Cushing’s Syndrome and Pregnancy
A Case Report


SUMMARY

The literature on Cushing’s syndrome associated with pregnancy is reviewed, and a case of this rare association is reported. The patient had an adrenal adenoma.

Investigations and interpretation of stimulation and suppression tests are discussed. Cortisol metabolism in normal pregnancy is referred to.


Patients with Cushing’s syndrome have a high incidence of infertility, associated with disturbed menstrual function and ovulation.1,2

Only 24 patients with the syndrome who have fallen pregnant have been reported,3-5 and most of these pregnancies ended in abortion, premature birth or stillbirth.

This report documents a case of florid Cushing’s syndrome associated with pregnancy. An adrenocortical adenoma was successfully removed and the patient was cured at 18 weeks’ gestation. Unfortunately, this was followed by an abortion 3 weeks later.

CASE REPORT

A 25-year-old Black woman presented at Tembisa Hospital with a short history of shortness of breath, palpitations and cough, and a 1-month history of easy bruising. She had rounded moon facies and obesity of the trunk, but not of the arms and legs. She had a dorsal neck ‘hump’, acne, hirsutism and purple striae over the abdomen, buttocks and thighs. There were bruises. This was a classic case of florid Cushing’s syndrome, and when, at our request, the patient produced a photograph of herself taken at the age of 18, we noticed that the change was remarkable and absolutely diagnostic.

On direct questioning, she admitted to a 6-year history of progressive weight gain and obesity, weakness and backache, and a very irregular menstrual cycle with long periods of amenorrhoea. She had had no menstrual period for the preceding 4 months. She had had no previous pregnancies, and did not know whether she was pregnant or not. She had also complained of abdominal pain, vomiting and melaena for a short while.

On examination she was very distressed, dyspnoeic and orthopnoeic. She was not cyanosed, but the jugular venous pressure was elevated and there were crepitations throughout both lung fields. The pulse was 140/min, the blood pressure 210/130 mmHg, and there was cardiomegaly and left ventricular failure.

Her urine contained protein but no glucose. A 14-16-week pregnant uterus was detected on examination, and latex test for chorionic gonadotrophin was persistently positive, confirming pregnancy.

Chest radiographs showed cardiomegaly and congestive changes in the lung fields, and skull radiographs revealed a normal pituitary fossa. Full blood count was normal, as were urea and electrolytes. A glucose tolerance test was indicative of diabetes.

Treatment was started with digitalis and diuretics for cardiac failure, and the blood pressure was lowered with methyldopa.

Once Cushing’s syndrome was suspected, minimal laboratory diagnostic criteria had to be met. Plasma cortisol levels were all elevated, and there was loss of the normal

<table>
<thead>
<tr>
<th>Pituitary lesion</th>
<th>Response to high dose dexamethasone</th>
<th>Response to metyrapone</th>
<th>Response to ACTH</th>
<th>Excretion of 17-hydroxy-cortico-steroids</th>
<th>Excretion of 17-keto-steroids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign adenoma</td>
<td>None</td>
<td>None</td>
<td>Variable</td>
<td>High</td>
<td>Normal</td>
<td>Variable</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>High</td>
<td>Very high (4x)</td>
<td></td>
</tr>
<tr>
<td>Ectopic ACTH syndrome</td>
<td>None</td>
<td>None</td>
<td>Variable</td>
<td>Minimal</td>
<td>Very high (4x)</td>
<td></td>
</tr>
</tbody>
</table>

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diurnal variation. In fact, nearly all the levels exceeded the highest measurable — 43 μg/100 ml (normal values at 08h00 are 6 - 24 μg/100 ml, at 16h00 4 - 18 μg/100 ml, and 3 - 14 μg/100 ml at 24h00).

In all forms of Cushing’s syndrome patients demonstrate some degree of autonomous secretion of excessive amounts of cortisol. If the administration of slightly supraphysiological amounts of a glucocorticoid will not suppress the pituitary-adrenal axis in an otherwise un­stressed individual, then the diagnosis is certain.

As a suppression test, dexamethasone 1 mg was given orally at midnight, and plasma cortisol was measured at 08h00. The level was above 43 μg/100 ml on two occasions, confirming the diagnosis. The 24-hour urinary 17-hydroxy­corticosteroid excretion was 27.2 mg (normal 4 - 18 mg). The urinary 17-ketosteroids in 24 hours was 19 mg and 20 mg (normal 4.5 - 20 mg).

Once the diagnosis of Cushing’s syndrome had been confirmed, we attempted to establish its aetiology. Immuno­assay of ACTH was not available, so we studied the steroid excretion pattern and response of the pituitary-adrenal axis to physiological manipulation.

In Table I the expected responses to dexamethasone suppression, ACTH stimulation and to metyrapone (Meto­pirone) (an 11-hydroxylase inhibitor) in each of the con­ditions which cause Cushing’s syndrome are shown. Table II shows the results in our patient, and explains the methods.

We thought that an adrenocortical adenoma was the most likely diagnosis, because (i) there was a lack of plasma cortisol suppression by dexamethasone; (ii) there was no response to metyrapone; (iii) there was positive ACTH stimulation of 24-hour urinary 17-hydroxy­corticosteroids; and (iv) 17-ketosteroids were normal or only slightly elevated.

Radiological techniques to demonstrate an adenoma could not be undertaken because of the early pregnancy. Because of the severity of the hypertension and its comp­lications, the abnormal glucose tolerance and the poor general state of the patient, surgery was planned. The patient was treated with steroids before, during and after the operation. Both adrenal glands were examined at surgery and a large benign adenoma was found on the right side. The remaining right adrenal tissue and the left adrenal gland did not appear atrophic. The tumour, which was removed, was 3 cm in length with a mass of 18 g. Histological examination showed two cell types originating from both the zone fasciculata and the zone reticularis. This was a cortical adenoma. The pregnancy was confirmed at surgery. Recovery was uneventful. ACTH was given for 3 days to stimulate possible atrophic or suppressed adrenal remnants. Beta-adrenergic stimulants were given to delay possible abortion or premature labour, but the patient unexpectedly aborted a 500-g fetus some 3 weeks later.

Adrenocortical function is now normal, plasma electrolytes are normal, plasma cortisol is normal and there are normal responses to both dexamethasone suppression and ACTH stimulation. The patient is now normotensive and takes no hypotensive drugs or diuretics. Vomiting was the only symptom which persisted, and after the abortion a
barium meal revealed a large duodenal ulcer, presumably accounting for her symptoms of abdominal pain, vomiting and melena on admission. No doubt this was related to the high levels of endogenous cortisol. This appears to be healing with medical therapy.

DISCUSSION

Early in normal pregnancy, 17-hydroxycorticosteroid and cortisol levels start increasing; they reach a level about 7 times the normal value immediately after delivery and then drop off, returning to the pre-pregnancy level by the 6th postpartum day. Plasma cortisol levels in normal pregnancy 'often approach those found in non-pregnant patients with Cushing's syndrome. Despite increased bound and free plasma cortisol levels in normal pregnancy, clinical features of hypercorticism are rarely seen, suggesting that a change in reactivity to cortisol may render it biologically less effective in pregnancy.'

The exaggerated response of plasma cortisol levels to ACTH stimulation in pregnancy suggests either an increased sensitivity of the adrenal cortex or a delay in the turnover of cortisol.

Patients with Cushing's syndrome have a high incidence of infertility, and we believe that our patient may be the 25th pregnant woman with Cushing's syndrome to be reported.

REFERENCES