Cushing’s disease treated by trans-sphenoidal selective adenomectomy in mid-pregnancy

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Summary
The clinical course and diagnosis of a patient with Cushing’s disease complicated by pregnancy is described, and the anaesthetic management of trans-sphenoidal selective adenomectomy performed during the second trimester outlined. Problems included obesity, diabetes, hypertension and a suboptimal airway. Fibreoptic awake intubation and intravenous anaesthesia were used. Insulin requirements decreased substantially after surgery. Early administration of hydrocortisone after surgery avoided the risk of an addisonian crisis but delayed biochemical confirmation of a metabolic cure. (Br. J. Anaesth. 1998; 80: 850–852)

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Cushing’s syndrome is caused by excess endogenous production of corticosteroids by the adrenal glands, or their exogenous administration. Most cases of endogenous hypercortisolaemia are caused by an adrenocorticotropic hormone (ACTH) secreting pituitary microadenoma and the condition is then known as Cushing’s disease. Of the remaining cases most are caused by a unilateral adrenal adenoma, rarer causes being an ACTH-secreting carcinoid tumour, adrenal carcinoma, micro- or macronodular adrenal hyperplasia, and aberrant expression of peptide hormone receptors within the adrenal cortex. In contrast, adrenal adenomas are the most common cause of Cushing’s syndrome when it occurs in pregnancy.¹

Cushing’s syndrome is rarely associated with pregnancy because of disturbances of menstruation and the associated infertility caused by the hypercortisolaemia. When pregnancy does occur maternal morbidity and mortality are increased as a result of hypertension, diabetes, pre-eclampsia, cardiac failure and poor wound healing after Caesarean section. For the fetus there is an increased risk of spontaneous abortion, stillbirth, premature labour, intrauterine growth retardation and perinatal death. Of 69 cases reviewed by Sheeler,² only 27 were attributable to pituitary disease, and 87% developed maternal or fetal complications. In a review of the management of Cushing’s syndrome during pregnancy Buescher³ described 17 patients who had received treatment directed at correcting the hypercortisolaemia, including unilateral or bilateral adrenalectomy, one case of trans-sphenoidal surgery,³ pituitary irradiation, and drug therapy with metyrapone and cyproheptadine. Within this small group there were no stillbirths in contrast to five in a group of 43 women who had received supportive therapy only. The perinatal death rate, however, remained high in the treated group (2/17 vs 8/43; treated vs untreated), and little different from that in cases where no attempt was made to treat the hypercortisolaemia. The major maternal adverse outcomes — death and congestive heart failure — were seen only in women who had received supportive treatment alone.

There have been three previous reports of Cushing’s disease treated successfully during pregnancy by trans-sphenoidal surgery.³,⁴ In this small number of uncontrolled cases the outcome of pregnancy was favourable for both mother and fetus. As the approach offers a relatively simple, non-pharmacological opportunity to correct the metabolic disturbance before the onset of perinatal maternal complications, it has been suggested that, provided confident diagnosis of a pituitary aetiology has been made, trans-sphenoidal surgery is the management of choice.⁵⁻⁶

We report a patient who underwent trans-sphenoidal resection of an ACTH-secreting pituitary microadenoma while pregnant.

Case Report
A morbidly obese 40-yr-old female (height 1.45 m, weight 120 kg, body mass index 57 kg m⁻²) presented with a recent history of weight gain and the development of diabetes mellitus, which was managed initially with diet and oral hypoglycaemic drugs. Subsequent investigation revealed a raised urinary free cortisol concentration of 928 nmol 24 h⁻¹ (normal value <340 nmol 24 h⁻¹) and a blood pressure of 210/130 mm Hg. Physical examination revealed the typical physical features of Cushing’s syndrome. The diagnosis was confirmed by a loss of the normal diurnal serum cortisol rhythm (sequential midnight sleeping cortisol levels 636 nmol 1⁻¹ and 336 nmol 1⁻¹), and a failure of the 09:00 serum cortisol to suppress below 50 nmol 1⁻¹ after oral dexamethasone 0.5 mg q.d.s. for 48 h (09:00 cortisol 152 nmol 1⁻¹). A probable pituitary aetiology was suggested by the finding of further suppression of serum cortisol to 46 nmol 1⁻¹ after high-dose dexamethasone...
(2 mg q.d.s. for 48 h), a plasma ACTH concentration within the normal range at 45 ng l⁻¹, and bilateral adrenal hypertrophy on a computed tomography scan. However sampling in the basal state from the inferior petrosal sinuses, which drain the pituitary, failed to demonstrate any gradient in plasma ACTH concentration between the sinuses and simultaneously sampled peripheral blood. (Post-stimulation samples were not possible as human corticotrophin releasing hormone (CRH) was temporarily unavailable in the UK at the time of investigation).

At this stage of her investigations the patient became pregnant and was started on insulin therapy. Control of the diabetes was difficult with initial HbA1c fractions of up to 10.3% (reference value < 6.2%). Up to 148 units of insulin per day were required to achieve near normoglycaemia.

During further investigation with a peripheral CRH test there was a significant rise in serum cortisol concentration from a baseline of 427 nmol l⁻¹ to a maximum of 983 nmol l⁻¹ at 1 h, suggesting a pituitary aetiology for the Cushing’s syndrome rather than an ectopic ACTH source, where the response is typically flat. Magnetic resonance imaging was unsuccessful at the first attempt because of claustrophobia, but subsequent imaging after sedation with oral temazepam showed a pituitary microadenoma, central and superior in the gland.

After careful discussion of the potential risks and potential benefits of surgery the patient agreed to an elective, mid-trimester trans-sphenoidal selective adenomectomy.

Her medical history was otherwise unremarkable, and included uncomplicated anaesthesia for tonsillectomy and a long history of obesity predating the onset of Cushing’s syndrome.

At the preoperative visit she was noted to have a short but mobile neck and a mobile larynx. Mouth opening was good but only the upper half of the uvula was visible. All the anterior teeth on the upper jaw were crowned. She found the supine position very uncomfortable and could not tolerate it for more than a minute. She was also claustrophobic and unable to tolerate a face mask. She was premedicated with glycopyrronium 0.6 mg i.m. and oral ranitidine 300 mg.

After establishing venous access and standard monitoring, and giving supplementary oxygen, she was lightly sedated with midazolam without loss of verbal contact (total dose 4 mg over 15 min). Following application of topical lidocaine an awake fibre-optic orotracheal intubation was performed. Anaesthesia was induced and maintained with propofol and alfentanil infusions and intermittent doses of atracurium. After induction of anaesthesia, arterial blood pressure was measured directly via a radial artery cannula. Fetal heart beat was confirmed before and after surgery using a Doppler device. Fetal movements were felt shortly after waking and recurred with normal frequency thereafter.

After induction of anaesthesia, systolic blood pressure was initially stable (115–135 mm Hg), but then rose to 160 mm Hg in spite of bolus doses of propofol and alfentanil. Subsequently, 50% nitrous oxide was added and haemodynamic stability was restored. A total of 1950 mg of propofol and 22 mg of alfentanil were given over 155 min (average rates of administration 6.3 mg kg⁻¹ h⁻¹ and 71 µg kg⁻¹ hr⁻¹ respectively). At the end of surgery, which lasted 140 min, neuromuscular block was antagonized and the patient extubated wide awake in a semi-upright position.

Perioperatively, the patient’s diabetes was managed with dextrose and insulin infusions begun on the evening before surgery and adjusted according to blood glucose estimations. Blood glucose concentration remained normal during surgery. Postoperatively, insulin requirement decreased dramatically from 150 units per day to 40 units in the 24 h after surgery. On the second and third days after operation, her insulin requirement fell to 30 and 20 units respectively. It is our usual practice to delay giving steroid replacement for 24 h after surgery for Cushing’s disease, to permit the measurement of serum cortisol as an early index of metabolic cure (cortisol < 50 nmol l⁻¹). However in this case the risks of delaying the first dose were deemed unacceptable and steroids were given i.v. at 6 h.

Histological examination of the operative specimen showed fragments of an ACTH-secreting pituitary tumour.

The patient was discharged from the neurosurgical unit to a hospital nearer her home 5 days after surgery, having made an uneventful recovery. Treatment on discharge comprised oral hydrocortisone 30 mg in divided doses, which was withdrawn for a brief period to facilitate a short synacthen test. This demonstrated a normal serum cortisol response to tetra-cosactrin, allowing for the pregnancy-induced elevation in cortisol-binding globulin, (0 min 467 nmol l⁻¹, 30 min 982 nmol l⁻¹) indicating early recovery of the hypothalamic—pituitary-adrenal axis. Serum thyroxine levels remained normal and there was a normal thyrotrophin (TSH) response to thyrotrophin-releasing hormone (TRH).

Hydrocortisone and insulin in reduced doses were continued for the remainder of the pregnancy, which was complicated by severe pre-eclampsia. The patient was delivered of a live male infant at 34 weeks gestation by an emergency Caesarean section under general anaesthesia, because of concern over impending eclampsia. The infant had a birth weight of 2300 g and APGAR scores of 7, 8 and 10 at 1, 5 and 10 min respectively. The child was admitted routinely to the special care baby unit, and was bottle fed, although normal lactation was established in the mother. Since the delivery, after which hydrocortisone therapy was discontinued, the patient’s urinary free cortisol excretion has been within the normal range and her insulin requirements have continued to decline.

Discussion

The diagnosis of Cushing’s disease in the patient described here was complicated by the difficulty in obtaining magnetic resonance images, the misleading petrosal sinus ACTH results, the initial unavailability of human CRH, and the effect of the oestrogen-induced elevation in cortisol-binding globulin on the interpretation of total serum cortisol levels. Interpretation of magnetic resonance images of the pituitary during pregnancy is also complicated by changes related to normal pregnancy.
The decision to operate on this patient was justified by the high incidence of maternal and fetal obstetric complications in the absence of intervention in Cushing's syndrome,¹ and the additional problem of steroid-induced diabetes with marked insulin resistance. The benefits of intervention for Cushing's syndrome during pregnancy remain uncertain,² and must be weighed against the potential risks of anaesthesia, the operative procedure and any drug therapy used. Given the rarity of the problem it is unlikely that randomized controlled trials will be performed, and existing publications are relatively unhelpful. Anecdotally, wound complications after caesarean section are less likely if the hypercortisolaeemia is corrected antenatally by definitive surgery.³ Drug therapy with metyrapone, an inhibitor of 11 β-hydroxylase, has been used with some success,⁴ but is theoretically unattractive. The drug can cross the placenta and hence inhibit fetal cortisol synthesis,⁵ while although maternal cortisol also crosses the placenta, little enters the fetal circulation because of the high activity of placental 11 β-hydroxysteroid dehydrogenase and its consequent conversion to biologically inactive cortisone.⁶

The middle trimester of pregnancy is generally regarded as a suitable period for essential elective surgery during pregnancy,¹² and there is no evidence that any well conducted anaesthetic technique is superior to any other.¹² We selected awake fibreoptic intubation of the trachea because of the combined risk factors of pregnancy, a suboptimal airway and morbid obesity. Use of a limited amount of sedation facilitated this procedure in an exceptionally anxious patient. Our anaesthetic technique was selected to give satisfactory conditions for neurosurgery with rapid recovery. The addition of nitrous oxide after 1 h was a pragmatic decision; the alternatives would have been additional narcotic or antihypertensive medication. Our anaesthetic technique worked well and we were able to achieve tracheal extubation without coughing with the patient wide awake and semi-upright, this being the only position in which she could breathe comfortably.

We considered using continuous fetal monitoring during and after surgery but the patient's extreme obesity made it likely that this would have been at best intermittent. We also felt that frequent interruptions in the fetal signal would seriously alarm both the patient and attending staff in a situation where there were few therapeutic options. Accordingly we used intermittent fetal monitoring before and after surgery with no fetal monitoring during surgery.

The high insulin requirement of this patient confirmed the experience of others.¹ The sharp fall in insulin requirement after surgery reflects the reduction in adrenal cortisol output and was suggestive of a successful procedure, although definitive confirmation of remission was not possible until after a trial of hydrocortisone withdrawal in the postpartum period. Although it would have been desirable to confirm a biochemical cure by withholding steroid treatment and finding a low serum cortisol immediately after operation, we considered the risks of hypotension or addisonian crisis to be unacceptable in mid-pregnancy. Accordingly steroid replacement was started early.

In summary the differential diagnosis and management of Cushing's syndrome during pregnancy poses a great challenge for both physician and obstetrician. In this case elective trans-sphenoidal selective adenomectomy during pregnancy produced an apparent metabolic cure without immediate anaesthetic or surgical complications. Although the outcome was favourable in that there was no long-term maternal morbidity, and a healthy live infant was delivered, the perinatal problems were nevertheless substantial and potentially life threatening for both mother and fetus as a result of the severe pre-eclampsia.

References