

# Remission during Pregnancy of Severe Chronic Hypertension due to 11- $\beta$ Hydroxylase Deficiency

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## Abstract

When hypertension is a result of an underlying identifiable abnormality, the latter's early discovery can lead to a timely cure of the hypertension and the prevention of its complications. We present a case of high blood pressure lowered by pregnancy, suggestive of an endocrine cause. This was confirmed following a detailed history which revealed severe hypertension intractable to therapy, yet which remitted during pregnancy. A diagnosis of 11-beta hydroxylase deficiency was made consequent upon the finding of raised serum 11-desoxycorticosterone levels. The blood pressure was finally controlled with glucocorticoid replacement therapy and spironolactone.

## Case Report

In August 2000, a 32-year-old lady was referred to the endocrine clinic with a six year history of uncontrolled hypertension despite aggressive medical treatment.

At the age of 26, her general practitioner found a blood pressure of 160/110 mmHg on routine checking. The only blood pressure readings taken prior to this occasion were during her first pregnancy, two and a half years previously. They were all within normal range. Her blood pressure was 140/98 mmHg at her first medical out-patients visit in July 1994 (Figure 1). Extensive investigations for a secondary cause were normal and included a renal ultrasound, an intravenous urogram and an isotope diethylenetriamine penta-acetic acid (DTPA) renal scan with captopril.

## Keywords

11-beta hydroxylase deficiency, pregnancy, hypertension

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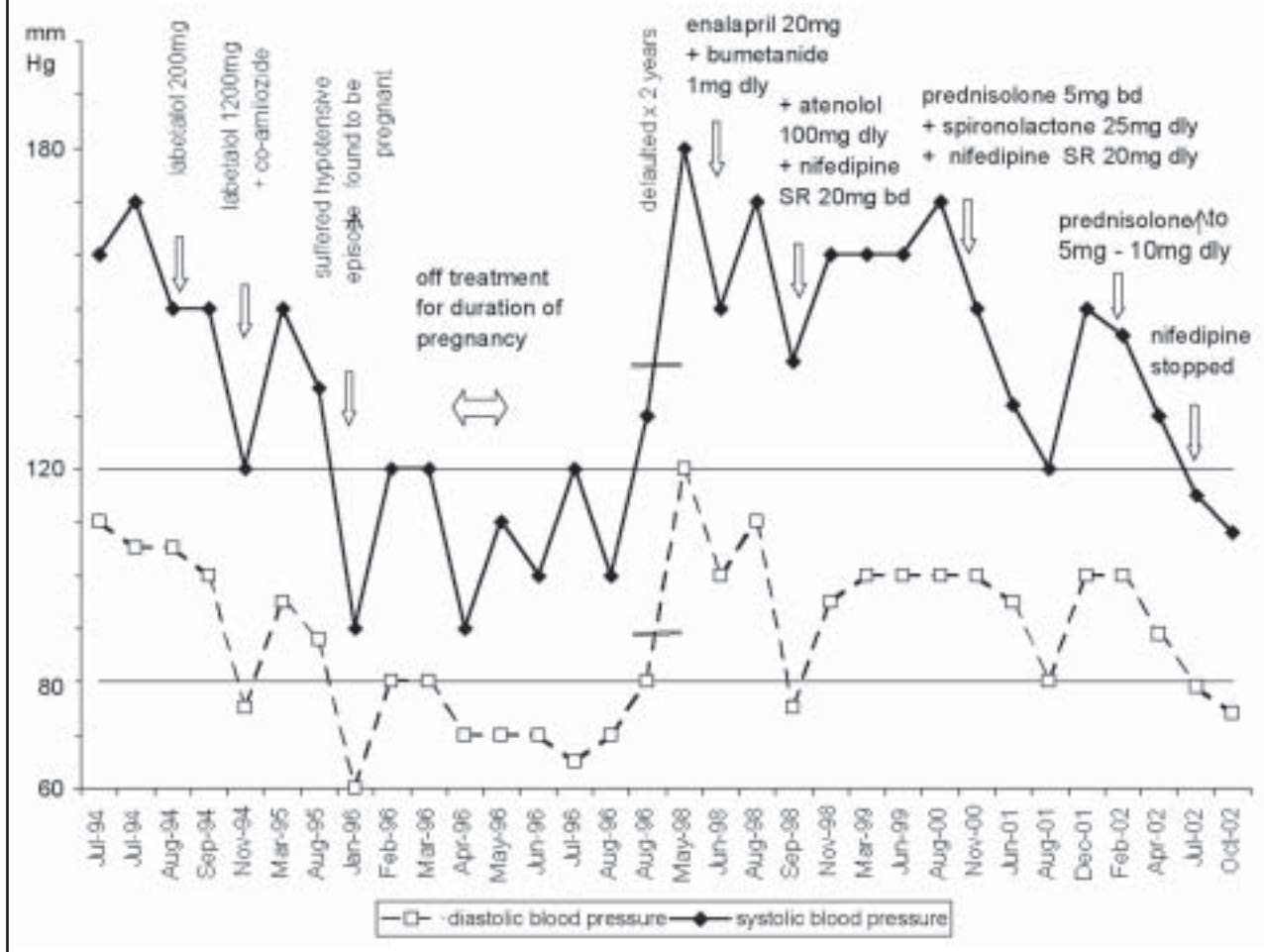
An echocardiogram showed mild mitral valve prolapse but normal sized ventricular walls. Her serum sodium and potassium were 144 mmol/l (normal range 135 - 145 mmol/l) and 3.8 mmol/l (normal range 3.5 - 5.1 mmol/l) respectively. Her blood pressure, over the next 18 months, remained persistently above 150/90 mmHg despite a step-wise increase in labetalol to a maximum dose of 1200 mg daily and the early addition of co-amlozide 2.5/25 mg once daily (Figure 1).

Her general practitioner reviewed her in the first week of January 1996 after an episode of syncope. Her blood pressure had dropped to 90/60 mmHg. She was six weeks pregnant with her second child. He stopped her treatment. One week later, at her first antenatal clinic visit, her blood pressure was 120/80 mmHg. She remained normotensive throughout her pregnancy, even though she had stopped all antihypertensive treatment (Figure 1).

She presented again one and a half years later, in April 1998, with a blood pressure of 180/120 mmHg despite treatment with enalapril 20 mg daily and bumetanide 1 mg daily (Figure 1). She was extensively reinvestigated for a renal cause; including a renal angiogram that was normal. The only abnormality was a serum potassium as low as 2.8 mmol/l. A suspicion of Conn's syndrome was excluded biochemically and her treatment was stepped up further. Increased doses of ACE inhibitors and the addition of a calcium-channel blocker failed to achieve satisfactory blood pressure control (Figure 1).

At her first endocrine clinic visit, her blood pressure was 170/100 mmHg in both arms whilst sitting. She was taking enalapril 20 mg, bumetanide 1 mg and atenolol 100 mg in once daily doses and nifedipine slow release 20 mg twice a day (Figure 1). Her menstrual cycles were regular since menarche at the age of 11.5 years. There was no abnormal pigmentation. On direct questioning, she admitted to a slight excess of body hair, especially in the peri-areolar region. Her sister suffered from central diabetes insipidus and a maternal aunt had had surgical removal of a pituitary macroadenoma. Her serum potassium was 2.8 mmol/l and her serum sodium was 140 mmol/l. 9 am cortisol was at the lower range of normal. It was important to exclude an endocrine cause for her hypertension in view of her age and low serum potassium. Although not a clearly described phenomenon, the normal blood pressure in both pregnancies strengthened the argument for an endocrine cause.

**Figure 1:** Blood pressure readings from 1994 - October 2002. Blood pressure in mmHg on y axis; date scaled by category (not time) on x axis



17-hydroxy progesterone was mildly elevated: 2.1 ng/ml (day 10; normal range 0.3-1.0 ng/ml). Urinary 17-ketosteroids and serum dihydroepiandrosterone (DHEA) sulphate were within the normal range. Erect and supine aldosterone and plasma renin activity were normal. Thyroid function tests (TFTs), day 10 follicular stimulating hormone (FSH), day 10 luteinising hormone (LH) and sex steroid levels were all normal for a menstruating female. Serum 11-desoxycorticosterone was 4081 pmol/l (normal range 30-420 pmol/l). Stimulation with adrenocorticotropin (ACTH) produced a rise at 60 minutes to 16570 pmol/l (forty times normal). Her cortisol and 17-alpha hydroxy progesterone levels showed a normal rise on dynamic testing with ACTH. This confirmed the diagnosis of partial 11-beta hydroxylase deficiency. An echocardiogram showed mild left ventricular hypertrophy and a hypocontractile left ventricle. A computed tomography scan with fine cuts of the adrenal glands confirmed mildly enlarged adrenals.

Glucocorticoid replacement therapy was started and stepped up until 24-hour ambulatory readings confirmed successful control of the blood pressure. 9 am cortisol and 11-desoxycorticosterone were successfully suppressed. Serum sodium and potassium remained in the normal range. The

antihypertensive treatment was successfully tailed down to spironolactone 25 mg daily (Figure 1).

## Discussion

Deficient 11-beta hydroxylase activity (mutation at CYP11B<sup>1</sup> on chromosome 8) accounts for 5-8% of cases of congenital adrenal hyperplasia.<sup>1</sup> This equates to a global incidence of 1 in 100,000 live births.<sup>2</sup> A considerably higher incidence is described in Turks and in Jews of Moroccan or Iranian descent.<sup>3</sup>

The patient discussed above has a mild type of the classical form of 11-beta hydroxylase deficiency. Patients in this group may have normal basal levels of ACTH, cortisol and its metabolites. However, dynamic testing with ACTH shows an exaggerated rise in cortisol metabolites. This indicates that there is partial impairment of 11-beta hydroxylation that, under basal conditions, does not result in maximum endogenous secretion of ACTH and plasma cortisol levels remain within normal range.<sup>4</sup> This group of patients is more likely to be diagnosed in early adulthood and to be hypertensive at diagnosis than patients with a complete defect.<sup>5</sup>

Patients with congenital adrenal hyperplasia and hypertension were first observed in the 1950s. Increased secretion of 11-deoxycortisol was assumed to be the cause of

hypertension in 11-beta hydroxylase deficiency but the correlation appears unclear. Blood pressure appears to be independent of 11-deoxycortisol levels. Importantly, hypertension may persist after suppression of 11-deoxycortisol<sup>5</sup> and in fact, continued treatment with anti-aldosterone agents is often required. Possibly, one of the metabolites of deoxycortisol that is a more potent mineralocorticoid, such as the 19-nor metabolite, is responsible for the raised blood pressure.<sup>6</sup>

Despite a striking expansion in blood volume and the activation of the renin-angiotension-aldosterone mechanism, blood pressure tends to fall during pregnancy in both normotensive and chronically hypertensive females up to a low at twenty eight weeks gestation, after which levels tend to return to non-pregnant ones.<sup>7</sup> It is likely that a number of mechanisms mediate this adaptation. Complete remission of hypertension during pregnancy has been described in cases of primary aldosteronism and it is suspected that this is secondary to raised progesterone antagonising the excessive aldosterone secretion.<sup>8,9</sup> Remission of hypertension in pregnant patients suffering from 11-beta hydroxylase deficiency has not been previously described. The authors speculate that this phenomenon is secondary to the direct suppression of ACTH levels by oestrogens or progesterones<sup>10</sup> with a consequent suppression of the feedback loop stimulating cortisol production in the adrenals. This hypothesis will be hard to prove due to the apparent rarity of this condition.

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## PALS undergoes a metamorphosis into the European fold

The Paediatric Advanced Life Support (PALS) Course continues to be an ever-popular, successful, annual event.

This year's course was notable for three reasons - firstly, it was the first course run along European and not UK guidelines, hence the metamorphosis to European Paediatric Life Support - EPLS (Malta). Secondly, this was one of the very few PALS or EPLS courses ever held locally and abroad, where no candidate was required to re-sit the basic life support testing! Full credit to this year's cohort who were extremely enthusiastic and, incidentally, included several paediatricians taking the course for a second time as a refresher! Thirdly, Dr Tanya Esposito established a 'first' by taking responsibility as the first home-grown Course Director.

As always, this initiative requires considerable organisation and support and remains indebted to the financial backing of the Health Division, as well as our fellow EPLS instructors from the United Kingdom who offer their time and services for no reward. We are also extremely

grateful to the Maltese Paediatric Association for their sponsorship, the Institute of Health Care for use of their excellent premises, the SAS Radisson for hosting the Course dinner, the ever-present Mr Charles Messina and the local EPLS Organising Committee and Faculty including Drs. Tanya Esposito, Mario Zerafa, Maryrose Cassar, Jonathan Joslin, Debbie St John and Mrs Annabelle Abela. To all those involved in EPLS - a heartfelt thank you! Ultimately, however, it is the enthusiasm and eagerness of the candidates themselves that makes this course such a pleasurable and worthwhile event. We are delighted to announce that we have recently applied to register Malta as a free-standing 'EPLS' training centre (rather than an offshoot of Great Ormond Street Hospital's training facility) and look forward to our official registration with enthusiasm.

**Simon Attard Montalto**

Secretary, EPLS (Malta) Organising Committee