inhibitory controls by the hypothalamus and its actions are not limited to just one or a few physiologic events Nicoll (1980). As a result of this, clinical abnormalities are most likely to occur when there is loss of the inhibitory control and the consequences - while sometimes subtle - are apt to be seen in a wide range of clinical settings.

Alterations in PRL levels in females are known to be associated with galactorrhoea, with disorders of the menstrual cycle such as amenorrhoea, oligomenorrhoea and with both male and female infertility - including some instances previously termed idiopathic. Evidence now suggest that elevated PRL levels may even play a role in premenstrual discomfort, anxiety, PCOD and osteoporosis. Present study was undertaken to rule out possible causes of PRL in sterility and its association with menstrual disorders.

MATERIALS & METHODS :

One hundred and ninety eight females with a history of infertility were referred to our clinic for endocrine investigations. Of these 66 had

Dept. Obst. & Gyn. Endocrine Unit Shah Pathology Lab Medicare Centre, Ahmedabad .

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primary sterility with regular menstrual cycles, 36 had oligomenorrhoea, 20 had polycystic-ovaries, 9 had galactorrhoea, 48 had amenorrhoea and 19 had ovulatory menstrual cycle. In the latter group serum PRL and serum P investigations were made on day 7 after ovulation. Patients with raised PRL were reinvestigated in early follicular phase of the cycle. In rest of the patients serum PRL estimation along with serum FSH and serum LH were carried out in early follicular phase of the cycle.

All sera samples were stored at - 20°C before assay. In all cases estimation was made within 3-4 days after blood collection. Serum PRL estimation was made using RIA kits of Diagnostic Product Corporation (U.S.A.). The intra and interassay variation was 5.6% and 10% in our assay system.

Serum P estimation was made using RIA kit of Leeco Diagnostics (U.S.A.). The intra and interassay variation was 3.22 and 8.22, respectively.

RESULTS :

An overall incidence of hyperprolactinemia found in the present study were shown in Table I. Serum PRL levels were significantly raised ($P < 0.00001$) in women with secondary amenorrhoea (104.2 ± 11.35 ng/ml) and galactorrhoea (75.0 ± 34.42, ng/ml). In other groups of patients with oligomenorrhoea, PCOD and primary sterility PRL levels were moderately raised i.e. (38.44 ± 0.88, 31.0 ± 3.45 and 33.5 ± 1.05 ng/ml mean + SE) respectively.

The incidence of hyperprolactinemia was 44% in patients with galactorrhea, 31.25% in secondary amenorrhoea, 30% in PCOD, 27.77% in oligomenorrhoea and 17.64% in primary of secondary sterility.

In 26.31% (5/19) of infertile women - inspite of normal ovulatory menstrual cycle serum PRL levels were raised in midluteal phase (35.2 ± 2.88) with low levels of serum P (7.8 ± 3.2 mean $\pm$ SE). Though their follicular phase PRL was normal (18.6 ± 0.9). Three of these patients have already conceived with Bromocryptine and luteal support with profassi injection.

DISCUSSION :

It has been well established that hyperprolactinemia can lead to a series of alterations in the menstrual cycle from the classic amenorrhoea to galactorrhoea syndrome. Though amenorrhoea does not always occur in hyperprolactinemic patients, a normal cycle or a variety of alterations like hypomenorrhoea, hypo-

TABLE - I

Prolactin Concentration in Different Groups of Infertile Women

		No. of Patients with raised PRL	Serum Prolactin mean $\pm$ SE	Total No. of Patients
1.	Oligomenorrhoea	9/27.7%	38.44 ± 0.88	36
2.	Primary sterility	15/17.64%	33.5 ± 1.05	85
3.	Polycystic ovarian disease	6/30.00%	31.0 ± 3.45	20
4.	Galactorrhoea	4/44.00%	75.0 ± 34.42	9
5.	Sec. amenorrhoea	15/31.25%	104.2 ± 11.35	48
	Patients	49		198

oligomenorrhoea, hypermenorrhoea may be present. In these cases the negative effect of hyperprolactinemia is represented by a selective inhibition of ovulation, luteal insufficiency or short luteal phase. Del Pozo (1976) It is therefore possible to affirm that the subjective response of female reproductive axis shows a larger degree of sensitivity to hyperprolactinemia. So the measurement of serum prolactin levels alone is a definitive stage in the exclusion of such a syndrome in subjects with different menstrual disorders.

In our study 44 percent of patients with galactorrhoea had hyperprolactinemia. This is in agreement with the study of Del Pozo 1878 where 30 - 40% patients with galactorrhoea had hyperprolactinemia. However, it is also present in 10% of normoprolactinemia amenorrhoea. A poor correlation between galactorrhoea and hyperprolactinemia has been found in patients with normal menstrual function. Kleinberg et al. 1977 has reported that about one third of women with galactorrhoea have normal menses. As the prolactin level increases, a patient may progress sequentially from normal ovalation to an inadequate luteal phase, to intermittent anovulation, to total anovulation, to complete amenorrhoea.

Thirty one percent of patients with secondary amenorrhoea were found to have hyperprolactinemia. Twenty percent patients with secondary amenorrhoea and hyperprolactinemia and pituitary adenoma in present study as evidenced by CAT scan. None of these had an abnormal sella turcica. As many as one third of patients with secondary amenorrhoea will have a pituitary adenoma and if galactorrhoea is present half will have an abnormal sella turcica. Kleinberg et al 1977 Though the clinical symptoms do not always correlate with the prolactin level and patients with normal PRL may have pituitary adenomas. The highest PRL levels however are associated with amenorrhoea with or without galactorrhoea Speroff et al 1979 have observed that women with untreated hyperprolactinemia whether or not they have an identifiable tumor are unlikely to have progression of their disease. They may in fact have clinical and radiographic improvement. This means that they do not have to be treated with long term dopamine agonists.

One patient with secondary amenorrhoea had persistent hyperprolactinemia even after 12.5 mg dose of bromocryptine per day. Her basal PRL was 300 ng/ml and with treatment it suppressed to 84 mg/ml. It is likely that this patient has a bromocryptine resistant prolactinoma. A similar observation was made by Pellegrini et al. 1989. It is likely that resistance to bromocryptine treatment results from deficient dopaminergic regulatory mechanisms in adenomatous cells. A decrease in D_2 dopamine receptor appears to be the main anomaly, but this phenomenon also might be associated with a postreceptor defect. In his critics in yearbook of infertility Lobo (1990) has suggested that tumor resistance to bromocryptine may be due to the fact that the tumor may not be a PRL - secreting adonoma that is being treated although the PRL level may be elevated and secondly PRL may be immunologically aberrant e.g. big-big.

Thirty percent of our patients with PCOD had hyperprolactinemia. Since chronic anovulation and disordered LH-FSH secretion appear to be basic features of PCOD, it is likely that endorphine liberation in the hypothalamus suppresses both dopamine and Gn-RH pathways leading to hyperprolactinemia. High prolactin levels also inhibit estrogen synthesis in the ovary leading to chronic anovulation and PCOD.

Twenty seven percent of women with oligomenorrhoea were found to have hyperprolactinemia. It is now well established that increased PRL levels produces anovulation because it prevents the LH pulsatility and interferes with the positive feedback action of estradiol at the hypothalamic level through blockage of the estrogenic receptors. This chronic anovulation leads to oligomenorhoea and other menstrual disorders. Hypothalamic resistance to the effect of oestrogens appears to be mediated by central receptors to progestrone in conjuction

with dopaminergic mechanism (Fluckiger et al 1982). The action of prolactin on the ovary may be due to a decreased number and affinity of the LH receptors in the corpus luteum with an associated decrease in the production and secretion of progesterone. Nevertheless, it should be born in mind that the ovarian sensitivity to prolactin is extremely variable and that moderately elevated levels may have no effect or may cause luteal insufficiency in some cases and amenorrhoea in others.

The interesting part of study is idiopathic hyperprolactinemia in normally menstruating women with ultrasonographically documented ovulation. Fifteen percent of patients had hyperprolactinemia during preovulatory phase and 26.31% of patients had hyperprolactinemia in midluteal phase. Hyperprolactinemia in a women with regular ovulatory menstrual cycles has been observed by Isao and Kyogo 1985. Recently Robert Harrison (1988) has reported stress spikes of hyperprolactinemia in couples with unexplained infertility. Pregnancy rate in such women when treated with clomiphene citrate and bromocryptine were found to be significantly more successful than placebo. Luteal phase hyperprolactinemia is also well documented in the literature. Anterior pituitary dysfunction due to hyperprolactinemia during the luteal phase following ovarian hyperstimulation has been observed by Hannu et al. (1987). So none of our patients on stimulation protocol were included in the study. What is important is whether to treat such patients with transient or stress spikes of hyperprolactinemia or not. In our personal experience we have observed pregnancies in three of these 5 patients with transient hyperprolactinemia.

Though transient hyperprolactinemia appears to be common in women attending infertility or general Gynaecologic clinics. Whether 2 or 3 random estimations of the PRL concentration make special testing to rule out stress-related hyperprolactinemia unnecessary remains controversial. Though an HPR (hyperprolactinemia rest) test limited to 3 blood samples for only PRL determination at 0,03 and 60 min. should suffice to diagnose this condition and to help avoid diagnostic pitfalls and unnecessary treatment Muneyyirci et al 1989.

From present study we conclude that all patients with sterility irrespective of menstrual disorders or ovulation should be screened for PRL estimation. And those with transient or intermittant spikes or hyperprolactinemia and long standing sterility may be considered for bromocryptine therapy.

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