BROMOCRIPTINE-INDUCED PREGNANCIES IN WOMEN WITH PROLACTIN — PRODUCING PITUITARY TUMORS

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Inappropriately elevated secretion of serum prolactin may represent a major dissturbance of the hypothalamic pituitary system from a variety of pathophysiologic causes. Most often the patient presents with complaints of anovulatory infertility, and the presence of galactorrhoea and/or menstsrual dysfunctions are the other manifestations of hyperprolactinaemia. The almost simultaneous development of radio-immuno assay for measurement of serum prolactin levels and the release of the anti-prolactin agent, bromocriptine, for the effective suppression of elevated prolactin levels have revolutionized the treatment of anovulatory infertility of hyperprolactinaemic origin (Archer *et al* 1974; Corunblum *et al* 1976; Wiebe *et al* 1977; Vaidya and Aloorkar, 1977; Chang, 1978; Gemzell and Wang, 1979; Corunblum, 1979; Vaughn and Hammond, 1980; Pepperell, 1981; Canales *et al* 1981 and Crosignani *et al* 1982).

It has been well recognised that a good proportion of hyperprolactinaemic subjects will be harboring a prolactin-secreting pituitary adenoma (prolactinoma) (Gemzell and Wang, 1979; Quigley and Hanag 1980; Corenblum, 1979). The incidence of tumours in patients with amenorrhoea and hyperprolactinaemia is between 36% (Franks *et al* 1977) and 48% (Kleinberg, *et al* 1977). Pregnancy is rare in these patients and occur only when effective anti-tumor treatment is instituted. However, as many of these women are young, wish to become pregnant, and very likely to have normal ovaries, they are good candidates for ovulation induction and are quite frequently treated with ovulation inducing agents (Gemzell and Wang 1979). So much so, infertility associated with pituitary prolactinomas is not an uncommon entity, and with the greater utilisation of serum prolactin assay and tomography of the sella tursica this problem is more readily recognized.

When fertility is desired in a patient with pituitary prolactin secreting adenoma, then the choice of therapy should be non-destructive to the otherwise normal non-adenomatous pituitary, yet bring normalization of serum prolactin levels with restoration of normal ovarian function (Corenblum, 1979). Furthermore, it is feared that any tumor expansion during pregnancy may produce neurological complaints such as visual field abnormalities or persistent headache (Pepperel, 1981).

The choices of therapy in patients wishing to become pregnant are controversial

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and vary depending on local clinical experience and abilities. There are advocates of pituitary microsurgery (Chang *et al* 1977; Husami *et al* 1977; Jaquet *et al* 1978; Post *et al* 1979; Kramer, 1980; Landolt, 1981 and Woosely *et al* 1982), or radiation therapy (Thorner, 1977) before conception is allowed whereas others believe that the use of prolactin-lowering drugs such as bromocriptine with careful observation is the treatment of choice (Corenblum *et al* 1975, Bergh *et al* 1978, Corenblum 1979, Thorner *et al* 1980, Canales *et al* 1981 and Corenblum 1981). Because the natural history of these adenomas is not known, nor the effects of pregnancy on these adenomas, many patients are merely being followed clinically without any intervention (Gemzell and Wang, 1979).

In view of this controversy surrounding the patients with pituitary adenoma desiring fertility, we report a series of 6 patients with prolactin-secreting pituitary tumours who were initially advised treatment with bromocriptine, 5 accepting the treatment, 3 conceived, 1 developing visual field defects and visual symptoms during pregnancy but successfully treated with bromocriptine and delivered normally.

Materials and Methods

From a personal series of the senior author of patients treated for hyperprolactinaemia and infertility,. there have been in total 6 women who have galactorrhoea, menstrual dysfunction (secondary amenorrhoea or oligomenorrhoea), hyperprolactinaemia and abnormal sella tursica tomography. All had normal thyroid function, and normal or low normal gonadotropin levels. Majority were clinically hypoestrogenised, and other infertility factors were maticulously excluded in all subjects. Results of visual field examinations were normal in all patients, and none had neurologic symptoms such as head ache or visual symptoms at the time of registration (Table I). No previous therapy had been directed at the prolactin-secreting adenomas. After giving informed consent, 5 of the 6 patients started taking bromocriptine in a dose of 2.5 mg twice daily. The dose was adjusted according to the ovulatory response. All who achieved conception were followed by frequent visual field examinations.

CASE REPORT

Case 1

A 26-year-old woman was first seen on 30th October, 1981 for evaluation of infertility (2 years) and secondary amenorrhoea (3 years). On initial examination bilateral profuse galactorrhoea was found. She was tall, fair and feminine, with hypo-estrogenised vagina and small uterus. Uterine and tubal factors were excluded by a HSG. No curettings were obtained at endometrial biopsy. Her serum prolactin value was 70 ng/ml, with normal FSH and LH values. T_3 and T_4 estimations were within normal limits. Lateral tomogram of the sella turcica demonstrated an enlarged sella (20 mm/9 mm) with dorsum sella rarified (Fig. A).

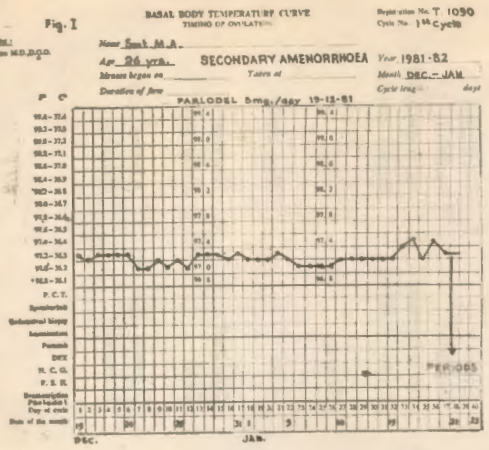
Diagnosis of macro-adenoma of the pituitary was made on (i) secondary amenorrhoea and galactorrhoea, (ii) hyperprolactinaemia, and (iii) obvious enlargement of pituitary fossa. The two alternative therapeutic approaches, namely, neurosurgical exploration and pituitary adenectomy, and medical treatment with bromocriptine were discussed. The couple preferred the latter form of treatment, and was started on 2.5 mg of bromocriptine twice daily after a trial dose of 1.25 mg twice daily for 2 days. Treatment was started on 15th December, 1981 and patient menstruated on 21st January, 1982 (on the 38th day of 5 mg bromoscriptine schedule. However, since the BBT failed to show a biphasic shift (Fig. I), the dose schedule was increased to 7.5 mg (3 tablets). In this second cycle she showed BBT evidence of ovulation around 26th of January, and the temperature

TABLE I

Case History of Infertile Patients with Pituitary Adenoma

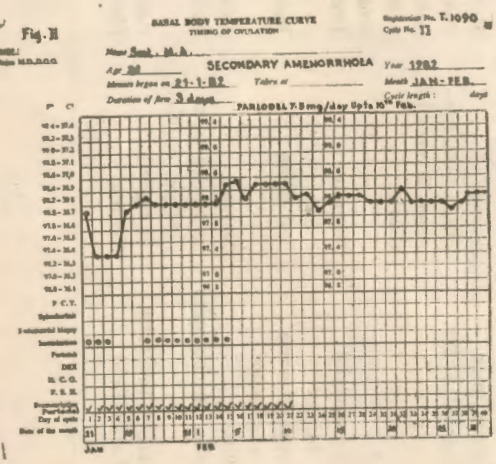
Case particulars	Patient No. I	Patient II	Patient III	Patient IV	Patient V	Patient VI
Age	26 yrs.	25 yrs.	20 yrs.	33 yrs.	28 yrs.	25 yrs.
Infertility	2 yrs.	2 yrs.	8 yrs.	1 yr.	6 yrs.	6 yrs.
Menstrual dysfunction	Secondary amenorrhoea 3 years	Oligo-menorrhoea & Secondary amenorrhoea	Oligo-menorrhoea & Second amenorrhoea	Secondary Amenorrhoea 5 yrs.	Secondary amenorrhoea 6 yrs.	Secondary amenorrhoea 10 yrs.
Galactorrhoea	Bilateral ++	Bilateral +	Bilateral ++	Bilateral +++	Bilateral +	Bilateral +++
Appearance	Feminine	Feminine	Feminine	Feminine	Stocky	Feminine
Vaginal exam.	Hypo-oestroge-nised & small uterus	Normal estrogenised & small uterus	Normal estrogenised & small uterus	Normal oestrogenised & small uterus	Normal oestrogenised & small uterus	Normal estrogenised & small uterus
Endometrial biopsy	Negative	Proliferative	—ve	Not done	Scanty	—ve
Progresterone challenge	Not done	Not done	—ve	—ve	+ve	Not done
HSG	Normal	Normal	Normal	Normal	Normal	Normal
Sella tomography	20 mm/9 mm dorsum rarified	Enlarged	Enlarged	18/6 double flooring	20/8	Enlarged
Serum prolactin	70 ng/ml	Above 100 ng	Above 150 ng	Above 150 ng	Above 150 ng	Above 150 ng
Visual field	Normal	Normal	Normal	Normal	Normal	Normal

Fig. I



remained elevated indicating the possibility of pregnancy. Bromocriptine was stopped on 10th February (Fig. II) Subsequently pregnancy was confirmed, and on 24th April was reported to be 12 weeks. At that time the patient complained of very much diminished vision in the right eye. It was found that the vision was reduced to 6/18, with marked central field loss in superior temporal quadrent. She was started on bromocriptine again on a dose of 2.5 mg thrice daily from 20th June, 1982. Her vision became clear on 26th of June, and her visual field and fundus were certified normal on 16th July, 1982. Subsequently she had regular visual field examinations and continued the drug in a dose of 2.5 mg twice daily till the time of delivery. She had a normal vaginal delivery on 23rd October, 1982, a 3.2 kg, male, healthy baby.

Fig. II



She had no difficulty in breast feeding the infant, nor she had any visual defects subsequently. She had no bromocriptine therapy in the puerperium

Case 2

This relates to a 25 year old infertile woman (2 years) who had earlier oligomenorrhoea and presently reporting with secondary amenorrhoea. She had mild galactorrhoea on both sides. She was average thin built, dark and feminine. Her vagina was soft supple and showed good rugae, uterus was normal in size, with endometrium in the proliferative phase. HSG excluded uterine and tubal disorders. Her serum prolactin level was reported to be more than 100 ng/ml, with normal FSH, LH, T_3 and T_4 values. Lateral tomogram showed a marked enlargement of sella turcica (Fig. B). With these findings, a diagnosis a pituitary macroadenoma producing hyperprolactinaemia depressing the fertility was made. After a proper counselling she was also started on bromocriptine in the regular dose of 2.5 mg twice daily. Treatment was started arbitrarily on 30th September, 1982, the BBT showed biphasic shift around 6th of October, maintained a continuous thermal elevation. On the 40th day of starting the drug (9th November, 1982) pregnancy was diagnosed and the treatment was discontinued. On 12th December, when she was 10 weeks pregnant she had complained of headache and pain in the left eye on the temporal side. However, visual field examination showed no abnormalities, nor she had any visual defects. The symptom was relieved spontaneously within a few days, and she has regular visual field examination every month and currently she is 26 weeks pregnant and has no complaints. (Fig. III).

Case 3

This is again yet another patient reporting to us at the age of 28 years for investigation and treatment of infertility of 8 years standing. She had oligomenorrhea earlier and presently is having secondary amenorrhoea which does not respond to pregesterone challenge. Earlier she had undergone endometrial biopsy with negative results. She was fair, tall healthy and feminine, and had profuse bilateral galactorrhoea. However, there was no clinical evidence