MEDICAL PRACTICE

Occasional Survey

Pregnancy, prolactin, and pituitary tumours

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British Medical Journal, 1975, 4, 87-89

Summary

Nine pregnancies are described in patients with pituitary tumours. All patients had definite radiological evidence of a pituitary tumour and no evidence of acromegaly or Cushing's disease. In seven patients serum prolactin levels were estimated before pregnancy and found to be raised.

Seven patients had been treated with pituitary implantation of yttrium-90. The remaining two developed complications of the tumour during pregnancy. One developed a bitemporal visual field defect in the second trimester which was successfully treated by emergency yttrium-90 implantation. The other developed diabetes insipidus in the third trimester which resolved spontaneously after delivery.

Six patients were treated with drugs to achieve pregnancy. Four took bromocriptine to suppress raised prolactin levels, one was treated with human menopausal gonadotrophin, and one was treated with clomiphene.

Introduction

Amenorrhoea with or without galactorrhoea has long been known to be common in women with radiologically evident pituitary tumours,[1] and when there is no associated acromegaly or Cushing's disease the tumours have usually been referred to as "functionless." It is now recognised, however, that most of these tumours may be associated with raised prolactin serum levels.[2]

Without treatment pregnancy is unusual in such patients. Now, with the advent of effective treatment, more successful pregnancies may be expected. Treatment may include a direct attack on the tumour by implantation of yttrium-90 or transsphenoidal surgery, the use of drugs to induce ovulation (since these agents may over-ride the inhibiting effect of the tumour), or the reduction of abnormal prolactin levels using bromocriptine (CB 154, Sandoz).[3]

Appreciable enlargement of the normal pituitary gland occurs in pregnancy with rapid but incomplete regression after delivery.[4] The effect of pregnancy on the size or growth rate of an intrasellar tumour has not yet been established. There have, however, been several case reports of rapid tumour growth in pregnancy requiring emergency treatment,[5 6] and one such case was included in this study.

This paper records the investigation, treatment, and management in pregnancy and labour of nine women with functionless pituitary tumours.

Patients and methods

The nine patients represent our experience of this condition at Hammersmith Hospital over the past six years (see table). The commonest presenting feature was amenorrhoea, which had lasted from 15 months to 19 years. Four patients also had galactorrhoea; two developed this subsequent to breast feeding after a previous pregnancy. One patient had galactorrhoea with regular periods while another had oligomenorrhoea only. The initial progress of two patients (cases 1 and 2) was reported by Burke *et al.*[7]

The diagnosis in all cases was made from radiological evidence of the pituitary tumour, and serum prolactin levels were raised in seven patients in whom this estimation was available.

INITIAL TREATMENT

Initial treatment for seven patients consisted of pituitary implantation of yttrium-90 giving a planned dose of 20 krads to the tumour

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Presenting features, serum prolactin levels, and treatment and outcome of pregnancies of 9 patients with pituitary tumours

Patient	Age (years)	Parity	Initial symptoms	Duration of initial symptoms (years)	Mean pre-treatment serum prolactin (μg/l)	Initial treatment	Mean post-initial treatment serum prolactin (μg/l)	Subsequent treatment	Mean pre-pregnancy serum prolactin (μg/l)	Pregnancy	Gestation (weeks)	Labour	Infant's Sex and birth weight (kg)	Tumour complications
1*	26	0	A, G	1	—	HMG	—	—	—	Pre-eclamptic toxaemia	33	Caesarean section	M 1·14	Bitemporal hemianopia, emergency ^{90}Y 150 krad
2	37	0	A	17	—	^{90}Y 20 krad	—	Clomiphene	—	Triplets	35	Spontaneous, caesarean section	M 2·54 M 2·16 M 1·40†	Nil
3	25	0	A, G	8	500	^{90}Y 20 krad +DXT 4 krad	255	Bromocriptine	9	Subnormal weight gain	39	Induced 8 h	M 3·24	Nil
4*	28	0	O	3	92	Nil	—	—	—	Normal	39	Induced 10h	M 3·56	Diabetes insipidus
5	42	1	A, G	1	65	^{90}Y 20 krad	23	Nil	23	Antepartum haemorrhage, placenta praevia	37	Caesarean section	M 3·84	Nil
6	37	1	A, G	4	42	^{90}Y 20 krad	13	Nil	13	Normal	40	Spontaneous	F 3·58	Nil
7	28	0	A	14	88	^{90}Y 20 krad	77	Bromocriptine	4	Spontaneous abortion	12	—	—	Nil
8	37	0	A	19	1800	^{90}Y 20 krad	1140	Bromocriptine	9	Normal	39	Induced, caesarean section	M 2·52	Nil
9	24	0	G	3	—	^{90}Y 20 krad	55	Bromocriptine	12	Induced abortion	8	—	—	Nil

*See case report in text. †Infant had meningocele.
A = Amenorrhoea. G = Galactorrhoea. O = Oligomenorrhoea. DXT = Deep x-ray therapy.

periphery.[8] Case 3 had external irradiation of 4 krads 14 months later because of continuing amenorrhoea and galactorrhoea.

Ovulation was successfully induced in case 1 with human menopausal gonadotrophin (HMG; Pergonal, Searle Scientific Services) despite an untreated tumour. Three injections were given on alternate days, the dose being monitored by total urinary oestrogen levels and followed by human chorionic gonadotrophin 5000 IU on day 8, and 2000 IU on day 10.[9]

Conception occurred spontaneously in case 4 after preliminary investigation and assessment of the pituitary tumour but before treatment could be arranged.

SUBSEQUENT TREATMENT

Two patients (cases 5 and 6), had their syndromes completely corrected and fertility restored after implantation of yttrium-90, and required no further treatment. One patient (case 2) resumed regular menstruation after pituitary implantation and ovulation was induced with clomiphene in a dose of 100 mg/day for five days.

Four patients with persistent amenorrhoea and hyperprolactinaemia after pituitary implantation were treated with bromocriptine 2·5 mg three times a day by mouth, taken with meals to prevent nausea. This resulted in the reduction of serum prolactin to normal levels, galactorrhoea when present ceased, and menstruation recurred 5-16 weeks after starting treatment. Pregnancy occurred in the 2nd to 5th cycle. After pituitary implantation and before receiving bromocriptine one of these patients (case 7) was given six courses of HMG without successful ovulation.

ANTENATAL CARE

Seven patients attended our combined antenatal/endocrine clinic and so were seen regularly throughout their pregnancy in the endocrine unit and the obstetrics department. Patients were always questioned about their vision and headache, visual fields were checked regularly by Bjerrum screen (2-mm white object), and the radiological size of the pituitary fossa was monitored by occasional coned lateral skull films.

PROLACTIN ASSAY

Serum prolactin was measured by double antibody radioimmunoassay using antiserum 65/5 and standard 72/4/9. The human prolactin for labelling was that supplied by the National Institutes of Health, Bethesda, Maryland (Batch VSL No 1). Our laboratory range for non-pregnant women is 2-25 μg/l.

Results

EFFECTS OF TUMOUR ON PREGNANCY AND LABOUR

Four pregnancies were uneventful from the obstetric viewpoint. In one patient (case 3) maternal weight gain was less than expected and labour was induced at 39 weeks. Labour was also induced in case 4 at 39 weeks because of progressive diabetes insipidus which had begun at 35 weeks. Induction entailed forewater rupture and oxytocin infusion, and the induction-to-delivery interval was 8-10 hours. In two patients the onset of labour was spontaneous.

Caesarean section was performed in four patients—at 33 weeks in one patient on account of severe toxaemia, at 35 weeks in one with triplets after the spontaneous onset of labour, and at 37 weeks in one with an antepartum haemorrhage due to a placenta praevia. In case 8 there was fetal distress after induction at 39 weeks (for mild hypertension), and hence a caesarean section was performed. One pregnancy (case 7) ended in spontaneous abortion at 12 weeks and one (case 9) was terminated at eight weeks by vacuum aspiration.

EFFECTS OF THE PREGNANCY ON THE TUMOUR

None of the seven pregnancies which occurred after pituitary implantation of yttrium-90 developed any pituitary complication; the visual fields remained normal and the radiological appearance of the pituitary fossa remained unchanged.

The two pregnancies which occurred without this initial treatment for the tumour were associated with the development of a visual field defect in one patient and diabetes insipidus in the other.

Case 1—This patient presented with a one-year history of amenorrhoea and galactorrhoea. Pregnancy was induced with HMG. She developed severe headache during the first eight weeks. *X*-ray examination of the pituitary fossa which had shown a double floor appearance before the HMG, showed a minor change in contour—slight undercutting of the tuberculum sellae. At 14 weeks she complained of blurring of vision in the left eye and over the next two weeks rapidly developed bitemporal field defect. This was treated by a high-dose yttrium-90 implant of 150 krads at the tumour periphery. A pituitary biopsy was performed and showed an intensively acidophil staining adenoma with much nuclear pleomorphism. The field defects regressed rapidly after her pituitary implant, and precautionary steroid replacement, prednisone 5 mg daily, was continued for the remainder of her pregnancy. This was complicated by severe pre-eclamptic toxaemia and terminated by caesarean section at 33 weeks. Amenorrhoea and expressive galactorrhoea persisted after this pregnancy. Serum prolactin was estimated two and a half years after delivery and was raised at 80 μg/l but pituitary function was otherwise normal. As she was anxious for a second pregnancy bromocriptine 2·5 mg three times a day was prescribed. Her first period occurred six weeks after starting this treatment and she became pregnant in her third cycle. The bromocriptine was continued for the first 12

weeks of this pregnancy, which at the time of writing progressed uneventfully to 18 weeks' gestation.

Case 4—This patient was referred to the endocrine unit for assessment of a pituitary tumour which had been discovered two years previously. Her presenting symptoms were a three-year history of oligomenorrhoea with associated infertility. It later emerged that when first seen by us she was already one to two weeks pregnant, ovulation having occurred spontaneously. Her serum prolactin was then 92 μg/l. At 35 weeks she rapidly developed thirst and polyuria; her daily urine volume was 4-5 l. A standard 50-g oral glucose tolerance test gave a normal result. At 36 weeks a fluid deprivation test was performed and after 11 hours her urine osmolality rose from 174 to 466 mmol/kg, the expected normal being >756 mmol/kg.[10] By 39 weeks her urine volume had increased to 6·5 l daily and labour was induced. Bromocriptine was then prescribed for one week to prevent lactation; severe pain and lactation occurred temporarily on cessation of this treatment. The urine volumes gradually decreased so that four weeks after delivery her daily urine volume was about 2 l. No change was seen in the sella configuration throughout this pregnancy.

Discussion

Six of these nine pregnancies followed the administration of drugs facilitating ovulation including clomiphene, HMG, and bromocriptine. Thus these agents may be successful in patients with amenorrhoea and infertility associated with a tumour of the pituitary gland. Conversely, the possibility of a pituitary tumour in an amenorrhoeic patient is not excluded by the advent of pregnancy after the use of these drugs, or even spontaneously.

In all patients in whom serum prolactin was measured immediately before pregnancy this value was normal. McNeilly[11] reported that high levels of prolactin inhibit progesterone synthesis even with levels of luteinising hormone and follicle-stimulating hormones normally sufficient to induce maximum steroidogenesis. It is interesting, therefore, that one of our patients (case 7) failed to respond to HMG while hyperprolactinaemic but ovulated spontaneously and conceived after correction of this hyperprolactinaemia by bromocriptine. In view of this effect of prolactin on progesterone synthesis we now continue treatment with bromocriptine for the first 12 weeks of pregnancy; this we did not do in one patient (case 7) and she aborted spontaneously at eight weeks, having discontinued bromocriptine when her period was overdue. Probably, however, ovulation occurred or was induced in two patients while still hyperprolactinaemic. A histologically proved acidophilic tumour was present in case 1, and the prolactin level was still raised after implantation of yttrium-90. In case 4 the serum prolactin level was 92 μg/l when the patient was about two weeks pregnant.

That the presence of a pituitary tumour may be highlighted by pregnancy as a result of rapid growth after conception is shown by case 1 and has been reported by others.[5 6] Persistent or worsening headache and visual disturbances were the presenting symptoms in all these cases. The possibility of this hazard emphasises the need for frequent assessment of the visual fields and for radiological investigation should tumour growth be suspected. In none of these cases did the treatment used to deal with the complications—implantation of yttrium-90 in our cases and hypophysectomy in the reported cases—seem to affect directly the progress of the pregnancy and labour.

The development of diabetes insipidus in our second untreated patient was probably due to transient swelling of the pituitary tumour. As the syndrome was relatively mild and not associated with any alteration in the radiological appearance of the sella and began as late as five weeks before term conservative treatment was decided on; also these tumour expansions may settle rapidly after delivery[12]. That the complication was directly due to the pregnancy and not coincidental is suggested by gradual decline in thirst and urinary output in the early weeks of the puerperium.

Pituitary tumour complications occurred only in patients who had not previously been treated by yttrium-90 implant. Recently it has been recognised that patients presenting with amenorrhoea and galactorrhoea may only have a microadenoma of the pituitary without an obvious radiological abnormality. Vezina and Sutton[13] found that all 20 patients with amenorrhoea, galactorrhoea, and hyperprolactinaemia had radiological evidence of a pituitary tumour after careful tomography, even though a plain *x*-ray examination of the pituitary fossa showed it to be of normal size in 14 patients. All their patients subsequently had transsphenoidal surgery, and pituitary tumours were found in each case. Jacobs and Franks[14] report an incidence of hyperprolactinaemia in 20% of patients with "functional" secondary amenorrhoea (lateral and posteroanterior tomography of the fossa was normal) and speculate that these patients too could have pituitary microadenomas.

Except for multiple pregnancy resulting from ovulation induction our group of patients did not appear prone to obstetric hazard and with the exception of the development of toxaemia in one patient and placenta praevia in another the pregnancies were relatively uneventful. Labour, too, was unaffected, being of spontaneous onset in two patients and having progressed satisfactorily after induction in another two patients. It seems, therefore, that these patients require no specific obstetric management.

Our current policy in managing women presenting with infertility and having suspected (because of raised prolactin levels) or proved pituitary tumours is as follows: (*a*) if the tumour is radiologically obvious we first do a low-dose (20 krads) pituitary implant with yttrium-90 so long as any suprasellar extension is not too large[14]. If this fails to restore ovulatory cycles we use a "fertility drug"—bromocriptine—if the prolactin levels are raised, otherwise clomiphene or HMG; (*b*) if the tumour is radiologically uncertain we use the same fertility drugs and watch the pituitary closely during the pregnancy lest yttrium-90 implantation should become urgently required. As these tumours can grow rapidly field defects may occur before the sella becomes deformed.

We thank Dr F H Doyle for his help with the radiological interpretation, Mr S Davidson and Dr J M Stuart for the report of the obstetric management of case 5, and Mr D Jefferies for that of case 6. We are also grateful to G D Searle and Co Ltd for the supply of HMG used in the treatment of case 1, and Sandoz Ltd for the supply of bromocriptine. We thank Professor H Friesen, who generously supplied antiserum 65/5 and standard 72/4/9.

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Which drugs taken by a nursing mother are excreted in her milk?

All drugs taken by the nursing mother should be suspected of being excreted in the milk until proved otherwise.[1] Examples of drugs excreted include antibiotics and antituberculous agents, antihistamines, antithyroid drugs, barbiturates, chlorpromazine, imipramine, mefenamic acid, phenylbutazone, narcotics, pyrimethamine, quinine, metronidazole, thiazides, and vitamin preparations.

1 Martin, E W, in *Hazards of Medication*, p 279. Philadelphia, Lippincott, 1971.