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Review

The medical management of Cushing's syndrome during pregnancy

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ABSTRACT

Cushing's syndrome during pregnancy is a rare metabolic condition that is associated with high maternal and foetal morbidity. Clinical symptoms may mimic those of normal pregnancy. A diagnosis is best made based on clinical presentation, laboratory and imaging findings as well as a high index of suspicion. Medical management with anti-steroidogenic agents such as metyrapone has been shown to be effective, but surgery is usually the recommended treatment option. Its main limitation is optimal timing of the procedure in late first trimester or early second trimester to prevent spontaneous termination of pregnancy. We describe our experience and management of a 39-year-old patient with uncontrolled hypertension at 25 weeks gestation which was later diagnosed as ACTH independent Cushing's syndrome and had a favourable pregnancy outcome. The role of medical therapy and its challenges, as well as its impact on pregnancy outcomes, were explored by a literature search conducted through Pubmed and Medline databases. A total of 12 patients with Cushing's syndrome during pregnancy were reported to have been managed with metyrapone, with ketoconazole being studied to a significant degree in three cases. Of these women, 53% delivered close to term and 20% developed pre-eclampsia. Despite two neonatal deaths and one stillborn reported, medical management appeared effective in controlling hypercortisolemia during pregnancy with strict monitoring of blood pressure and foetal surveillance. It remains the only active management in the setting of pregnancy-induced Cushing's syndrome, and has shown to be a viable option in controlling serum cortisol levels especially as an adjunct to surgery as reflected in four cases. A multidisciplinary approach towards an individualised management process is warranted with medical management to ensure a safe maternal and foetal outcome.

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1. Introduction

Cushing's syndrome (CS) is a disorder caused by prolonged abnormal exposure to excess glucocorticoids, leading to significant consequences in the patient if left untreated [1]. Fortunately its association in pregnancy is rare, with only small and multiple case

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series reports in the literature. CS that occurs during pregnancy is a condition of great concern as it increases the risk of maternal and foetal morbidity [2]. Despite major advances in diagnosis and therapy, identifying CS is frequently a challenge for the clinician due to the normal physiological hypercortisolemia that accompanies pregnancy. Clinical features of weight gain, stretch marks, fatigue, back pain, mood changes and facial roundness are common in pregnancy but may also be symptoms of CS. In addition, the development of elevated blood pressure and blood glucose levels – both common in CS – may further affect the outcome of the pregnancy itself. Active management of hypercortisolemia with either medical or surgical therapy is associated with a trend towards live births [2], and should be individualised due to the rarity of disease and lack of treatment guidelines. The aim of the present paper is to share our experience in diagnosing and managing a case of CS in one of our patients while she was pregnant, and to present a review of the current literature which guided our treatment choice.

1.1. Case study

A 39-year-old Caucasian woman, gravida 3 para 2, was admitted at 25 weeks' gestation from the antenatal clinic with hypertension. Her last two pregnancies had been uncomplicated, with the first delivery carried out through emergency caesarean section for a failed instrumental delivery at 39 weeks' gestation, and the next a spontaneous vaginal delivery at 30 weeks' gestation. This current pregnancy was of the same paternity as the previous two, and her medical history was significant for hypothyroidism that was being treated with thyroxine.

On presentation the patient's blood pressure was 173/99 mmHg. Clinically she exhibited a number of features associated with Cushing's syndrome: obesity (body mass index 31 kg/m^2), an obvious buffalo hump with supraclavicular fat pads, abdominal striae and facial acne. Her laboratory investigations are described in Table 1. A magnetic resonance imaging (MRI) of the abdomen revealed a 40 mm diameter bi-lobed homogenous lesion in the left adrenal gland. She was diagnosed with adrenocorticotrophic hormone (ACTH) independent CS. Her ACTH and serum cortisol levels were measured twice-hourly for a 24 h period, with ACTH levels consistently less than 10 ng/L and cortisol levels between 980 and 1091 nmol/L. Given her late gestation and previous history of preterm labour, surgical intervention was considered inappropriate.

The patient was medically managed with 250 mg of metyrapone, given twice daily from 27 weeks' gestation onwards, where the dose was titrated in response to her weekly urinary free cortisol (UFC) levels to ensure a downward trend (Fig. 1). She was further commenced on dual anti-hypertensive treatment with methyldopa and nifedipine, and was subsequently diagnosed with gestational diabetes that was in turn managed with insulin. Pre-eclampsia was suspected at 32 weeks, with the patient undergoing successful vaginal delivery at 35 weeks after spontaneous onset of labour. She delivered a liveborn male infant weighing 2800 g (75th centile) with Apgar scores of 6 and 8 at 1 and 5 min, respectively.

Postnatally the patient's serum cortisol remained elevated (420–489 nmol/L) with no diurnal variation. Bone densitometry showed no evidence of osteoporosis. Metyrapone and nifedipine were continued until a laparoscopic adrenalectomy was performed six weeks post-partum. Histopathology confirmed a 40 mm benign adenoma comprised of large polygonal richly vascular cells with no evidence of malignancy. On follow-up over the next two years she has remained free of any signs or symptoms to suggest a relapse of her CS.

Table 1
Laboratory investigations.

Investigations	Case values	Non-pregnant reference range[a]
Morning serum cortisol (nmol/L)	890	120–620
Midnight serum cortisol (nmol/L)	853	85–460
Plasma ACTH (ng/L)	<10	10–60
24 h UFC (nmol/24 h)	4882	200–1460
Serum cortisol following low dose (1 mg) DST (nmol/L)	892	<50
Serum cortisol following high dose (8 mg) DST (nmol/L)	824	<5

ACTH, adrenocorticotrophic hormone; UFC, urinary free cortisol; DST, dexamethasone suppression test.
[a] Reference ranges for Institute of Medical Veterinary Sciences (IMVS) Laboratory, South Australia.

2. Materials and methods

A literature search of all case studies published in English was conducted using the Pubmed database. Following this, we reviewed all the reported cases of hypercortisolemia during pregnancy that had been managed with medical therapy, including those that were managed in preparation for surgery. The earliest publication dated back to 1975, with the most recent in 2011. Keywords used were "Cushing's syndrome", "pregnancy", "hypercortisolism", "metyrapone", and "ketoconazole". Primary end points were maternal characteristics as well as foetal outcome.

3. Results

Twelve reports showing a total of 15 women with medically managed CS were identified (Table 2). Metyrapone was the most commonly used medical therapy (n = 12), with doses ranging from

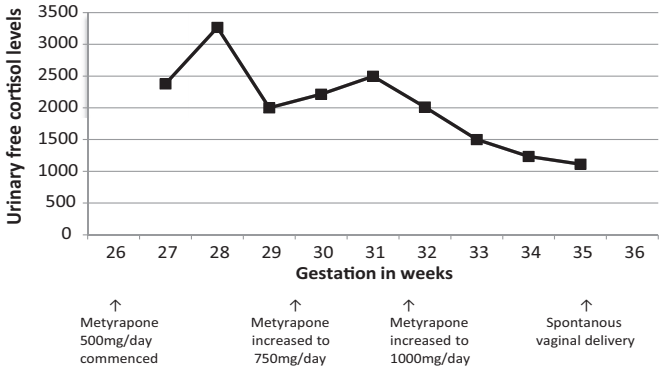

Fig. 1. Biochemical course of 24-h UFC levels (black line) shown over the second and third trimester with metyrapone treatment.