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Iatrogenic Cushing's Syndrome secondary to the Combined Oral Contraceptive Pill in a patient with Congenital Adrenal Hyperplasia

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Introduction:

Congenital Adrenal Hyperplasia (CAH) is a rare genetic disorder characterised by deficiency of cortisol and/or mineralocorticoid hormones with over production of sex steroids.

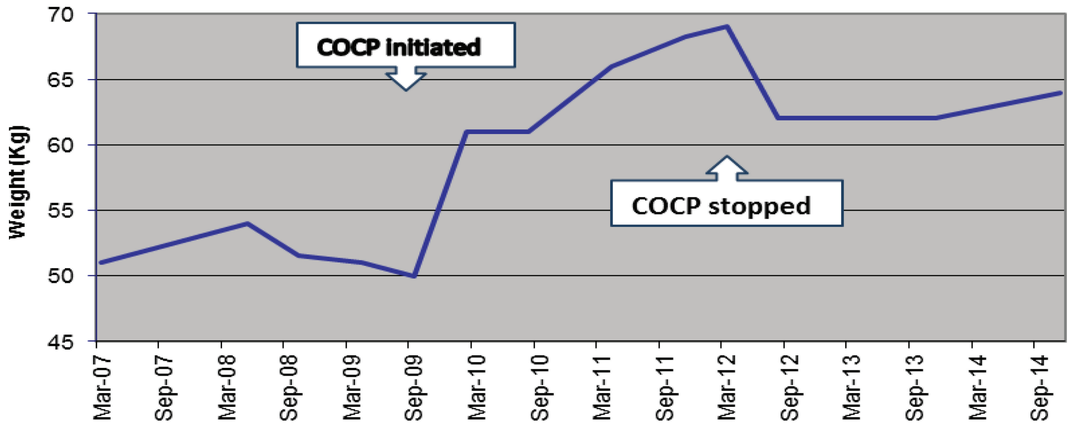
21-hydroxylase deficiency is the commonest cause of CAH accounting for 95% of cases[1,2]. Severe form of classic CAH occurs in 1 in 15,000 livebirths worldwide[3,4].

The goals of treating 21-hydroxylase deficiency in women is to replace the deficient steroid hormones, to lower the adrenal precursors and sex steroids. Most commonly used regimens are prednisolone once a day or hydrocortisone split into two or three doses.

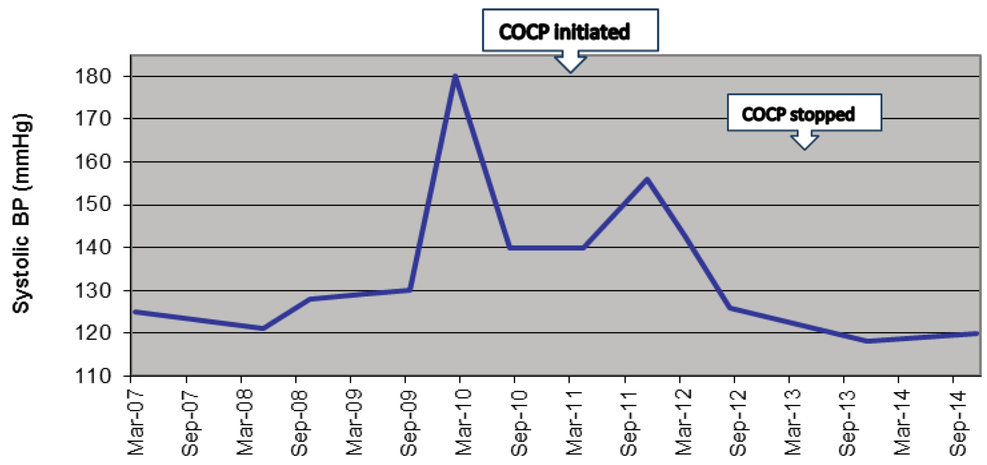
Case:

A 30 year old women with CAH diagnosed at birth was on replacement with hydrocortisone and fludrocortisone. She was investigated for ongoing diarrhoea by the gastroenterologist and was subsequently diagnosed with Irritable Bowel Syndrome (IBS). She was then started on buscopan and codeine phosphate for symptom relief. However during her menstrual cycle her abdominal symptoms were not sufficiently controlled. She was thus commenced on Microgynon, a Combined Oral Contraceptive Pill (COCP). Within a year of initiation she developed cushingoid features, became hypertensive and started gaining weight. Her weight increased from 50kg to 61kg at five months, 66kg at 12 months and 69kg at 24 months. Her blood pressure increased from 130/82mmHg to 180/100mmHg with in five months after starting on COCP. As her IBS symptoms were well controlled on the COCP initially the dose of fludrocortisone and hydrocortisone were reduced. Blood pressure improved but her weight was persistently high. The COCP was then changed to a progesterone only pill which resulted in improvement of her Cushingoid features. She lost 7kg in weight and her blood pressure improved within six months.

Weight:



Systolic blood pressure:



Discussion:

Cortisol is the main glucocorticoid hormone, the majority of which is circulated bound to Cortisol Binding Globulin (CBG). Only about 5% of the circulating cortisol is free. Cortisol action is terminated by conversion into inactive forms by various enzymes. It is mainly metabolised in the liver. It is reduced, oxidised and hydroxylated, the products of which are made water soluble by conjugation to sulphate or glucuronic acid to facilitate excretion in urine. 6-beta hydroxylation of cortisol occurs in the liver by the CYP3A4 enzyme. Medications which can affect hepatic enzymes can impair cortisol metabolism leading to either increased accumulation or increased excretion.

Pregnancy and oestrogen replacement increases total cortisol by increasing CBG. Sanna et al. demonstrated that the COCP can cause modest reduction in CYP3A activity7 which could result in increase in free cortisol. Slayter et al. studied the effects of the COCP on the pharmacokinetics and pharmacodynamics of methyrprednisolone. They found reduced methylprednisolone clearance with subsequent increased in its half-life in these patients6. In addition Pleger et al8 showed that both unbound and total plasma cortisol levels are increased in oestrogen treated patients.

Our patient developed cushingoid features after starting the COCP. She clinically improved within 6 months of stopping the COCP with no significant change in steroid dose. It is highly likely that she developed increased total and free cortisol due to effect of the COCP on cortisol metabolism resulting in ICS.

Conclusion:

This case illustrates that apart from over-replacement with glucocorticoids, ICS may also develop secondary to drug interactions causing an increase in both free and total cortisol. Clinicians should be wary of starting such oestrogen containing oral drugs in patients on glucocorticoids. Transdermal oestrogen replacement doesn't cause an increase in CBG and is thus safe to use in such patients.

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