PAPERS AND ORIGINALS

Clinical course and outcome of pregnancies in amenorrhoeic women with hyperprolactinaemia and pituitary tumours

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Summary and conclusions

Seventeen term pregnancies occurred in 14 amenorrhoeic women with hyperprolactinaemia and radiological evidence of pituitary tumour. The abortion rate was high (32%). All but one of the term pregnancies occurred after ovulation-inducing treatment with human gonadotrophins and bromocriptine (four and 12 pregnancies respectively). Two of the 14 women had visual complications during pregnancy, but neither had serious residual visual impairment. Two patients had possible pituitary enlargement during pregnancy.

Bromocriptine may be the most suitable primary treatment for many infertile women with prolactin-secreting tumours. Tumour complications during pregnancy are a definite risk, but most pregnancies went uneventfully to term. Patients with pituitary tumour should be carefully evaluated before starting ovulation-inducing treatment with bromocriptine alone, and they should be told of the possible risks and of the advantages and disadvantages of pretreatment with irradiation or surgery. Patients should be carefully monitored during pregnancy and have their visual fields checked frequently. If visual complications due to tumour enlargement occur during a pregnancy, reinstituting bromocriptine may be the treatment of choice. If this fails, other forms of treatment such as induction of labour, high-dose corticosteroid treatment, pituitary implantation of yttrium-90, or surgery may be effective.

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Introduction

Pregnancies in patients with pituitary tumours are associated with a risk of tumour complications.[1 2] Raised oestrogen concentrations during pregnancy induce hypertrophy and hyperplasia of the lactotrophic cells,[3 4] leading to an increased size of the pituitary.[4 5] In patients with pituitary tumours pregnancy may induce rapid tumour enlargement with development of symptoms, mainly affecting the visual fields.[6] Hyperprolactinaemia is common in patients with pituitary tumours,[7-10] and is associated with hypogonadism, which was previously resistant to treatment. Most amenorrhoeic women with pituitary tumours needed human gonadotrophin treatment to become pregnant.

The dopaminergic agent bromocriptine provides a highly effective means of restoring fertility in hyperprolactinaemic patients.[11] Many patients with hyperprolactinaemia, however, have radiological evidence of a pituitary adenoma,[12-15] and treatment of infertile, hyperprolactinaemic patients with pituitary tumours remains problematic. Such patients usually undergo surgery or pituitary irradiation before starting treatment to induce ovulation.[11 14 16-21]

We describe the outcome of 25 pregnancies in 15 women with prolactin-producing pituitary adenomas. None of the patients were pretreated with irradiation or surgery. Most of the pregnancies occurred after treatment with bromocriptine.

Patients and methods

Fifteen women aged 22-34 years (mean 28·8) with amenorrhoea of 36 months' to 12 years' duration (median 74 months), hyperprolactinaemia, and radiological signs of pituitary tumour were treated with bromocriptine. All but one had secondary amenorrhoea. Clinical details of the patients are shown in the table. Galactorrhoea, defined as any secretion from the breast, spontaneously or on compression, was detected in 14 of the 15 women. All the patients had an asymmetric or enlarged pituitary fossa, or both, which in combination with amenorrhoea and hyperprolactinaemia was taken as evidence of a pituitary tumour. The visual fields, examined by Goldman perimetry and a colour saturation test,[22] were normal in all the women. Routine clinical and endocrinological tests showed normal thyroid and adrenal function. None of the women were taking any drugs known to stimulate prolactin secretion.

Serum prolactin concentrations were measured with a radioimmunosorbent technique.[23] The mean concentration in the patients

was 75·1 μg/l (range 23-565 μg/l) (table). The normal range for healthy women of fertile age is 2-15 μg/l (mean 6·5 μg/l). Prolactin and anti-prolactin preparations were supplied by the National Institute of Health, Bethesda, Maryland, reults being expressed in micrograms of this preparation per litre of serum.

Serum gonadotrophin concentrations were measured with a radio-immunosorbent technique.[24] The pituitary reserve capacity for gonadotrophin secretion was evaluated in 14 of the 15 women by an intravenous luteinising hormone-releasing hormone (LH-RH) test (100 μg).[25] The basal follicle-stimulating hormone (FSH) concentration was normal in all but one of the women, whose concentration was below the lower limit of the normal range for women of fertile age.[24] Twelve of the 15 women had low or undetectable basal luteinising hormone (LH) concentrations.[24] The LH response to LH-RH was normal in five patients and exaggerated in nine compared with responses in healthy women in the early follicular phase of the menstrual cycle.[25] Exaggerated FSH responses to LH-RH were observed in eight women, while six had normal responses (table). In seven women (cases 1, 2, 3, 5, 11, 13, and 14) the serum concentration of immunoreactive oestradiol was within the range for women in the early follicular phase of the menstrual cycle, while the other eight women had serum oestrogen concentrations below that range.

Insulin-induced hypoglycaemia caused a normal growth-hormone (GH) response in 10 of the women, while the other two women tested had impaired responses (cases 3 and 11). The thyroid-stimulating-hormone (TSH) response to TSH-releasing hormone (TSH-RH; 200 μg intravenously) and the cortisol response to hypoglycaemia were normal in all 12 women tested.

Radiography of the skull and pituitary fossa included coned lateral and anteroposterior views of the sella turcica and polytomography. Four of the patients (cases 2, 3, 7, and 12) had only slight asymmetry of the sella corresponding to the category 3 abnormality defined by Doyle and McLachlan.[26] The other 11 patients had more pronounced changes of the pituitary fossa, corresponding to category 1 or 2.[26]

TREATMENT

None of the 15 women were treated for their pituitary tumour by irradiation or surgery.

Clomiphene citrate or human gonadotrophins or both had been given to 11 of the 15 women before they were known to have hyperprolactinaemia. Nine women received clomiphene in daily doses of 50-200 mg for five days. Only one of them ovulated, and she also conceived but had a late abortion (case 13). Human gonadotrophins were given to six patients (cases 6, 7, 9, 10, 11, and 15). Four of them conceived and had seven pregnancies. They were given a mean total gonadotrophin dose of 3170 (range 2400-4275) IU. Two patients did not respond to total doses of 750 and 1800 IU respectively (cases 9 and 11). They were referred to us for gonadotrophin treatment with daily oestrogen monitoring but were found to have hyperprolactinaemia and were given bromocriptine instead.

Bromocriptine was given to all the women. Prolactin concentrations decreased and ovulation occurred in all cases after an average of five weeks of treatment (range 2-10 weeks). Two women (cases 3 and 5) conceived at the first ovulation after two and eight weeks of treatment respectively. Fourteen of the 15 women responded to daily doses of 2·5-7·5 mg. One patient (case 11) ovulated after nine weeks' treatment with 15 mg daily. Treatment was discontinued as soon as pregnancy was suspected—that is, 2-20 days (median 7·5) after the expected date of menstruation. Fourteen of the women were infertile at the start of bromocriptine treatment. Three of them (cases 4, 14, and 15) were advised not to become pregnant until their pituitary tumour had been further investigated and possibly treated surgically; two subsequently avoided pregnancy but one (case 4) conceived. All the other 11 infertile women conceived and had a total of 15 bromocriptine-induced pregnancies. During the pregnancies the patients were carefully supervised and had their visual fields examined monthly. All the patients had immediate postpartum sellar *x*-ray examinations to check whether the pituitary fossa had enlarged.

Results

CLINICAL COURSE AND OUTCOME OF PREGNANCIES

During the 17 pregnancies that went to term three of the 14 women had symptoms of pituitary-tumour complications. Two developed visual-field defects, and in the third severe headache began during the second trimester and radiological signs of pituitary enlargement were found after delivery. A fourth patient who had no symptoms or signs of pituitary-tumour complications during pregnancy, was also found to have an increase in sellar volume post partum.

The abortion rate was 32% (six early and two late abortions) (table). None of these eight pregnancies were complicated by symptoms or signs of tumour enlargement. Eighteen healthy children were born after the 17 term pregnancies.

All but one of the 25 pregnancies occurred after ovulation-inducing treatment. One pregnancy occurred during substitution treatment with oestrogens in a 32-year-old woman with 10 years of amenorrhoea and galactorrhoea after a previous delivery (case 14). She conceived during a temporary pause in her cyclical treatment with 50 μg ethinyl-

Clinical details of 15 women with radiological signs of prolactin-producing pituitary tumours and outcome of pregnancies after treatment to induce conception

Case No	Age (years)	Duration of amenorrhoea (months)	Follicle-stimulating hormone		Luteinising hormone		Prolactin concentration (μg/l)	Radiological appearances of sella turcica	Treatment	Outcome of pregnancy and complications
			Basal concentration (μg/l)	Response to LH-RH	Basal concentration (μg/l)	Response to LH-RH				
1	22	42	Normal	Exaggerated	Low	Exaggerated	57	Asymmetric (940 mm³)	(1) Bromocriptine (2) Bromocriptine	Abortion (week 13) Normal
2	24	52	,,	,,	,,	,,	97	Asymmetric (680 mm³)	(1) Bromocriptine (2) Bromocriptine	Abortion (week 7) Normal
3	25	Primary	,,	,,	,,	,,	46	Asymmetric (950 mm³)	(1) Bromocriptine	Headache
4	25	36	,,	ND	,,	ND	72	Asymmetric, enlarged (1250 mm³)	(1) Bromocriptine	Visual-field defects
5	28	76	,,	Normal	,,	Normal	60	Asymmetric, enlarged (1400 mm³)	(1) Bromocriptine	Sellar enlargement to 1800 mm³
6	28	72	Low	Exaggerated	,,	Exaggerated	52	Asymmetric, enlarged (1800 mm³)	(1) HMG	Normal
7	29	84	Normal	Normal	Normal	Normal	40	Asymmetric (860 mm³)	(1) HMG (2) Bromocriptine	Abortion (week 13) Normal
8	30	72	,,	,,	Low	,,	30	Asymmetric (1180 mm³)	(1) Bromocriptine	Normal
9	30	84	,,	,,	,,	,,	50	Asymmetric, enlarged (1240 mm³)	(1) Bromocriptine	Normal
10	30	84	,,	,,	Normal	Exaggerated	34	Enlarged (1300 mm³)	(1) HMG (2) HMG (3) HMG (4) Bromocriptine	Abortion (week 12) Normal Abortion (week 14) Normal
11	31	96	,,	Exaggerated	Low	Normal	50	Asymmetric, enlarged (1980 mm³)	(1) Bromocriptine (2) Bromocriptine	Normal Normal
12	32	60	,,	,,	Normal	Exaggerated	23	Asymmetric (800 mm³)	(1) Bromocriptine (2) Bromocriptine	Abortion (week 10) Abortion (week 22)
13	32	36	,,	,,	Low	,,	565	Asymmetric (1150 mm³)	(1) Clomiphene (2) Bromocriptine	Abortion (week 18) Normal
14	32	120	,,	Normal	,,	,,	420	Asymmetric, enlarged (1240 mm³)	(1) Oestrogen	Normal
15	34	144	,,	Exaggerated	,,	,,	430	Asymmetric, enlarged (1250 mm³)	(1) HMG (2) HMG	Visual-field defects Normal

LH-RH = Luteinising hormone-releasing hormone. HMG = Human menopausal gonadotrophin. ND = Test not done.

oestradiol. The pregnancy went uneventfully to term, and the asymmetric and enlarged pituitary fossa did not change. Amenorrhoea and galactorrhoea continued after her second delivery. Three years later hyperprolactinaemia was detected and she was treated with bromocriptine. Regular ovulatory menstrual cycles rapidly reappeared but she was advised against starting a new pregnancy.

GONADOTROPHINS

Gonadotrophin treatment resulted in seven pregnancies in four of the patients (cases 6, 7, 10, and 15). Four of these went to term while three ended in early abortions. One 34-year-old woman (case 15) with five years of amenorrhoea and galactorrhoea developed bitemporal visual-field defects during the 28th week of her first pregnancy.[6] The visual-field defects did not worsen during the pregnancy, which was allowed to continue to term. Radiography showed pronounced enlargement of the asymmetric pituitary fossa, and air encephalography after delivery showed slight suprasellar extension of the pituitary tumour. A second gonadotrophin-induced pregnancy two years later went uneventfully to term, and the pituitary fossa had not enlarged after delivery. Hyperprolactinaemia was diagnosed three years later, and bromocriptine treatment was begun. Ovulatory menstrual cycles returned after five weeks of treatment. Computerised tomography continued to show a suprasellar extension and she was advised against a new pregnancy.

No complications occurred in the other gonadotrophin-induced pregnancies. One patient (case 6) had an uneventful twin pregnancy. The pituitary fossa was still asymmetric and greatly enlarged on *x*-ray examination three years later, when bromocriptine treatment was begun. She did not want to become pregnant again. Another patient (case 10) had three gonadotrophin-induced pregnancies, two of which ended in early abortions. The full-term pregnancy was uncomplicated, and the pituitary fossa did not enlarge further. She subsequently had another uneventful pregnancy after bromocriptine treatment.

BROMOCRIPTINE

Bromocriptine treatment resulted in 16 pregnancies (12 term pregnancies, and three early and one late abortion) in 12 of the women. Conception occurred after 2-22 weeks of treatment (median 7 weeks) at the first to fourth ovulations (mean 2·2). Visual-field defects due to rapid tumour enlargement were detected in a 25-year-old woman with three years of amenorrhoea and galactorrhoea (case 4). She had been referred to our department from abroad for treatment with human gonadotrophins. She was found to have galactorrhoea, hyperprolactinaemia, and pronounced asymmetry of the pituitary fossa. She was told that a pregnancy should not be attempted until she had undergone further investigations and possibly treatment for her tumour, and she was referred back to her home country. Bromocriptine treatment was started and she conceived within a few months. Visual-field defects occurred at 30 weeks of pregnancy. The visual impairment improved when bromocriptine treatment was reinstituted, and the pregnancy went to term with delivery of a normal child. After delivery the visual fields returned to normal, but *x*-ray examination showed destruction of the pituitary fossa.

Symptoms from tumour enlargement during bromocriptine-induced pregnancy also occurred in a 25-year-old woman with primary amenorrhoea who had a slightly asymmetric sella (case 3). In the second trimester she began to have severe headache, which persisted throughout the pregnancy. Neurological examination showed nothing abnormal. The visual fields remained normal and the pregnancy continued to term. After delivery the headache rapidly disappeared, and *x*-ray examination showed enlargement and a change in the shape of the sella (fig 1).

The other 10 bromocriptine-induced term pregnancies proceeded uneventfully with no symptoms or signs of complications of pituitary-tumour enlargement. Postpartum *x*-ray examination of the pituitary fossa showed an increase of the sellar volume in one of these patients (case 5), while the fossae of the other eight showed no changes. One 31-year-old woman (case 11) had two pregnancies without complications, though she had the most pronounced sellar abnormality of all the patients who became pregnant (fig 2). She had been initially investigated at her local hospital for amenorrhoea, but was referred to a neurosurgical department because of a suspected pituitary tumour. The visual fields were normal. An air encephalogram showed no suprasellar extension, and the tumour was not regarded as a contraindication to pregnancy. The patient was treated three times with human gonadotrophins but never ovulated, and she was referred to us. Hyperprolactinaemia was found. Bromocriptine treatment was begun and she conceived. There were no complications during the pregnancy and she breast-fed for two months. After that she continued to have galactorrhoea and remained amenorrhoeic. One year later she wanted to become pregnant again, and after consultation with neurosurgeons was treated with bromocriptine; again she conceived. This pregnancy also proceeded without complications or radiological evidence of sellar changes.

Most of the women wanted to breast-feed their children and did so without difficulty. Two women (cases 5 and 11) produced too little milk for breast-feeding beyond two months. Spontaneous menstruation did not return in either patient.

Discussion

Two of our 14 hyperprolactinaemic patients with radiological evidence of a pituitary tumour had visual complications during pregnancy. A third patient had headache and was found to have radiological signs of tumour enlargement after delivery. Increased sellar volume post partum was also seen in a fourth woman, but she had no clinical tumour complications during the pregnancy. The other 13 term pregnancies were completed without symptoms or signs of tumour enlargement during or after pregnancy. The abortion rate was 32% (eight out of 25 pregnancies).

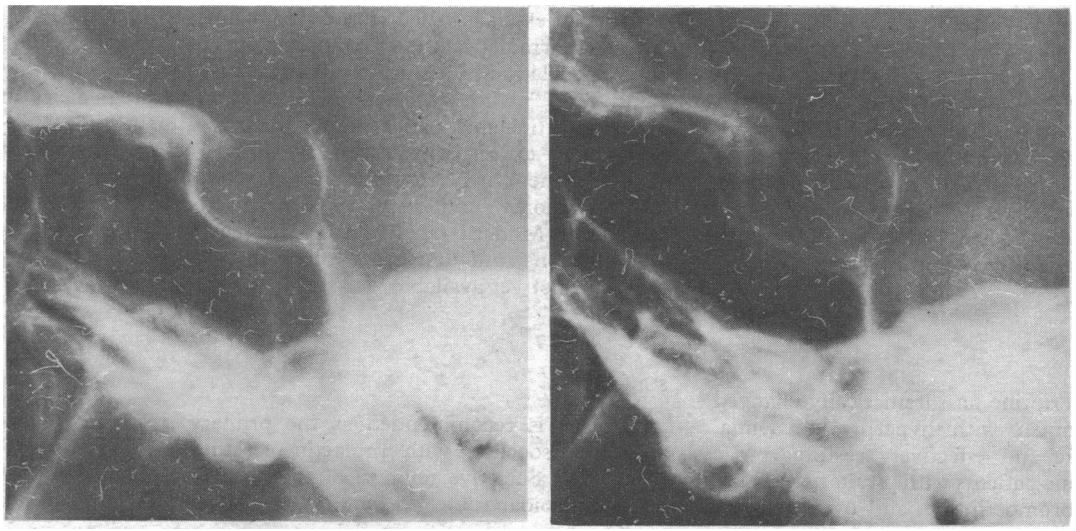

FIG 1—Case 3. *X*-ray pictures of pituitary fossa before (left) and after bromocriptine-induced pregnancy (right) in 25-year-old hyperprolactinaemic woman with primary amenorrhoea who developed severe headache during second trimester. Before pregnancy sella is slightly asymmetric; after pregnancy sella is changed in shape and enlarged.

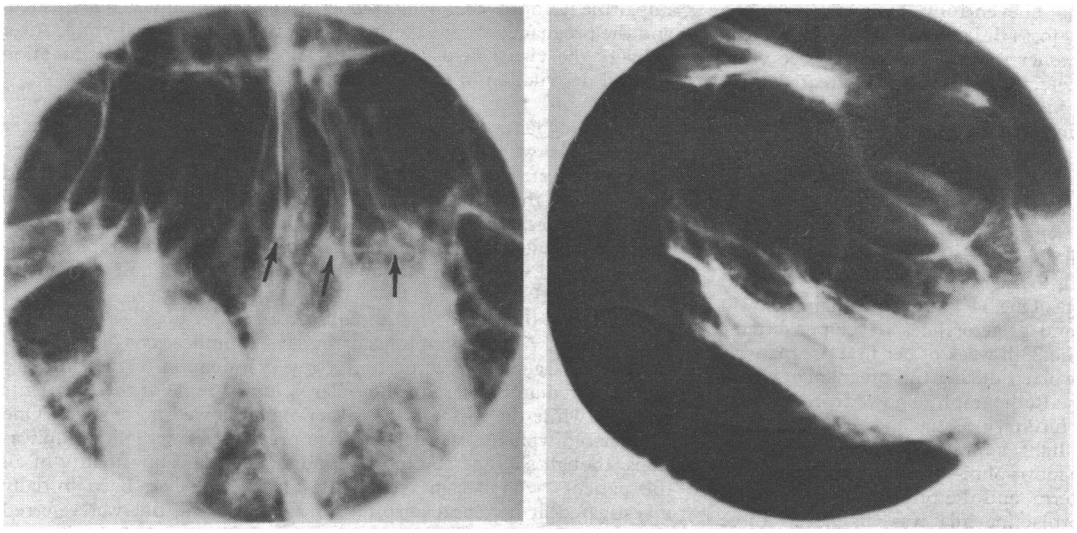

FIG 2—Case 11. Frontal (left) and lateral (right) x-ray pictures showing pronounced asymmetry and enlargement of pituitary fossa (arrowed) in a 31-year-old hyperprolactinaemic woman with eight years of amenorrhoea and galactorrhoea who had two uneventful bromocriptine-induced pregnancies.

Women with pituitary tumours may develop visual complications during pregnancy.[27–30] Mostly these develop late in pregnancy, but they may also occur during the first two trimesters.[6 21 30–33] Visual-field defects have been reported in pregnant patients with pituitary tumours who had been given ovulation-inducing treatment with human gonadotrophins.[21 34–36] These reports are mainly of individual cases and give no information on the incidence of the complication. Gemzell[6] induced ovulation with human gonadotrophins in about 700 anovulatory women, resulting in 250 full-term pregnancies. Only three of them were complicated by visual disturbances. The incidence of pituitary tumours in this large series, however, was unknown as sellar radiography was not routinely performed before or after pregnancy.

Before bromocriptine became available human gonadotrophins were used to induce ovulation in most anovulatory women with hyperprolactinaemia, since these patients rarely ovulate after clomiphene treatment.[37 38] Only one out of nine patients in the present series ovulated after clomiphene treatment. Gonadotrophin treatment, on the other hand, proved to be very effective in women with amenorrhoea and galactorrhoea. A pregnancy rate of 80% was obtained by Rabau *et al*[39] in 30 women with this syndrome. The mean dose of human gonadotrophins in patients with postpartum amenorrhoea and galactorrhoea was not greatly different from that in the other anovulatory patients, and the mean duration of treatment was even shorter than that of amenorrhoeic women with lack of endogenous oestrogen activity.[39] All four of our hyperprolactinaemic patients, who were treated with individually adjusted gonadotrophin doses under daily oestrogen monitoring, ovulated and conceived seven times. Their mean dose was not different from that required by patients with normal prolactin concentrations, which agrees with other reported findings.[40 41] Thus there is no evidence of ovarian resistance to exogenous gonadotrophins in amenorrhoeic women with hyperprolactinaemia. Nevertheless, human gonadotrophin treatment has considerable disadvantages, and serious complications may occur. It is expensive and must be given in specialised centres where adequate laboratory service is available for daily oestrogen monitoring.

BROMOCRIPTINE TREATMENT

The introduction of bromocriptine has dramatically changed the outlook for infertile women with hyperprolactinaemia, allowing fertility to be easily and effectively restored.[11 13 18] Most of our hyperprolactinaemic patients with pituitary tumours also responded promptly to bromocriptine, and ovulation can be induced even in patients with severe gonadotrophin deficiency and large pituitary tumours with high doses of bromocriptine.[15] Nevertheless, if they become pregnant these patients are at a definite risk of developing serious complications from rapid tumour enlargement. This was shown in one of our patients (case 4), who developed extensive visual-field defects during the third trimester of her bromocriptine-induced pregnancy. Corbey *et al*[42] described another hyperprolactinaemic patient with a large pituitary tumour who developed progressive visual-field defects from the 29th week of a bromocriptine-induced pregnancy.

In infertile hyperprolactinaemic patients with radiological evidence of pituitary tumour Besser *et al*[11 20] advise external pituitary irradiation (4500 rads) from a linear accelerator to prevent tumour growth during pregnancy. Irradiation must usually be combined with bromocriptine treatment as reduction of raised prolactin concentrations is slow and often incomplete after radiotherapy.[14 18 43] Pretreatment with irradiation resulted in uneventful pregnancies in three of four hyperprolactinaemic patients with tumours.[11] The fourth patient developed temporary visual-field loss to red during the 38th week of pregnancy. She had shown variable visual fields before pregnancy; hence the change during pregnancy might have been unrelated to treatment. Labour was induced and the field loss disappeared after delivery. Lamberts *et al*[44] described a similar case of visual-field defects developing after irradiation during a bromocriptine-induced pregnancy, and concluded that prior radiotherapy may not prevent visual complications from tumour growth during pregnancy. Nevertheless, their patient had a moderate suprasellar extension before the pregnancy.

Internal irradiation with yttrium implants in pituitary tumours before ovulation-inducing treatment was recommended by Child *et al*,[21] who described seven uneventful pregnancies in hyperprolactinaemic patients after such treatment. But long-term follow-up results of earlier radiation treatment show that such treatment may result in serious complications, such as loss of vision,[45] brain necrosis,[46 47] and the development of sarcoma.[48] Modern irradiation techniques may prevent such complications, but long-term follow-up results of such treatment are not yet available.

SURGERY

Surgery is recommended as the primary treatment of infertility associated with prolactin-secreting pituitary adenomas.[14 16–19] Selective removal of the pituitary adenoma by the transsphenoidal route[49] seems to be the method of choice if

there is no suprasellar extension of the tumour. In 1973 Hardy[16] reported that galactorrhoea disappeared after surgery in 18 women with amenorrhoea and galactorrhoea, but only five of them resumed regular menstruation. Gomez *et al*[14] described the outcome of transsphenoidal microsurgery performed by Hardy on 10 hyperprolactinaemic women with suspected pituitary tumours: menstruation returned in six, and four of them conceived. In three of the patients no adenoma was found at surgery. Kleinberg *et al*[13] described 15 patients with tumour who underwent operation by the transsphenoidal route. Only two of them resumed menstruation and became pregnant. In contrast, 17 out of 20 hyperprolactinaemic patients with tumour were recently reported to have resumed menstruation after transsphenoidal microsurgical exploration of the sella.[17] Nevertheless, only two previously infertile patients were reported to have become pregnant. Ovulatory cycles returned after transsphenoidal surgery in five out of eight hyperprolactinaemic women described by Franks *et al*.[18] Thus the results of selective transsphenoidal removal of prolactin-secreting pituitary adenomas are variable, and no data on recurrence rate on long-term follow-up are yet available. Postoperative hypopituitarism still seems to be a risk: one of the eight patients reported on by Franks *et al* developed panhypopituitarism after surgery.

Published results of radiological or surgical treatment of prolactin-producing pituitary adenomas give no clear indication of subsequent management of infertile hyperprolactinaemic patients with pituitary tumours. Our study shows that even patients with large pituitary tumours have uneventful pregnancies after ovulation-inducing treatment. Nevertheless, rapid tumour enlargement during pregnancy may result in serious complications, such as visual-field defects, which occurred in two of our patients. Treatment with irradiation or surgery before pregnancy is attempted may benefit some patients though it is difficult to identify those who risk developing tumour complications during pregnancy. Two of our patients (cases 10 and 11) had greatly enlarged pituitary fossae, but their gonadotrophin-induced pregnancies were uneventful, whereas another patient (case 3) who had slight radiological evidence of enlargement (fig 1) developed tumour complications. One patient (case 15) who developed reversible visual-field defects during a gonadotrophin-induced pregnancy later had a second, uneventful pregnancy despite suprasellar extension of the tumour.[6]

VISUAL IMPAIRMENT

Patients are unlikely to develop serious irreversible visual impairment when adequately supervised. If complications due to tumour growth occur during pregnancy, they can be successfully treated by high doses of corticosteroids,[36] induction of labour,[11 42] pituitary implantation of yttrium,[21] or emergency surgery[6 30 34 50 51] with favourable outcome for mother and child. If the visual impairment is mild, conservative management under careful observation may be satisfactory.[6]

Bromocriptine may be the best primary treatment of tumour complications during pregnancy. The visual-field defects in one of our patients (case 4) rapidly regressed during bromocriptine treatment. Improvement of visual-field defects on bromocriptine treatment have been reported in non-pregnant patients with pituitary tumours.[13 52 53] Experimental studies have shown bromocriptine to be capable of reducing mitotic activity and inhibiting oestrogen-induced proliferation of the pituitary[54] and dopamine agonists can inhibit growth of pituitary tumours in rats, and even cause tumour regression.[55 56] Bromocriptine is non-teratogenic.[2] Nearly 300 children have been born after bromocriptine-induced pregnancies without increased incidence of malformations, and four women have been given bromocriptine deliberately for long periods during pregnancy without adverse effects.[57]

Infertile patients with prolactin-secreting pituitary adenomas should be thoroughly informed of the risk of tumour complications during pregnancy and of the advantages and disadvantages of current forms of treatment. Some patients should perhaps be allowed to choose treatment with bromocriptine alone, provided that careful monitoring with frequent clinical examinations and visual-field determinations is performed during the pregnancy. If visual complications still occur reinstitution of bromocriptine might be the primary treatment of choice. If this treatment fails alternative treatments as described above, have proved successful in preventing irreversible visual impairment. More experience is needed before the optimal management of anovulatory patients with hyperprolactinaemia, radiological signs of a pituitary tumour, and a desire for pregnancy can be ascertained.

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Interrelation of age, obesity, cigarette smoking, and blood pressure in hypertensive patients

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Summary and conclusions

The relations between age, obesity, cigarette smoking, and blood pressure were investigated in 637 men and 835 women who had attended the Glasgow Blood Pressure Clinic with untreated hypertension. In contrast to results of population surveys of mainly normotensive people no relation was found between cigarette consumption and either systolic or diastolic blood pressure. Moreover, contrary to results of epidemiological studies a relation between adiposity and blood pressure was found in only male non-smokers. Thus the relations established for largely normotensive populations do not apply to hypertensive patients.

Introduction

In 1969 seven hypertension clinics at four hospitals were amalgamated to form the Glasgow Blood Pressure Clinic. New patients are extensively documented, and the data are stored on computer data files.[1] To investigate the interrelation of age, obesity, cigarette smoking, and blood pressure we analysed the initial data on new, untreated patients who had attended the clinic since its inception.

Patients and methods

Data on 637 men and 835 women not receiving treatment when first seen at the clinic were analysed. Patients were considered to be hypertensive if their recumbent diastolic blood pressure, measured with a sphygmomanometer, was greater than 90 mm Hg on at least two but usually three occasions before treatment. The means of these untreated values were used for analysis. During the initial clinic visit all patients were asked about their smoking habits, and smokers estimated the number of cigarettes they smoked daily. Cigarette smokers and non-smokers were analysed separately. To simplify interpretation of the results we excluded from the study patients who had stopped smoking cigarettes in the previous year and pipe and cigar smokers. The ponderal index, defined as (height in inches)/(weight in lb)$^{\frac{1}{3}}$, was calculated for each patient.

Men and women were analysed separately. The mean ($\pm$SD) age, number of cigarettes smoked daily, ponderal index, and recumbent systolic and diastolic blood pressures were calculated for each group. The interrelation of these variables was investigated by correlation analysis.

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Results

Table I shows the mean age, cigarette consumption, ponderal index, and systolic and diastolic blood pressures for each of the four groups (male smokers and non-smokers; female smokers and non-smokers). Age, ponderal index, and diastolic blood pressure were similar in all groups. Male smokers consumed more cigarettes each day than female smokers, and men had a lower mean systolic blood pressure than women.

PARTIAL-CORRELATION ANALYSIS

Male smokers—Partial-correlation analysis, controlled for age and ponderal index, indicated that in male smokers (table II) there was no significant correlation between the number of cigarettes smoked daily and either systolic or diastolic blood pressure. Similarly, there was no significant relation between ponderal index and blood pressure. The correlations between age and both systolic and diastolic blood pressures, however, were highly significant ($P < 0{\cdot}001$).

Male non-smokers—As with the smokers, age was significantly related to both blood pressures ($P < 0{\cdot}001$). There were also significant relations between ponderal index and systolic and diastolic blood pressures ($P < 0{\cdot}05$ and $P < 0{\cdot}001$ respectively).

Female smokers—The relations found in female smokers were essentially similar to those found in male smokers but the correlations between age and blood pressures, although significant ($P < 0{\cdot}05$), were weaker.

Female non-smokers—No relation was found between ponderal index and blood pressure, and only systolic blood pressure correlated significantly with age ($P < 0{\cdot}001$).

Discussion

Acute experiments[2 3] have shown that cigarette smoking causes a rise in blood pressure. In contrast, cross-sectional