HYPERPROLACTINEMIA IN SUBFERTILE PATIENTS — AN ANALYSIS OF TWENTY-NINE CASES

Charles Lim
Mary Rauff
Victor H H Goh
S S Ratnam

SYNOPSIS

Twenty-nine subfertile cases with hyperprolactinemia detected in 1979 were analysed. Pituitary microadenoma was detected in seventeen cases. Seven patients became pregnant, six of them while on bromocriptine treatment.

INTRODUCTION

Since the radio-immunoassay identification of human prolactin (1), there has been increasing understanding of the role of prolactin in human reproduction.

One field of special interest is the role of hyperprolactinemia in anovulation in general and anovulatory subfertility in particular.

The actual mechanism of anovulation in cases of hyperprolactinemia is not known. Raised concentrations apparently inhibit steroidogenesis by the ovary (2). There may be an additional central effect in suppressing the observed luteinising hormone surge on estrogen challenge (3).

Lowering the level with bromocriptine results in ovulation and pregnancy (4). This has given fresh hope to a group of anovulatory subfertile patients who were unresponsive to the usual anti-estrogenic ovulation-induction drugs like clomiphene citrate and cylofenil.

This paper reports the experience in the detection and management of hyperprolactinemic patients in the University Department of Obstetrics & Gynaecology at the Kandang Kerbau Hospital.

MATERIALS AND METHODS

(A) Patients:

A total of one hundred cases of hyperprolactinemia were collected in 1979. One patient was pregnant and another was breast-feeding at the time of blood sampling. Twenty-nine patients did not have notes available for viewing. Twenty-one patients did not present with subfertility. There were fifty-one subfertile cases of whom twenty-nine had complete data for analysis.

Blood sampling was done through an indwelling venous cannula. Three samples were taken at five minute intervals after an hour's rest with the cannula in situ. The serum was aliquoted and kept at – 20°C until analysis.

(B) Hormone Assays:

Prolactin was assayed by the RIA technique using IRP for prolactin 75/504 reference standard. The average level of the three samples was taken as the level for each patient.

The criterion of hyperprolactinemia is >500 mIu/lit (unpublished data).

Thyroid stimulating hormone (TSH) was also assayed by RIA technique using Serono Diagnostic Hypolab. kit.

**Department of Obstetrics & Gynaecology
National University of Singapore
Kandang Kerbau Hospital
Singapore 0821**

Charles Lim MBBS, M Med(O&G), MRCOG, FRCS(E)(G)

Mary Rauff MBBS, M Med(O&G), MRCOG

Victor H H Goh BSc(Hons) Phd.

S S Ratnam MBBS, M.D., FRCS, FRCS(E) (G), FRCOG, AM

(C) Other Investigations:
Patients had plain skull x-rays taken with coned-down views of the pituitary fossa. Ordinary tomography or computer assisted tomography was also performed.

(D) Treatment:
Twenty-seven patients were prescribed bromocriptine, starting with 1.25 mg nightly and gradually increasing to a maximum of 2.5 mgbd or tds after two to four weeks. Two patients out of the twenty-seven were subsequently found to have raised TSH levels and were then referred to the internists for management of hypothyroidism. One patient underwent transfrontal surgical removal of a pituitary macroadenoma which had a suprasellar extension.

RESULTS

(A) Clinical Features:
Out of the total of twenty-nine cases, only one patient had symptomatic galactorrhea and thirteen had demonstrable galactorrhea on breast expression.

Six cases had secondary amenorrhoea. Ten cases had no symptoms other than subfertility.

Visual field perimetry was done in fourteen cases and all were normal. All twenty-nine cases were tested by confrontation and bitemporal field loss was not detected.

(B) Hormone Levels:
Of the twenty-nine cases of hyperprolactinemia, three had levels greater than 2,500 mlu/lit, eleven had levels between 1,000 and 2,500, the remaining fifteen had levels between 500 mlu/lit and 1,000 mlu/lit.

TSH assay on all twenty-nine patients revealed that only two had raised levels suggestive of hypothyroidism.

(C) Radiological Features:
These are summarised in Table I.

Plain x-ray of the pituitary fossa was not sensitive enough to detect microadenoma. Of the 16 cases with microadenoma detected on tomogram or CTAT, eleven had plain x-rays of the pituitary fossa done. Plain x-rays were reported as abnormal in two cases. One had a double floor in the pituitary fossa and the other showed a ballooned pituitary fossa.

Tomography picked up more cases than did CTAT. Of the twelve cases that had both tomography and CTAT done, six were positive by both methods five cases were positive on tomography but negative on CTAT and one case was negative on tomography but positive on CTAT.

(D) Results of Treatment:
This is summarised in Table II.

Out of twenty-seven patients treated with bromocriptine, nineteen ovulated and six became pregnant.

Table III summarises the pregnancies occuring with the various pituitary abnormalities.

Amongst cases with microadenoma, all who got pregnant belong to the category with pre-treatment prolactin levels of above 1000 mlu/lit. Of the seven patients who achieved pregnancy, six have not yet delivered at the time of writing this paper. One had delivered a 3000 gm normal male infant.

DISCUSSION

This study has illustrated that hyperprolactinemia can occur in cases without features of secondary amenorrhoea and symptomatic galactorrhea. All cases of anovulatory subfertility should have their breasts examined for galactorrhea and their blood taken for prolactin assay.

Since prolactin levels are raised with stress (5, 6), it is important to take blood under resting conditions. In our department we minimise the stress factor by inserting a plastic venous cannula and then wait for an hour before sampling the blood. As a counter-check, we take three samples of blood at five minute intervals to look for comparability. If a high initial level with subsequent falling levels is detected, it would indicate stress and we would repeat the sampling.

Hyperprolactinemic patients are asked whether they are taking any medications like sedatives or anti-hypertensives (e.g. Chlorpromazine or Methyl Dopa) as they may raise prolactin levels (7).

This study showed that 58% of our hyperprolactinemic subfertile patients had a demonstrable pituitary adenoma. The true proportion of patients with hyperprolactinemia who have "microadenomata" is unknown since the diagnosis is dependent upon fine neuro-radiological technique which sets the limits for detection (8).

Non-symptomatic pituitary tumours are very common (9). Although the majority are probably innocuous, a small number may behave differently and grow rapidly with suprasellar extension and exert pressure on the optic chiasma producing bitemporal hemianopsia initially and total blindness eventually. This can happen when pregnancy occurs (10).

It is thus necessary to test the visual fields of all hyperprolactinemic patients and get a baseline tomogram or CTAT assessment before proceeding to ovulation induction with bromocriptine.

Patients with suprasellar extension and visual field impairment should have the tumour excised (11). Patients with pituitary microadenoma who get pregnant with bromocriptine therapy require monthly visual field perimetry in order to detect the odd case that develops visual field loss (12).

A small proportion of hyperprolactinemic patients actually have hypothyrodism as the underlying cause. These are detected by their raised circulating TSH levels. Specific treatment involves thyroid hormone replacement.

TABLE I: RESULTS OF CTAT OF TOMOGRAM OR BOTH

Normal	Micro-adenoma	Macro-adenoma	Empty Sella	Cyst	Total
9	16	1	2	1	29

TABLE II: RESULTS OF TREATMENT

	Ovulation On BBT	Pregnancy	Still No Ovulation Based on BBT	Total
No Treatment	-	1	-	1
Bromocriptine	13	6	8	27
Surgery	-	-	1	1

TABLE III: PREGNANCIES OCCURING WITH THE VARIOUS PITUITARY ABNORMALITIES

	Normal	Micro-adenoma	Macro-adenoma	Empty Sella	Pituitary Cyst	Total
Cases	9	16	1	2	1	29
Pregnancy Cases	1	5	0	1	0	7

REFERENCES

1. Hwang, P., Guyda, H., Friesen, H.: A Radioimmunoassay for Human Prolactin. Proceedings of the National Academy of Sciences of the United States of America, 1971; 68: 1902-1906.
2. McNatty, K.T., Sawyers, R.S., McNeilly, A.S.: A Possible Role for Prolactin in Control of Steroid Secretion by the Human Graafian Follicle. Nature, 1974; 250: 635-653.
3. Glass, M.R., Shaw, R.W., Butt, W.R., Logan Edwards, R., London, D.R.: An Abnormality of Estrogen Feedback in Amenorrhoea-Galactorrhea. British Medical Journal, 1975; 3: 274-275.
4. Thorner, M.D., Besser, G.M., Jones, A., Dacie, J., Jones, A.E.: Bromocriptine Treatment of Female Infertility: Report of 13 Pregnancies. British Medical Journal, 1975; 4: 694-697.
5. Frantz, A.G., Kleinberg, D.L., Noel, G.L.: Studies in Prolactin in Man. Recent Progress in Hormone Research, 1972; 28: 527-590.
6. Goh, H.H., Karim, S.M.M., Ratnam, S.S.: Effect of Catheterisation on the Secretion of Prolactin and Cortisol in Male Transsexuals. Singapore Journal of Obstetrics & Gynaecology, 10(2)56-60.
7. Besser, G.M., Thorner, M.O.: In Advances in Medicine, Symposium II, Ed. Lant, A.F., Turnbridge Wells, Pitman Medical, 1975; 255, 1975.
8. Vezina, J., Sutton, J.J.: Prolactin Secreting Pituitary Microadenomas. American Journal of Roentgenology, 1974; 120: 46-54.
9. Costello, R.T.: Subclinical Adenoma of the Pituitary Gland. American Journal of Pathology, 1936; 12: 205-215.
10. Gemzell, C.: Induction of Ovulation in Infertile Women with Pituitary Tumors. American Journal of Obstetrics and Gynaecology, 1975; 121: 311-315.
11. Besser, G.M., Moult, P.J.A.: Prolactinomas and their Management. In Advances in Gynaecological Endocrinology, Ed. Jacobs, H.S., Proceedings of the Sixth Study Group of the Royal College of Obstetricians and Gynaecologists, R.C.O.G., 1978; 234-247.
12. Hancock, K., Scott, J.S., Gibson, R.M., Lamb, J.T.: Pituitary Tumors and Pregnancy. British Medical Journal, 1978; 1: 1487-1488.