Occasional Survey

Bromocriptine treatment of female infertility: report of 13 pregnancies

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Summary
Thirteen pregnancies occurred in 12 women who were treated with bromocriptine for infertility. Pretreatment prolactin levels were recorded in 11 patients and were normal in three. Five patients had suspected pituitary tumours, and they received irradiation to prevent swelling of the pituitary and the consequent visual field defects caused by the pressure of the swollen gland on the optic nerve. Ten of the 13 pregnancies have come to term, and all the babies were normal. When a patient with a pituitary tumour developed a visual field defect in the 38th week of pregnancy labour was induced and the defect disappeared after delivery. No multiple pregnancies occurred and there were no major complications.

Introduction
Raised prolactin levels are usually associated with hypogonadism whether or not there is associated galactorrhoea. Bromocriptine (2 brom-a-ergocryptine, CB 154), a long-acting dopamine receptor agonist, lowers prolactin levels and this is associated with a return of normal ovarian function, even in patients with pituitary tumours.1-7 An unresolved problem exists in patients with pituitary tumours, however, when gonadotrophin treatment is used to induce pregnancy in such patients there is a risk that visual field defects may develop from the swelling of the pituitary and consequent optic nerve compression.8-13 This complication occurs during gonadotrophin therapy in at least 3% of cases.11 Presumably the same risk exists in any patient with a pituitary tumour who becomes pregnant.

We report here our experience of 13 pregnancies in 12 infertile women who were treated with bromocriptine and discuss the management policy adopted in these patients, with particular reference to those suspected of having pituitary tumours.

Patients and methods
The 12 patients were first seen at St Bartholomew's Hospital between 1969 and 1974 with infertility (see table). Seven of them (cases 1-3, 6, 8, 10, and 12) have been referred to elsewhere.8 No patient had evidence of hepatic or renal disease and none had taken any drugs likely to raise prolactin levels except for an oral contraceptive in cases 8 and 9. None had evidence of acromegaly and all patients had normal thyroid function; only one patient (case 1) had a reduced ACTH reserve, and three (cases 2, 3, and 4) had a reduced growth hormone (GH) reserve when tested with insulin-induced hypoglycaemia. The patients' husbands were all normal on seminal analysis.

Galactorrhoea had been present in 10 of the 12 patients for eight to 96 months, and in one other patient it was found only on expression of the breast during routine examination.

Menstrual history—Nine patients had amenorrhoea for six months to 16 years before treatment. Three patients had had irregular periods for four to five years before treatment. Infertility had been present for six months to 12 years.

Oestrogen-progesterone treatment—In two patients amenorrhoea supervened after combined oestrogen-progesterone treatment had been prescribed for irregular menstruation; in one spontaneous galactorrhoea appeared during this treatment, but it was not present in the other.

Normal prolactin levels—Three patients with normal serum prolactin levels were given bromocriptine; one had galactorrhoea in association with amenorrhoea, another had galactorrhoea with irregular periods, and the third had developed amenorrhoea after combined oestrogen-progesterone treatment and we thought it worthwhile to try bromocriptine as this often promotes fertility in patients who develop amenorrhoea, hyperprolactinaemia, and galactorrhoea after taking oral contraceptives.

MEASUREMENTS AND TESTS
All basal blood samples were taken between 9 and 10 am, at which time all dynamic function tests were started.

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**Clinical**

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Gn-RH, was often and treatment pituitary they encephalography available. Our Management exposed to She bromocriptine. She conceived amenorrhoea and menstrual bleeding (irregular, because of liquor and suspected mass effect on liquor. Two patients had been treated previously. One patient (case 2) was treated before conception. The second group of patients was treated after conception. Three patients stopped bromocriptine when their expected period was overdue by 24-48 hours. The other patients continued it for up to 36 days. Breast-feeding—Patients with apparent pituitary tumours were discouraged from breast-feeding because of the suspected stimulatory effects of feeding on the pituitary. Four of the other patients attempted to breast-feed and three developed painful and grossly engorged breasts. Lactation was successfully suppressed in ten patients with bromocriptine. Two patients were able to breast-feed successfully. Resumption of gonadal function after delivery—The four patients with pituitary tumours who delivered were restarted on bromocriptine after delivery, and periods returned after two months. Of the remaining six patients who delivered two resumed menstruation spontaneously. The remainder were given bromocriptine for suppression of lactation and their periods started again after five to seven weeks.

**Discussion**

The advent of a sensitive radioimmunoassay for prolactin has made it possible to identify a large group of patients who present with infertility and who have disorders of prolactin secretion. This group is heterogeneous, however, and includes patients with hypothyroidic diseases, pituitary tumours, drug-
induced galactorrhea and amenorrhoea, and amenorrhoea after oral contraception and some without overt disease. We have found that if prolactin levels are raised and the gonadotrophin reserve is normal after Gn-RH then bromocriptine will restore normal gonadal function. We have also treated patients with normal immunoreactive prolactin levels in whom gonadal functions have returned to normal after suppression of prolactin with bromocriptine.

VISUAL FIELD DEFECTS

Because of the danger of visual field defects, or even blindness, during pregnancy induced by exogenous gonadotrophins in patients with pituitary tumours we adopted a cautious and anticipatory policy and accepted any of the following as an indication to proceed to air encephalography: any slight abnormality of the pituitary fossa on plain skull x-ray film or tomograms of the fossa; any reduction of anterior pituitary reserve for GH and ACTH during insulin-induced hypoglycaemia; TSH during a TRH test; or LH and FSH after Gn-RH. Evidence of suprasellar extension was sought and the distance between the diaphragm sellae and the optic nerves gauged. If there was any evidence for the existence of a pituitary tumour the patient underwent external pituitary irradiation in the hope that it would prevent swelling of the gland during pregnancy.

In our small series we did not see any serious visual deterioration during pregnancy, but the central visual fields must be assessed regularly during pregnancy and we obtained field plots every four weeks. One patient had labour induced at 38 weeks because of a minor field defect to red vision only, which then reversed. She had, however, shown variable visual fields before her pregnancy, including similar changes, and the change at 38 weeks may not have been significant. This policy may be criticised for being too conservative and arbitrary, but the development of a field defect during pregnancy is a serious complication, and it should be avoided if possible. Some patients have progressed almost to blindness although vision usually improves after delivery. It has recently been suggested that, except in patients with ballooned fossae, the clinical situation can be left until field defects occur and then they can be dealt with by pituitary implants of radioactive yttrium. We do not agree with this.

IRRADIATION

We cannot prove that external irradiation offsets the risks of rapid enlargement of a pituitary tumour, but it seems wise to do so if localised x-ray fields can be used as a sufficiently effective treatment. The treatment was carefully planned with full isodosimetry for each patient, the smallest appropriate fields were used so as to spare vital structures, and the dose was assessed at each point in the irradiated volume. The use of an x-ray treatment simulator in planning is essential; so too are exact immobilisation and routine x-ray checks on the accuracy of positioning during the treatment. No patient in this series had an adverse reaction during treatment, other than transient headaches in some cases and local oedema in the treatment fields lasting a few months. Radiation effects have rarely been recorded as early as 14 weeks after irradiation, but the long-term risks to be considered are neurological deficit in the hypothalamus, optic tracts, brain stem, or temporal lobes; hypopituitarism; and radiation-induced neoplasms.

No long-term ill-effects have occurred in 118 patients irradiated by this technique in this department since 1961. Forty-nine of these patients were treated more than five years earlier, and the latent period for radiation-induced neurological deficit is usually one to five years. At a pituitary dose of 4500 rads in 35 days induced hypopituitarism is unlikely to occur unless tumour has already destroyed much of the gland. Finally, radiation-induced neoplasms after irradiation of pituitary tumours is extremely rare and has been recorded only many years after high and repeated doses of a different order from those we used. Hence we considered that pituitary irradiation by this technique was a justifiable component in the management of these patients. Clearly minor abnormalities of the pituitary fossa, usually accepted as being within normal limits, such as a slight asymmetry or dip in the floor on x-ray examination, must be considered to be significant in this clinical context. It is also possible that patients with normal fossae may have microadenomata. As Cushing originally noted, visual field defects may occur as a result of rapid expansion of a tumour which lies in what has been previously considered to be a normal pituitary fossa since such a tumour is more likely to enlarge upwards than one present in a ballooned fossa. Such rapid expansion may occur in pregnancy.

RESTORATION OF FERTILITY

The restoration of normal fertility in this group of patients has been a major problem in the past, treatment having been largely with exogenous gonadotrophin. From our experience it appears that only patients who are deficient in gonadotrophins but have normal prolactin levels need to be treated with exogenous gonadotrophins. Patients with hyperprolactinaemia rarely ovulate on clomiphene treatment unless prolactin levels are reduced to normal. Patients with raised prolactin levels and a normal gonadotrophin reserve will regularly respond to bromocriptine, and normal gonadal function is usually restored within two months of starting treatment. Some normoprolactinaemic patients also seem to respond successfully to bromocriptine if their basal gonadotrophin levels are normal. Since there is no evidence that bromocriptine itself alters gonadotrophin secretion we must presume that the reduction of the normal immunoreactive prolactin concentrations in these patients is enough to improve their fertility. Alternatively bromocriptine may act on dopaminergic receptors in the gonad.

Bromocriptine treatment in patients with infertility due to various causes has resulted in a rapid return of normal gonadal function and restoration of fertility. There were no multiple pregnancies, and, unlike gonadotrophin therapy, this treatment does not require daily monitoring of blood or urine to avoid overstimulation of the ovaries. There is no clinical or experimental evidence to suggest that bromocriptine is teratogenic but treatment should be withheld at the first sign of pregnancy.

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References

Outside Europe

Bites by puff-adder (Bitis arietans) in Nigeria, and value of antivenom

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Summary

Ten patients bitten by the puff-adder (Bitis arietans) were studied in the North of Nigeria. Six showed severe local signs, and four also had evidence of systemic envenoming, including spontaneous bleeding with thrombocytopenia, hypotension, and bradycardia. Two patients died after developing circulatory collapse and renal failure. Antivenom and intravenous fluid restored blood pressure in two hypotensive patients, and antivenom probably prevented the development of local necrosis in four others with massive local swelling. Victims of B arietans who have swelling of more than half the bitten limb or show signs of systemic envenoming should be given at least 80 ml of specific polyvalent antivenom and watched carefully for signs of circulatory collapse. Debridement of necrotic tissue may be necessary.

Introduction

The puff-adder (Bitis arietans) (fig 1), which is probably the most common and widespread African snake (fig 2), has been accused of causing more bites and deaths in man and domestic animals than all the other African snakes put together. Despite this there have been few clinical studies of patients with proved puff-adder bite.

Patients and methods

Ten patients with proved B arietans bite (table) were admitted to Ahmadu Bello University Hospital, Zaria, between 1971 and 1974. Eight brought the snake, which ranged in length from 30 to 132 cm (mean 86.8 cm), for identification. Seven of these have been deposited in the British Museum (Natural History) (accession numbers BMNH 1975, 21-26 and 88). The other two cases were diagnosed by detecting B arietans venom in fluid aspirated from the site of the bite and in the urine. Methods for clinical assessment and laboratory investigation have been described.

Treatment

Seven patients were given specific polyvalent antivenom intravenously over 10-30 minutes (table) (Behringwerke, Bitis, Echis, Naja; FitzSimons, Bitis, Hemachatus, Naja; South African Institute for Medical Research (SAIMR), Bitis, Dendroaspis, Hemachatus). Two others (cases 7 and 10) were thought not to need it, and it was not available in case 2. Bitten limbs were rested in the most comfortable