CASE REPORT

Use of cabergoline for the management of persistent Cushing's disease in pregnancy

Kathleen Su-Yen Sek, Doddabele Srinivasa Deepak, Kok Onn Lee

Department of Medicine,
National University Hospital,
Singapore, Singapore

Correspondence to
Dr Kathleen Su-Yen Sek,
kathleen_sy_sek@nuhs.edu.sg

Accepted 16 June 2017

SUMMARY

Cushing's disease (CD) is rare during pregnancy and is associated with significant maternal and fetal complications. It is important to control hypercortisolism during pregnancy, either surgically or medically, for a successful maternal and fetal outcome. We report a patient with recurrent CD who was treated with low-dose cabergoline (CAB) for persistent hypercortisolism throughout pregnancy. A 36-year-old woman was diagnosed with CD at the age of 23. She underwent trans-sphenoidal surgery with initial complete remission. However, 4 years after surgery, CD recurred and she underwent Gamma Knife radiosurgery (GKRS). Following GKRS, her cortisol levels remained elevated despite no evidence of visible tumour on pituitary MRI. Medical treatment was commenced with ketoconazole and cyproheptadine. This was changed to CAB as she was keen for pregnancy. She conceived spontaneously and was on CAB throughout pregnancy. She delivered a healthy male neonate, weighing 3195 g at 40 weeks of gestation.

BACKGROUND

Cushing's disease (CD) is rare during pregnancy and is associated with significant maternal and fetal complications. It is important to control hypercortisolism during pregnancy, either surgically or medically, for a successful maternal and fetal outcome.

We report a successful pregnancy outcome in a patient with recurrent CD who was treated with low-dose cabergoline (CAB) for persistent hypercortisolism throughout gestation.

CASE PRESENTATION

The patient first presented to the endocrine clinic in 2001, at the age of 23, with hypertension.

On physical examination, she had features of Cushing's syndrome such as facial rounding, hirsutism, supraclavicular fat pads, purple abdominal striae, easy bruising and proximal myopathy. Her blood pressure was elevated at 160/100 mm Hg.

Screening tests showed an elevated 24 hours urinary-free cortisol (UFC) that was >4.8 times the upper limit of normal (ULN) at 2006 nmol/day (normal range: 59–413 nmol/day). This was repeated and confirmed to be elevated (UFC 1533 nmol/day, >3.5x ULN). Additionally, she had a non-suppressed adrenocorticotrophic hormone (ACTH) of 6.5 pmol/L (normal range: 0.0–10.1 pmol/L) and mildly elevated dehydroepiandrosterone

sulphate (DHEAS) at 8.2 µmol/L (normal range: 1.8–7.7 µmol/L).

A high-dose dexamethasone suppression test showed more than 50% suppression of cortisol (table 1).

MRI of the pituitary showed a nodular lesion, measuring 9×6×8 mm on the right side of the pituitary gland, compatible with a pituitary microadenoma with no compression on the optic chiasm (figure 1).

A diagnosis of CD was made and she subsequently underwent trans-sphenoidal surgery to excise the pituitary adenoma. Histology was consistent with pituitary adenoma that showed uniform ACTH immunostaining confirming a corticotroph tumour. Tumour tissue did not show any immunostaining for prolactin.

She was started on oral hydrocortisone replacement immediately after surgery. Postoperative day 8 early morning serum cortisol was 12 nmol/L with an ACTH of <2 pmol/L and she was continued on oral hydrocortisone. One year following adenectomy, assessment was indicative of disease remission as evidenced by improvement in clinical features (weight loss of 15 kg, reduction in facial rounding and supraclavicular fat pads) and evidence of eucortisolism (24 hours UFC had fallen to the normal range (110 nmol/day)). Glucocorticoid replacement therapy was withdrawn 40 months after initial pituitary surgery.

In 2005, 4 years after the initial surgery, she developed relapse of hypercortisolism as evidenced by weight gain of 10 kg over 12 months and re-emergence of supraclavicular fat pads. Repeat 24 hours UFC was elevated on two occasions at 1138 nmol/day and 820 nmol/day. Serum cortisol at 08:00 was 425 nmol/L and ACTH was 10 pmol/L at that point.

Given the suspicion of recurrent CD, an MRI pituitary was repeated which did not show any visible pituitary tumour. She proceeded to have Gamma Knife radiosurgery (GKRS) in July 2006. Two months after GKRS, she remained clinically Cushingoid with persistent hypercortisolism (24 hours UFC was elevated at 1235 nmol/day (>3xULN)). Adjuvant medical therapy was commenced with ketoconazole 100 mg twice daily and cyproheptadine 4 mg twice daily in September 2006 with successful control of hypercortisolism for the subsequent 2.5 years (table 2). MRI pituitary obtained 14 months after initiation of medical treatment showed stable remnant pituitary gland with no visible recurrence.

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To cite: Sek KS-Y, Deepak DS, Lee KO. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-217855

Table 1 Results of high-dose dexamethasone suppression test

	Baseline	48 hours
Cortisol at 08:00 (123–626 nmol/L)	862	293
ACTH (0.0–10.1 pmol/L)	2.1	13.1

ACTH, adrenocorticotropic hormone.

As she was keen for pregnancy, medical treatment was changed to CAB 0.25 mg twice weekly from April 2011 to avoid the potential antiandrogenic side effects of ketoconazole in pregnancy.

The aim of treatment was to achieve eucortisolism. We were not able to get 24 hours UFC measurements after April 2009 as the patient found it inconvenient to have the test done. At that time, we did not have the facility in our hospital to measure midnight salivary cortisol as an alternative method of assessing the patient's clinical status. As a compromise, we chose to monitor disease remission using clinical symptoms and basal (08:00) serum cortisol. Over the subsequent 20 months of follow-up, the patient did not develop any new clinical features to suggest hypercortisolism and the basal cortisol stayed within the reference range (table 3). Due to the prior adjuvant pituitary radiotherapy, we acknowledge that the control of hypercortisolism may have been due to both the CAB and previous pituitary radiotherapy. We realise that this a major limitation of our case report.

The patient subsequently conceived spontaneously in June 2013 and was maintained on CAB 0.25 mg twice weekly throughout the pregnancy (table 4). She had an uneventful pregnancy, without any blood pressure or glucose abnormalities, supporting our conclusion that there was no significant hypercortisolism throughout the pregnancy. An oral glucose tolerance test done at 28 weeks gestation was completely normal. She developed secondary hypothyroidism (low free thyroxine of 7.4 pmol/L with an inappropriately normal thyroid-stimulating hormone of 2.74 mIU/L) during her pregnancy that required thyroxine replacement. The patient went into spontaneous labour at 40 weeks of gestation and delivered a healthy male neonate, weighing 3195 g, with an Apgar score of 9 in March 2014.

Figure 1 MRI pituitary showing a microadenoma on the right side of the sella.

Postpregnancy cortisol and prolactin on CAB therapy are described in table 5.

INVESTIGATIONS

Investigations are described in tables 1–5 and figure 1.

TREATMENT

After delivery, the patient did not breastfeed the baby and continued treatment with CAB 0.5 mg/week and thyroxine 50 µg every morning.

OUTCOME AND FOLLOW-UP

Two years following pregnancy, she remains well with no Cushingoid features.

DISCUSSION

CD is caused by an ACTH-producing pituitary adenoma (either microadenoma or macroadenoma), which chronically stimulates the production of cortisol by the adrenal glands. Pregnancy is very rare in patients with CD, as hypercortisolaemia, hyperandrogenaemia and hyperprolactinaemia can lead to anovulation, oligomenorrhoea or amenorrhoea and eventually, impaired fertility. However, if pregnancy does occur, this is often associated with significant maternal and fetal morbidity and mortality. Lindsay *et al* reviewed 136 pregnancies in patients with Cushing's syndrome and found higher rates of hypertension (68%), diabetes or impaired glucose tolerance (25%), pre-eclampsia (14%) and maternal death (2%). Fetal complications that were observed include premature births (43%), intrauterine growth retardation (21%), stillbirths (6%) and fetal hypoadrenalism (2%).^{1 2} Given the risks and poor outcomes of Cushing's syndrome in pregnancy, it is crucial to control hypercortisolism during pregnancy.

Trans-sphenoidal surgery remains the gold standard treatment for CD with a remission rate of 65%–90%.³ However, when surgery does not normalise cortisol levels, medical therapy can be used. The options include adrenal blocking drugs, such as ketoconazole, mitotane, metyrapone and etomidate, which inhibit steroidogenic enzyme activity. Other medical options include pituitary-directed therapy such as CAB and pasireotide, and glucocorticoid receptor antagonist such as mifepristone. Cyproheptadine, which is a serotonin antagonist has also been used in CD to lower ACTH and cortisol levels by inhibiting corticotropin releasing hormone (CRH) and vasopressin secretion.⁴

Our patient achieved remission from hypercortisolism following initial pituitary surgery as supported by a postoperative morning serum cortisol level of less than 50 nmol/L and need for physiological steroid replacement therapy. Studies have shown that persistent postoperative morning serum cortisol levels of less than 50 nmol/L are associated with remission and a low recurrence rate of approximately 10% at 10 years.³

Unfortunately, in our patient, CD recurred 4 years later and she went on to have GKRS since there was no visible residual tumour on pituitary imaging. In view of persistent hypercortisolism post-GKRS, she was started on adjuvant medical therapy with ketoconazole and cyproheptadine that successfully achieved eucortisolism. As she was keen for pregnancy, ketoconazole and cyproheptadine were both stopped and treatment changed to CAB. This was required due to the questionable teratogenic effects of ketoconazole, which has been reported to be embryotoxic and teratogenic when administered to pregnant rats in high doses. Although studies in humans are limited, there are concerns that ketoconazole could inhibit testosterone synthesis

Table 2 Biochemical trends on medical therapy for CD showing normalisation of 24 hours UFC

	November 2006	March 2007	January 2008	August 2008	April 2009	April 2010	November 2010	April 2011
Cortisol at 08:00 (123–626 nmol/L)	366	346	449	341	356		234	341
ACTH (0.0–10.1 pmol/L)	13.1	20	9	9	8.8	7.4	7	10.5
24 hours UFC (59–413 nmol/day)	624	86	114	25	41			

ACTH, adrenocorticotrophic hormone; CD, Cushing's disease; UFC, urinary-free cortisol.

Table 3 Cortisol, ACTH and prolactin trend on cabergoline monotherapy

	April 2011	May 2011	June 2011	September 2011	February 2012	July 2012	January 2013
Cortisol at 08:00 (123–626 nmol/L)	341	371	277	274	242	375	303
ACTH (0.0–10.1 pmol/L)	10.5	8.4	5.2	5.2	3.9	7.2	6.5
Prolactin (78–540 mIU/L)				<7			

ACTH, adrenocorticotrophic hormone.

Table 4 Cortisol and prolactin trend on cabergoline during pregnancy

	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014
Cortisol at 08:00* (123–626 nmol/L)	532	309	300	304	386	291	328	463	576
Prolactin (78–540 mIU/L)	20					230	217	265	195
ACTH (0.0–10.1 pmol/L)	5.4								

*Trimester-specific reference ranges for cortisol at 08:00 during pregnancy is not available.

in utero leading to feminisation of the male fetus.⁵ As a result, ketoconazole is classified by the US Food and Drug Administration as pregnancy category C. Mitotane is not recommended in pregnancy as it crosses the placenta and is teratogenic. There is paucity of evidence in the literature about the safety of cyproheptadine use in pregnancy, although two case reports have demonstrated no fetal abnormalities when cyproheptadine was used during pregnancy in patients with Cushing's syndrome.^{6,7} Mifepristone, a glucocorticoid receptor antagonist is also contraindicated in pregnancy as it has abortifacient properties due to the antagonism of progesterone action.

Metyrapone may lead to hypertension with higher risk of pre-eclampsia and an increased risk of preterm delivery.¹ This was not considered in our patient as metyrapone is not available in our country.

CAB, which is a dopamine receptor agonist, is a useful therapeutic agent in CD. The drug acts via the dopamine receptor subtype 2 on the pituitary corticotroph adenoma to reduce ACTH secretion.⁴ In adults with CD, the usual doses of CAB required to control cortisol levels are, on an average higher (1–7 mg/week, median 3.5 mg/week) compared with those used in patients with hyperprolactinaemia (2 mg/week).⁸ Low doses of CAB (0.125–4.0 mg/week) have been used to treat pregnant patients harbouring prolactinoma with no adverse outcomes, such as spontaneous miscarriages or congenital malformations.⁹

There has, however, been limited experience with the use of CAB in managing CD during pregnancy. Woo *et al*, reported on a favourable maternal and fetal outcome in a patient with recurrent CD who was managed with high doses of CAB (4.5 mg twice a week) throughout her pregnancy.¹⁰ A previous publication by Berwaerts *et al* in 1999¹¹ additionally reported an uneventful pregnancy outcome in their patient with CD due to a corticotroph microadenoma who refused pituitary surgery. In that patient, hypercortisolism was managed throughout pregnancy with ketoconazole (100 mg twice daily) and low-dose CAB (1.75 mg/week). We now report a case of recurrent CD also managed with CAB throughout pregnancy but requiring

an even lower dose of this drug (0.5 mg/week). In our patient, even before pregnancy, we had already established good disease control on this dose as evidenced by basal (08:00) serum cortisol that was within the reference range. It was interesting to note that she did not require escalation of CAB dose during pregnancy to achieve this target basal cortisol in contrast to the case report by Woo *et al*,¹⁰ whose patient needed a CAB dose as high as 10 mg/week at the time of delivery. We can only speculate that this difference was due to prior adjuvant pituitary radiotherapy (GKRS) that our patient had received, thereby achieving some control of ACTH hypersecretion than the former patient, even though both patients had undergone trans-sphenoidal pituitary surgery as the first therapeutic intervention. The development of secondary hypothyroidism in our patient also supports this hypothesis. In women with recurrent CD who are trying to conceive, bilateral adrenalectomy should be considered as a last resort if medical therapies are ineffective or not tolerated in controlling hypercortisolism.

One of the main limitations of our case report that we recognise is the lack of objective biochemical measurements to demonstrate remission from hypercortisolism following initial pituitary surgery and GKRS. Of the two available modalities, the patient was unwilling to get 24 hours UFC measurements done after April 2009 due to the inconvenience of this test. Also, midnight salivary cortisol was not done as this was not available in our institution at that time. As a compromise, we chose to monitor disease remission using clinical symptoms and basal (08:00) serum cortisol after discussion with the patient. However, the

Table 5 Cortisol and prolactin trend postpregnancy

	April 2014	August 2014	January 2015	February 2016
Cortisol at 08:00 (123–626 nmol/L)	403	363	347	279
Prolactin (78–540 mIU/L)	88	11	6	<6

Learning points

- ▶ Pregnancy is very rare in patients with Cushing's disease
- ▶ Management of uncontrolled hypercortisolism in pregnant patients can be challenging. The choices available for medical therapy are limited. If these are ineffective or not tolerated in controlling hypercortisolism, the other options available are pituitary surgery or bilateral adrenalectomy.
- ▶ It is encouraging to note, from individual case reports and our own experience, that cabergoline has shown to have a good safety profile in this patient population.

outcome of the pregnancy, the absence of hypertension and the absence of glucose intolerance would support our conclusion that there was no significant hypercortisolism in our patient throughout her pregnancy. Due to the prior adjuvant pituitary radiotherapy, we also acknowledge that the control of hypercortisolism may have been due to both the CAB and previous pituitary radiotherapy.

In conclusion, pregnancy is very rare in patients with CD. The management of uncontrolled hypercortisolism in pregnant patients can be challenging and in this situation, endocrinologists may need to resort to the use of medical therapy to ensure a favourable outcome for both the mother and the fetus. Despite the rarity of pregnancy in patients with CD, it is encouraging to note, from individual case reports and our own experience, that CAB has shown to have a good safety profile in this patient population.

Contributors KO was involved in the care of the patient and conceived this study. KSS wrote the first draft. KSS, DSD and KOL reviewed and revised the draft. All authors approved the submitted version of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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