Singapore Journal of Obstetrics and Gynaecology
March 2002; 33(1): 47-50

CASE REPORT

Cushing's Syndrome in Pregnancy: A Case Report

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ABSTRACT

Cushing's syndrome in pregnancy is an uncommon entity in obstetric practice. We present a case of Cushing's syndrome in pregnancy presenting with severe hypertension at 26 weeks gestation. The etiology, diagnosis, complications and management of Cushing's syndrome in pregnancy is discussed.

Key words: Cushing's Syndrome, Adrenal adenoma, Cortisol, Metyrapone.

HISTORY

A 26 years old primigravida was transferred to our hospital for management of severe hypertension at 26 weeks gestation. She did not have any significant past medical history nor was she on any chronic medication. Her menstrual cycles had always been regular and she had only been married for nine months.

Since the beginning of her pregnancy, she had noticed progressive changes in her appearance. There was an abundance of stretched marks over her limbs and abdomen with increasing erythema over her face and body. She also developed more acne and her husband noticed a change in her facial appearance towards a rounded feature. About six weeks prior to admission (around 18 to 22 weeks gestation), she was experiencing difficulty in getting up from a squatting position. At no time were there complains of persistent headache, visual disturbances, vomiting, epigastic discomfort or increasing lower limb swelling.

Physical examination revealed a young lady with diagnostic features of Cushing's syndrome. She had a round and flushed face with overt truncal obesity and disproportionately slim limbs. The classical buffalo hump and supraclavicular fat pads were present. Numerous acne and mild hirsutism were noted on her face and her skin appeared atrophic with wide red striae over the proximal upper limbs, abdomen and thigh. Cardiorespiratory examination was normal and there were no palpable masses in the abdomen. Proximal weakness was elicited in all four limbs. Visual field examination by confrontational method did not reveal any bitemporal hemianopia. Funduscopic examination revealed sharp disc margins with no hypertensive changes.

A diagnosis of Cushing's syndrome was made and later confirmed with biochemical investigations. There was a markedly raised 24hours urine free cortisol level with suppressed ACTH levels. The raised serum cortisol levels exhibited a lost of the diurnal variation and were not suppressible by low dose or high does Dexamethasone. (Table 1)

The etiology of the Cushing's syndrome was elicited by MRI (Figure 1). A mass measuring 4.0cm by 3.5cm by 2.4cm with well-defined margins and homogeneous signal intensity was seen in the location of the left adrenal gland. It showed loss of intensity with the out of phase sequence consistent with a lesion with fat composition. These findings were consistent with a left adrenal adenoma. The right adrenal gland was noted to be small.

Her initial blood pressure on admission was 166/102 mmHg and this was controlled with 500mg of Methyldopa thrice a day. Serum level of Uric Acid was 267 umol/L and her 24hours urine protein loss was 0.63 gm with a urine volume of 3.4 litres. She was also found to have glucose intolerance (with a

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Glycosylated Hemoglobin of 6.4%) and this was managed with insulin. Further biochemical investigations revealed normal renal function but hypokalemia that was replaced appropriately. A screening ultrasound revealed a grossly normal singleton fetus with parameters corresponding to the third percentile of the gestation.

The patient underwent an adrenalectomy through a left subcostal incision at 28 weeks gestation. An encapsulated adrenal tumor was removed and the histological finding was that of an adrenal cortical adrenoma. The patient recovered uneventfully after the operation and was discharged five days later with oral Hydrocortisone.

At 32 weeks gestation, the patient presented with preterm prelabour rupture of membranes. At 33 weeks gestation, she went into spontaneous labour despite inhibition with intravenous Salbutamol. A male baby of 1460gm was delivered vaginally with APGAR of 9 at 5 minutes. The baby exhibited no signs of adrenal failure.

Fortunately for the mother, there were no tears sustained through the vaginal delivery. Postpartum insulin was stopped as her glucose intolerance resolved after delivery. She however required a small dose of Nifedipine to control her hypertension. Hydrocortisone was continued and serum cortisol levels will be measured 3 months later with a view to stop Hydrocortisone therapy when the levels return to normal.

TABLE 1
Cortisol and ACTH levels with Dexamethasone suppression

		Dexamethasone Suppression	
	Baseline	Low Dose	High Dose
Plasma Cortisol at 8am (nmol/l)	1622	1191	1646
Plasma Cortisol at 12am (nmol/l)	1062		
24hr Urine free Cortisol (nmol/day)	5558	3429	5525
ACTH (ng/l)	3.1		

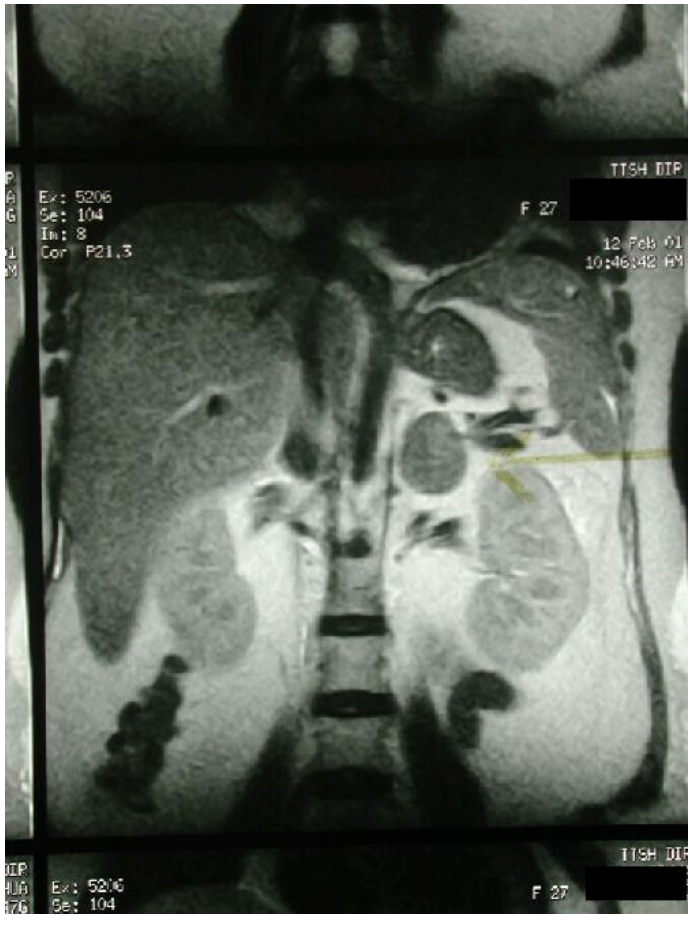

Fig. 1. MRI image of the left adrenal adenoma.

DISCUSSION

Patients with Cushing's syndrome are often subfertile presenting typically with ammenorhoea or oligomenorrhoea. Ovulation is usually suppressed because of the excessive production of adrenal androgens and the low gonadotrophin levels secondary to high glucocorticoid levels. Pregnancy in patients with Cushing's syndrome is thus rare. However when patient do get pregnant, the course of pregnancy is usually complicated by severe maternal and fetal morbidity. Abortions, exaggerated pregnancy symptoms, hypertension, congestive cardiac failure, diabetes and preterm labour often lead to birth of a premature growth restricted baby[1].

There are many etiologies of Cushing's syndrome and differences exist between gravid and non gravid patients. In a review of 108 non-gravid patients, Orth and Liddle found that the most common cause of Cushing's syndrome was pituitary-dependent adrenal hyperplasia[2]. In contrast Buescher et al found that in 58 gravid patients, the main etiology was benign adrenal adenoma[1]. A possible explanation for this difference is that adrenal adenomas are purely cortisol producing tumors with minimal androgen production, thus ovulation and subsequent pregnancy is possible as in the case for this patient. In addition, cases of exacerbation of Cushing's syndrome in pregnancy have been documented with symptoms aborting after termination of pregnancy[3,4]. Placenta ACTH as well as corticotropin releasing hormone-like compounds may have stimulated a latent or intermittently functioning adrenal adenoma in these cases[5]. Such cases may well remain undiagnosed and especially in primigravid patients, the aggravated symptoms experienced as a result of Cushing's syndrome may well be attributed to pregnancy itself.

Diagnosis of Cushing's syndrome in pregnancy may be difficult because of the similarities between the normal physiological changes in pregnancy and the Cushingoid state. Weight gain, striae, edema, hypertension and diabetes are not uncommon findings in pregnancy. Biochemical diagnosis of Cushing's syndrome is also complicated by the hypercortisolism associated with pregnancy. In addition, estrogen induces an increase in corticosteroid binding protein leading to a raised total serum cortisol concentration[6]. Diurnal variations of plasma cortisol though preserved may be blunted slightly and this remains the most significant difference between Cushing's syndrome and the normal hypercortisolism state of pregnancy[7]. Plasma levels of ACTH increases in pregnancy although the absolute levels remain lower in the gravid compared to the non-gravid patient.

Maternal morbidity associated with Cushing's syndrome in pregnancy includes hypertension, preeclampsia, heart failure, diabetes, wound breakdown and even death[8]. Hypertension is the most common complication in pregnant patients with Cushing's syndrome occurring in up to two thirds of patients reported[1]. The hypertension is usually severe and when uncontrolled can lead to heart failure and maternal mortality. Symptoms of congestive cardiac failure may be confused with pulmonary and peripheral edema of preeclampsia.

Pregnancy outcomes are associated with high perinatal morbidity and mortality. Premature birth forms the majority of complications often with the birth of a growth restricted baby. Though the cause of the growth restriction may be contributed by the associated complications of hypertension and diabetes, the excessive cortisol state may be a contributory factor as well[9]. In addition to the problems associated with premature birth, neonatal Addisonian crisis have also been documented[10].

The aim of treatment in Cushing's syndrome in pregnancy is to eliminate the hypercortisolism state. This often results in better maternal and fetal outcome[1].

Surgical intervention is the mainstay of treatment when there is an adrenal adenoma. Surgery can be carried out safely in midtrimester via the transabdominal, lateral or posterior approaches. The transabdominal and lateral approaches provides better exposure for larger tumors. In addition, the transabdominal approach also provides assess to the fetus. The posterior approach provides a more superficial and extraperitoneal surgical access. Meticulous control of maternal blood pressure must be undertaken in the perioperative phase to prevent a compromise of placenta perfusion to the fetus. Replacement steroid therapy after surgery must be continued postoperatively to prevent Addisonian crisis.

Medical treatment of Cushing's syndrome in pregnancy includes the administration of Metyrapone, Aminoglutethimide and Cyproheptadine. Metyrapone is an inhibitor of 11-β-hydroxylase and it reduces the serum cortisol levels in gravid patients with adrenal adenoma. Aminoglutethimide is a glutarimide that inhibits several steps of the steroid biosynthetic pathway[13] whereas Cyproheptadine is a serotonin antagonist that decreases production of corticotrophin-releasing hormone[14]. Although these medications have been used in the treatment of Cushing's syndrome in pregnancy, the control of cortisol level with Metyrapone was found to be unsatisfactory with a resultant exacerbation of hypertension[11,12]. There is also a lack of information available with regards to their treatment success as well as fetal effects. Hence medical treatment of Cushing's syndrome remains an unpopular choice.

This patient was referred for the problem of severe hypertension at 26 weeks gestation. On admission, her blood pressure was 166/102 mmHg and there was significant proteinuria. In this patient, the physical signs of Cushing's syndrome at presentation were fairly obvious and the diagnosis was established without much difficulty. Following initial management to stabilize her blood pressure, a detailed history suggested that the onset of her Cushing's syndrome was rather insidious. Her initial changes in the skin and body figure were previously attributed to pregnancy. In addition, as this was her first pregnancy, it was not uncommon for her to develop early pre-eclampsia.

This case highlights the importance of considering secondary causes of hypertension in pregnancy especially when the presentation is early. A keen sense of suspicion is required such that features of Cushing's syndrome may be differentiated from the physiological changes in pregnancy.

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