BROMOCRIPTINE-INDUCED PREGNANCIES IN THE AMENORRHOEA-GALACTORRHOEA SYNDROME

B. E. MUSTAFFA

B. A. K. KHALID

N. SATGUNASINGAM

N. ADEEB

P. L. TAN

S. CHANDRAN

SUMMARY

13 patients with the amenorrhoea-galactorrhoea syndrome who conceived during treatment with bromocriptine were reported. Mean period of amenorrhoea was 3.0 years. In ten patients galactorrhoea was noted for a mean period of 4.2 years while in three it was discovered during examination. Seven patients presented with primary infertility. Menses returned in all cases after a mean duration of 2 months of treatment with bromocriptine at an average dose of 5.86 mg daily. Mean serum prolactin was 4344 mU/l (range 750 mU/l to 23,000 mU/l) before treatment and this declined to 186 mU/l with treatment.

Seven patients became pregnant 5 to 25 months of treatment while six conceived after first menses. 21 pregnancies resulted from the thirteen patients. There was one spontaneous abortion and one premature delivery in which the baby died. Of the 16 live-births, there were twelve girls and four boys and their mean birth-weight was 2932 g. All were normal at birth and during subsequent developments except one with congenital dislocation of hip.

It is concluded that bromocriptine is effective in restoring menstrual cycles and fertility by lowering serum prolactin in patients with the amenorrhoea-galactorrhoea syndrome. Bromocriptine may be safe for use during pregnancy, but it is suggested that the medication should be stopped immediately after conception unless tumour growth is apparent.

B. E. Mustaffa,
B. A. K. Khalid,
Diabetes and Endocrine Clinic,
Department of Medicine,
N. Adeeb,
Department of Obstetrics and Gynaecology,
P. L. Tan,
Dept. of Ophthalmology,
Faculty of Medicine,
University Kebangsaan Malaysia,
Kuala Lumpur, Malaysia.
N. Satgunasingam,
Division of Radiochemistry,
Institute of Medical Research,
Kuala Lumpur.
S. Chandran,
Department of Radiology,
General Hospital,
Kuala Lumpur.

INTRODUCTION

The amenorrhoea-galactorrhoea syndrome is usually associated with a prolactin-producing tumour or prolactinoma. [1,2] Patients with this condition are infertile due to the raised serum prolactin. [3] Bromocriptine, a long-acting dopamine agonist is effective in lowering serum prolactin resulting in a return of normal periods and restoration of fertility. [4,5]

The potential risk of teratogenicity of bromocriptine has been raised and its use during pregnancy cautioned. [6] Further, rapid growth of pituitary tumours may occur during pregnancy, [7] and it has been suggested that patients with prolactinomas should receive definitive treatment for the tumour before allowing pregnancy. [8,9]

We report here our experience of 21 pregnancies in 13 hyperprolactinaemic patients treated with bromocriptine.

PATIENTS AND MATERIALS

Thirteen patients with the amenorrhoea-galactorrhoea syndrome who attended the Endocrine and Diabetes Clinic, Universiti Kebangsaan Malaysia, Kuala Lumpur for periods of 10 to 65 months who conceived during treatment with bromocriptine are included in this report. Their ages ranged from 20 to 38 years.

The patients had had amenorrhoea for a mean period of 3.0 years (range 6 months to 14 years). In all cases this was preceded by menstrual irregularity for periods ranging from 1 to 18 years. In four patients, oligomenorrhoea was present since menarche. In ten patients bilateral galactorrhoea was noted for 1 month to 8 years (mean 4.2 years) whilst in three it was discovered only during examination (Table I). Seven patients had spontaneous milk discharge while the rest had expressible galactorrhoea.

Six patients presented with secondary infertility, the last childbirth being 2 to 9 years before diagnosis. Four patients had primary infertility with a barren marriage ranging from 5 to 14 years while another three were diagnosed before marriage (Table II). None of the patients were on medication and there were no evidence of hypothyroidism, Cushing's syndrome or acromegaly.

TABLE I
PATIENTS' AGES, DURATION OF AMENORRHOEA AND GALACTORRHOEA

Patient	Age (yrs)	Duration of Amenorrhoea (yrs)	Duration of Galactorrhoea (yrs)
1. LNC	33	5	5
2. OSN	31	1	1
3. OSY	27	3	8
4. LY	23	2	N
5. MK	20	2	7
6. SZ	28	9 mths	2.5
7. NS	30	1.5	N
8. SM	30	3	8
9. DH	30	1	3
10. RH	22	6 mths	1 mth
11. MN	26	2	2
12. MA	30	3	5
13. MC	38	14	N

N - noted during examination.

TABLE II
NUMBER OF PREVIOUS CHILDREN, DURATION OF MARRIAGE AND PERIOD OF INFERTILITY

Patient	No. of children	Duration of marriage (yrs)	Period of infertility (yrs)
1. LNC	1	7	5
2. OSN	1	3	2
3. OSY	0	6	6
4. LY*	0	1	1
5. MK*	0	2	2
6. SZ	1	5	2.5
7. NS	1	8	3
8. SM	0	7	7
9. DH	3	13	9
10. RH*	0	6 mths	6 mths
11. MN	1	6	3
12. MA	0	5	5
13. MC	0	14	14

* Diagnosis made and treatment started before marriage.

Skull X-rays including pituitary fossa tomograms were performed on all patients and visual fields assessed formally using the Goldman's and Bjerrum's screens. Serum prolactin was assessed by a radio-immunoassay method in accordance with WHO protocol [10] and standardised against reference preparation 75/504. The normal range for women in the reproductive age is between 115 and 500 mU/l. Thyroid function tests were performed using commercial kits (Abbot Laboratories, North Chicago, II., USA). The reference range for serum thyroxine (T_4) was 65 to 170 nmol/l, free thyroxine index (FT_4I) 15 to 55 and TSH less than 5 mU/l. Serum FSH, LH and oestradiol were also measured according to WHO methods. [10]

Patients were treated with bromocriptine at an average dose of 5.86 mg daily (range 2.5 mg to 15 mg). All patients were advised to stop bromocriptine if periods were delayed for one week except in five patients with previous visual field defects where they were instructed to continue with the medication. Patients had monthly follow-up during pregnancy whereby visual fields and serum prolactin were assessed. When there was evidence of tumour enlargement, patients were admitted and bromocriptine reinstituted. These patients were reviewed weekly and bromocriptine dosage

TABLE III
DAILY DOSAGE OF BROMOCRIPTINE AND THE DURATION BEFORE MENSES RETURNED AND CONCEPTION

Patient	Bromocriptine dosage (mg/day)	Duration of treatment (mths) before	
		Restoration of menses	Conception
1. LNC	5 - 10	3	8
2. OSN	5	2 wks	IM
3. OSY	2.5 - 7.5	3	6
4. LY	7.5	2 wks	12
5. MK	7.5	2	24
6. SZ	7.5	2 wks	IM
7. NS	5	2	5
8. SM	5	4	IM
9. DH	5	2 wks	IM
10. RH	2.5	1	6
11. MN	2.5 - 5	1	IM
12. MA	2.5 - 5	4	6
13. MC	7.5 - 15	1	IM

IM - Conception occured immediately after the first menses.

TABLE IV
SERUM PROLACTIN BEFORE AND DURING TREATMENT WITH BROMOCRIPTINE

Patient	Serum Prolactin (mU/l)	
	Before	During
1. LNC	3655	195
2. OSN	2392	347
3. OSY	13200	<78
4. LY	750	172
5. MK	2775	213
6. SZ	3505	175
7. NS	2213	<78
8. SM	4839	226
9. DH	7365	172
10. RH	1821	301
11. MN	7117	<78
12. MA	2500	202
13. MC	23000	<90

adjusted according to clinical response and visual field changes.

RESULTS

With the institution of bromocriptine, menstrual cycles were restored in all cases after a mean duration of 2 months with four patients having menses after 2 weeks of treatment (Table III). Eight patients ceased to have galactorrhoea after one to 14 months of treatment while the rest noted a decrease.

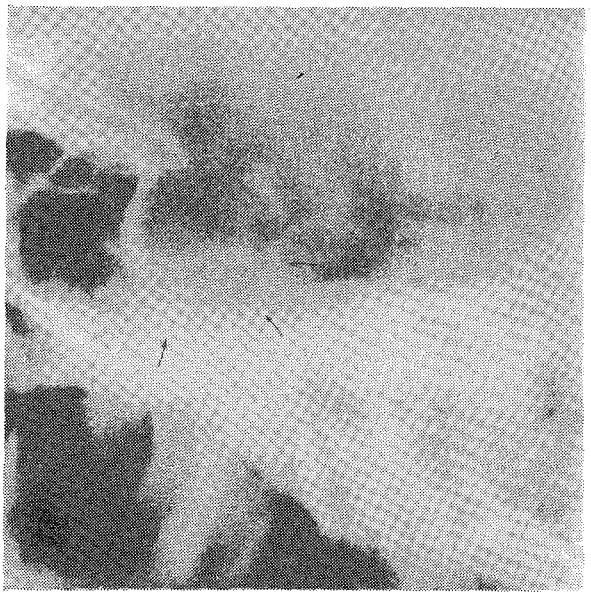

Fig. 1 Lateral skull X-ray (cone view) showing enlarged and eroded pituitary fossa of patient MC.

Mean serum prolactin was 4344 mU/l (range 750 mU/l to 23,000 mU/l) before treatment and this declined to 186 mU/l with treatment (Table IV). Serum FSH, LH and oestradiol were within normal limits as were serum T_4 (102 $\pm$ 23 nmol/l) and TSH (2.2 $\pm$ 0.9 mU/l). At diagnosis, five patients had normal-sized pituitary fossae: three with cortical thinning and two with erosion. Four patients had double-flooring with erosion while four had grossly-enlarged and eroded fossae (Fig. 1). In those that had delivered, repeat skull X-rays did not show significant fossa changes except for one with slight deepening of the floor.

Seven patients became pregnant after treatment for 5 to 25 months (mean 11.3 months) while six conceived after their first menses (Table III). Three patients stopped medication when periods were delayed for one week while in 11 pregnancies, bromocriptine was continued for two weeks to two months. Four patients were restarted on bromocriptine at an average dose of 13.96 mg daily the last one to three months before term due to the development of visual field defects. In seven cases (five patients), bromocriptine was used throughout pregnancy to prevent a recurrence of visual field defects present previously. The dose of

TABLE V
DOSAGE AND DURATION OF EXPOSURE TO BROMOCRIPTINE DURING PREGNANCY

Patient	Pregnancy number	Bromocriptine during pregnancy			
		Early		Late	
		Dosage (mg/day)	Duration (wks)*	Dosage (mg/day)	Duration (wks)
1. LNC	1	10	8	-	-
	2	15	4	-	-
2. OSN	1	5	1	-	-
3. OSY	1	7.5	8	22.5	4
	2	15	Throughout		
	3	15	Throughout		
4. LY	1	7.5	2	-	-
	2	5	2	-	-
	3	2.5	2	-	-
	4	2.5 - 5	Throughout		
5. MK	1	7.5 - 15	Throughout		
6. SZ	1	7.5	4	7.5	12
7. NS	1	5	1	7.5 - 30	12
8. SM	1	5	2	15 - 30	12
9. DH	1	5	1	5	4
10. RH	1	2.5	2	-	-
	2	5	2	-	-
11. MN	1	5 - 7.5	Throughout		
	2	5	Throughout		
12. MA	1	5	2	7.5	4
12. MC	1	15 - 45	Throughout		

* Calculated from the date of missed menses.

bromocriptine and duration of exposure to the drug during pregnancy are presented in Table V.

21 pregnancies resulted from the thirteen patients: two patients had conceived twice, one thrice and another patient was pregnant four times over the 5-year period. There were three abortions (two elective and one spontaneous) and one was premature breech delivery at 30 weeks in which the baby died. Ten pregnancies were completed by normal vaginal delivery at term, four by caesarean and two by forceps delivery. One pregnancy is still in progress. Of the livebirths, there were twelve girls and four boys and their mean birthweight was 2932 g (range 2337 to 3442 g) (Table VI). All were normal at birth and during subsequent development, except for one girl who had congenital dislocation of the left hip.

DISCUSSION

The amenorrhoea-galactorrhoea syndrome is usually associated with prolactinomas. Most of these patients are infertile due to the hyperprolactinaemia and a number of authors recommend pituitary surgery or irradiation to eradicate the tumour. [8,9] Pituitary surgery is successful only in certain established neurosurgical centres especially with microprolactinomas but the result is disappointing when the tumours are large. [11] The response to pituitary irradiation is usually incomplete. [12] Furthermore, its effect is slow and may not be obvious in the first few years. [13] Currently, it is possible to reduce hyperprolactinaemia with bromocriptine, a long-acting dopamine agonist. [14]

In our series, bromocriptine was able to restore menses in all patients and reduced or abolished galactorrhoea coincident with the lowering of serum prolactin level. Six patients conceived immediately after their first menses while the rest between 5 to 25 months of treatment. Our findings thus concur with previous reports that bromocriptine is effective in restoring normal menstrual cycles and fertility in patients with the amenorrhoea-galactorrhoea syndrome due to hyperprolactinaemia. [4,5]

TABLE VI
OUTCOME OF PREGNANCY, SEX AND BIRTHWEIGHT OF BABY

Patient	Pregnancy number	Outcome of pregnancy		Baby	
		Birth	Term	Sex	Weight (g)
1. LNC	1	livebirth	Fullterm	F	2857
	2	IP	-	-	-
2. OSN	1	livebirth	Fullterm	F	2337
3. OSY	1	"	"	M	3019
	2	"	"	F	3442
	3	"	"	M	3052
4. LY	1	Aborted	-	-	-
	2	livebirth (Died after 2 weeks)	Premature	-	-
	3	Aborted	-	-	-
	4	livebirth	Fullterm	F	3068
5. MK	1	"	"	M	2722
6. SZ	1	"	"	F	2890
7. NS	1	"	"	M	3247
8. SM	1	"	"	F	2662
9. DH	1	"	"	F	3247
10. RH	1	Aborted*	-	-	-
	2	livebirth	Fullterm	F	2954
11. MN	1	"	"	F	2922
	2	"	"	F	3182
12. MA	1	"	"	F	2922
13. MC	1	"	"	F	2386

IP - Pregnancy still in progress; * Spontaneous abortion.

In pregnancy increased pituitary tumour growth may occur resulting in pressure symptoms such as optic chiasma compression. [2] Because of this, several authors have recommended external irradiation or pituitary surgery before allowing patients with prolactinomas to be pregnant. [8,9] There is however, no conclusive proof of the effectiveness of prior external pituitary irradiation in preventing tumour growth during pregnancy. [15,16] Surgical intervention may not be able to completely remove the tumour and/or may damage normal pituitary tissue resulting in hypopituitarism. [17,18]

Bromocriptine on the other hand, has been shown to not only lower serum prolactin but also reduce tumour size. [19,20] In some cases this tumour reduction is associated with an improvement in pituitary function. [21] Our approach therefore was to allow patients to conceive without prior irradiation or surgical intervention but keeping them under close supervision during pregnancy and reinstituting bromocriptine when tumour growth was detected. A similar approach has been adopted by a number of other authors. [22,23]

Five of our patients developed visual field defects during pregnancy. One of these (patient MC) in addition had unilateral sixth nerve palsy. She was to continue bromocriptine throughout pregnancy but stopped the medication after two months. Two weeks later she developed the field defects and the cranial nerve palsy. Reinstitution of bromocriptine improved or restored visual fields to normal and improved the nerve palsy allowing pregnancy to proceed to term in all cases. Subsequently, after delivery visual field defects and the cranial nerve palsy resolved completely. The effectiveness of bromocriptine in preventing tumour growth was also reflected in the five patients with previous visual field defects in which bromocriptine was used throughout pregnancy. In these patients, visual fields remained full and there was no other evidence to suggest significant tumour enlargement such as an increasingly severe headache, giddiness or vomiting.

In each of the 21 pregnancies, the foetus was exposed to bromocriptine at some stage of gestation. In fourteen cases, bromocriptine was continued for upto 8 weeks after the menses were

delayed, in seven it was used throughout whilst in six it was reinstituted later in pregnancy because of visual field defects. In eight of the pregnancies, high doses of bromocriptine ($\geq$ 15 mg/day) were used. In contrast, previous authors have reported use of lower doses of bromocriptine during pregnancy. [23] This exposure to bromocriptine at low or high doses (upto 45 mg/day) during early, late or throughout gestation did not appear to have any deleterious effect on the pregnancy nor the foetus. The incidence of spontaneous abortion (4.7%), perinatal death due to prematurity and congenital dislocation of hip was no different from that expected in the general population. [24] Our experience would be in agreement with the pooled result of bromocriptine-induced pregnancies which showed no increase in abortion rate, prematurity or congenital abnormality in babies exposed to bromocriptine compared to those of normal population. [25] There was no multiple pregnancy in our series though this was reported to be fairly common in bromocriptine-treated patients. [25] Similarly, we have no definite explanation for the preponderance of baby girls in our series which was not observed in the collective data.

In conclusion, we found that bromocriptine was effective in restoring normal menstrual cycles and fertility by lowering serum prolactin in patients with the amenorrhoea-galactorrhoea syndrome. Our study also suggests that this drug even at high doses may be safe for use during pregnancy. While this observation may prove to be accurate, the possible long term detrimental effects of the drug on the offsprings could not be totally discounted as yet based on previous experience of drugs used during pregnancy. [26] Cessation of bromocriptine therapy after conception has been shown not to influence the course of the pregnancy. [24] Therefore, we would suggest that while it is prudent to continue or to reinstitute bromocriptine when tumour growth is apparent, unnecessary exposure to drugs, including bromocriptine, during pregnancy should be avoided.

ACKNOWLEDGEMENT

The authors wish to acknowledge the secretarial help of Miss Poh Siew Kuan and the technical assistance of Mr A. Balasubramaniam and Mr J. Timor. Reagents for the RIA of prolactin, FSH, LH and oestradiol were kindly supplied by WHO.

REFERENCES

[1] Friesen H G, Tolis G. The use of bromocriptine in the galactorrhoea-amenorrhoea syndromes. The Canadian Cooperative Study. *Clin Endocrinol (Suppl)* 1977, **6**, 91s-99s.

[2] Chang R J, Keye W R, Young J R, Wilson C B and Jaffe R B. Detection, evaluation and treatment of pituitary micro-adenomas in patients with galactorrhoea and amenorrhoea. *Am J Obstet Gynecol* 1977, **128**, 356-363.

[3] Besser G M. Bromocriptine and the tuberoinfundibular system : Hyperprolactinaemia. *Triangle* 1978, **17**, 33-39.

[4] Franks S, Jacobs H S, Hull M G, Steele S J and Nabarro J D N. Management of hyperprolactinaemia amenorrhoea. *Br J Obstet Gynaecol* 1977, **84**, 241-253.

[5] Bergh T, Nillius S J and Wide L. Hyperprolactinaemic amenorrhoea — results of treatment with bromocriptine. *Acta Endocrinol (Suppl 216)* 1978, **88**, 147-164.

[6] Thorner M O, Evans W S, MacLeod R M, Nunley W C, Rogol A D, Morris J L and Besser G M. Hyperprolactinaemia: Current concepts of management including medical therapy with bromocriptine. In : Ergot compounds and brain function : Neuroendocrine and neuropsychiatric aspects. Goldstein M, D B, Lieberman A and Thorner M O. Eds. *Raven Press, New York*, 1980, pp. 165-189.

[7] Gamzell C. Induction of ovulation in infertile women with pituitary tumors. *Am J Obstet Gynaecol* 1975, **121**, 311-315.

[8] Thorner M O, Edwards C R W, Charlesworth M B, Dacie J E, Moult P J A, and Rees L H. Pregnancy in patients presenting with hyperprolactinaemia. *Br Med J* 1979, **2**, 771-774.

[9] Child D F, Gordon H, Mashiter K and Joplin G F. Pregnancy prolactin and pituitary tumours. *Br Med J* 1975, **4**, 87-89.

[10] Sufi S B, Donaldson A and Jeffcoate S L. Method manual for the radioimmunoassay of hormones in reproductive physiology, 6th Edition, 1982. Geneva: World Health Organisation.

[11] Hardy J, Beauregard H, and Robert F. Prolactin-secreting pituitary adenomas : Transsphenoidal microsurgical treatment. In : Progress in Prolactin Physiology and Pathology Robyn C and Harter M. Eds. *North-Holland Biomedical Press, New York*, 1978, pp. 361-370.

[12] Thorner M O, Fluckiger E and Calne D B, Eds. Bromocriptine: A clinical and pharmacological review. *Raven Press, New York*, 1980, pp. 79-80.

[13] Gomez F, Reyes F I and Faiman C. Non-Puerperal galactorrhoea and hyperprolactinaemia. Clinical findings, endocrine therapeutic responses in 56 cases. *Am J Med* 1977, **62**, 648-660.

[14] Clark B J, Fluckiger E, Lowe D M and Vigouret J M. How does bromocriptine work? *Triangle* 1978, **17**, 21-23.

[15] Thorner M O, Fluckiger E and Calne D B, Eds.

Bromocriptine: A clinical and pharmacological review. *Raven Press, New York,* 1980, pp. 77.

[16] Lamberts S W J, Klijn J G M, deLange S, Singh R, Stefanko S Z and Birkenhager J C. The incidence of complications during pregnancy after treatment of hyperprolactinaemia with bromocriptine in patients with radiologically evident pituitary tumours. *Fertil Steril* 1979, **31**, 614-619.

[17] Fluckiger E, del Pozo E and Von Werder K. Eds. Prolactin : Physiology, Pharmacology and Clinical Findings. *Springer-Verlag, New York* 1982, pp. 194-196.

[18] Williams R A, Jacobs H S, Kurtz A B, Millar J G B, Oakley A W, and Spathis G S. The treatment of acromegaly with special reference to transsphenoidal hypophysectomy. *Q J Med* 1975, **44**, 79-88.

[19] Corenblum B. Bromocriptine in Pituitary Tumours. *Lancet* 1978, **II**, 786.

[20] McGregor A M, Scanlon M F, Hall R and Hall K. Effects of bromocriptine on pituitary tumour size. *Br Med J* 1979, **2**,700-703.

[21] McGregor A M, Scanlon M F, Hall K, Cook D B and Hall R. Reduction in size of a pituitary tumour by bromocriptine therapy. *N Engl J Med* 1979, **300**, 291-293.

[22] Bergh T, Nillius S J, Larsson S G and Wide L. Effects of bromocriptine-induced pregnancy on prolactin-secreting pituitary tumours. *Acta Endocr (Kbh.)* 1981, **98**, 333-338.

[23] Canales E S, Garcia I C, Ruiz J E and Zarate A. Bromocriptine as prophylactic therapy in prolactinoma during pregnancy. *Fertil Steril,* 1981, **36**, 524-526.

[24] Drew J H, Parksinson P, Walstab J E and Beischer N A. Incidences and types of malformations in newborn infants. *Med J Aust* 1977, **2**, 945-949.

[25] Turkalj I and Braun P. Comps: Status report. Outcome of pregnancy in mothers taking Parlodel. Drug Monitoring Centre, Sandoz Ltd., Switzerland. 1980.

[26] Herbst A L, Poskanzer D C, Robboy S J, Friedlander L and Scully R E. Prenatal exposure to stilbestrol : A prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 1975, **292**, 334-339.