Carney's complex: a successful pregnancy after bilateral adrenalectomy

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Carney's complex is a rare inherited disease of multicentric tumours of multiple organs. It is inherited in autosomal dominant fashion. Primary pigmented nodular adrenocortical dysplasia (PPNAD) is a component of Carney's complex [1].

Primary pigmented nodular adrenocortical dysplasia is an exceedingly rare cause of Cushing's syndrome in young adults. It is characterized by non-adrenocorticotropic hormone-dependent hypersecretion of cortisol by multiple, pigmented nodules of hyperplastic adrenocortical cells. Treatment for PPNAD involves bilateral adrenalectomy because of high recurrence risk after unilateral or partial adrenalectomy. Cohen *et al.* reported a successful pregnancy after unilateral adrenalectomy for PPNAD [2]. Kidney stones were reported in about 15% of Cushing's syndrome cases [3]. The susceptibility of the patients to nephrolithiasis is probably due to the synergic effect of several lithogenic factors, such as increased urinary excretion of calcium, phosphorus, potassium, uric acid, cystine, and oxalate and decreased urinary excretion of citrate. Chronically elevated urinary excretion of these elements represents a direct and/or indirect risk factor for kidney stone formation. Unlike these factors, citrate and potassium are protective factors by inhibiting urinary crystal formation. The prevalence of nephrolithiasis in the patients remained still higher than in the general population after disease remission, even if lithogenic factors had normalized [4]. All Cushing's syndrome patients must be evaluated very carefully for lithogenic factors and kidney disease.

Here we present a successful pregnancy three years after bilateral adrenalectomy due to Cushing's syndrome secondary to Carney complex in a 28-year-old nulliparous woman.

A 24-year-old previously healthy female presented with a 4-week history of fatigue, weight gain and alopecia. Clinical examination revealed central obesity, plethora, moon face, buffalo hump, atrophy in muscles of extremities, pigmented skin lesion, arrhythmia and severe hypertension. Serum ACTH level was low and cortisol was high at 09:00 h. Serum cortisol at 09:00 h also failed to suppress with either low-dose or high-dose dexamethasone suppression tests according to standard criteria [5]. Her plasma electrolytes, fasting glucose, thyroid function tests and liver function tests were in the normal range. Electrocardiogram (ECG) showed sinus

tachycardia and Wolf Parkinson White syndrome which subsequently responded well to propafenone 150 mg tid. Echocardiogram was reported to be normal. Magnetic resonance imaging (MRI) of pituitary and hypothalamus revealed a cyst of Rathke's cleft around a millimetre in size. An abdominopelvic MRI showed bilateral multinodular appearance in adrenal glands, supporting a diagnosis of hyperplasia, and bilateral renal calculi. She had a right femoral neck fracture secondary to osteoporosis whilst under therapy for Cushing syndrome. Surgery for this fracture was planned after bilateral adrenalectomy. Preoperatively she received metyrapone for 6 weeks in order to normalize her serum cortisol in preparation for surgery. The pathology report for the bilateral adrenalectomy specimen revealed PPNAD. This pathological finding, combined with the presence of pigmented skin lesions, established the diagnosis of Carney complex. The post-operative course of the patient was unremarkable while she was on prednisolone 5 mg bid and fludrocortisone 0.1 mg daily replacement therapy. A prosthesis for femoral neck fracture was inserted 6 months after bilateral adrenalectomy. She subsequently had extracorporeal shock wave lithotripsy (ESWL) for multiple calculi. One year later her weight was decreased to 51 kg and 2 years later she had normal serum Ca, P and PTH levels along with a bone density which was appropriate for her age. She had regular menses 1 year after bilateral adrenalectomy and she was married at 26 years. Her ACTH levels were stable and Nelson syndrome did not complicate the course.

She got pregnant under replacement therapy at the age of 27 years. She had an uncomplicated pregnancy until 32 weeks of gestation. At this stage she was hospitalized for the diagnosis of suspected preterm premature rupture of membranes (PPROM) and intrauterine growth retardation (IUGR). Preterm premature rupture of membranes was not confirmed but the fetus was monitored for IUGR. The fludrocortisone dose was stable throughout pregnancy but the prednisolone dose was increased 1.5 times at the third trimester. Signs and symptoms of neither hypo/hypercortisolism nor electrolyte imbalance were noted during pregnancy. Gestational diabetes did not develop. She was given a stress dose of 100 mg of IV hydrocortisone before caesarean section for breech presentation and hydrocortisone weaning was scheduled for the following 3 days. The dose regimen prior to pregnancy for fludrocortisone and prednisolone was resumed 3 days after the operation. A 2850 g healthy male infant was delivered at gestational age of 37 years. No fetal or maternal complications were observed.

Although women with Cushing's syndrome rarely conceive, successful pregnancies have been reported [6]. But maternal and fetal mortality and morbidity rates of such pregnancies are high [7]. Such mothers are prone to diabetes mellitus, hypertensive disorders of pregnancy, cardiac failure, pulmonary oedema and even death, and their fetuses are also prone to abortion, and intrauterine and neonatal death [7].

Primary pigmented nodular adrenocortical dysplasia is a rare cause of Cushing's syndrome and is generally treated with bilateral total adrenalectomy due to high recurrence risk following partial or unilateral adrenalectomy. The main risks of bilateral adrenalectomy are hypoadrenalism and adrenal crisis. Pregnancy planning in patients with PPNAD requires meticulous multidisciplinary medical care and detailed patient information because hypoadrenalism after operative treatment may also be associated with maternal and fetal complications during pregnancy and puerperium. Cohen *et al.* reported a PPNAD case managed with unilateral adrenalectomy in order to preserve adrenal function for an anticipated pregnancy [2]. The pregnancy was uneventful and the fetal development was normal without any steroid therapy. But he also emphasized the need for long-term meticulous follow-up due to the fact that remission might be temporary. The long-term outcome of this case was not available.

Successful pregnancy outcomes in women with Addison's disease have been reported by several authors since the mid-1960s [8]. Many cases of bilateral adrenalectomy have also been reported, but no data related to their fertility after the procedure are available in the English literature. On the other hand, scarce case reports of bilateral adrenalectomy during pregnancy are available. Berends *et al.* first reported a case of bilateral adrenalectomy due to bilateral pheochromocytoma during pregnancy but they did not give further details on postoperative follow-up of the case [9]. Phupong *et al.* also reported a case of bilateral adrenalectomy during pregnancy [10]. But this case received glucocorticoid replacement only and a growth-retarded fetus was delivered due to fetal compromise at gestational age of 31 years. Glucocorticoid treatment during pregnancy reduces birth weight in animal models, including non-human primates and humans [11-14]. Birth weight reduction is most notable when glucocorticoids are administered in the latter stages of pregnancy [12], presumably reflecting the catabolic actions of these steroids, actions most likely to become manifest as reduced birth weight during the period of maximum fetal somatic growth. In some studies, antenatal glucocorticoids are associated with a reduction in birth weight [13]. Compared with betamethasone and dexamethasone, which cross the placental barrier in ratios of 3 : 1 and 2 : 1, respectively, only 10% of

prednisolone crosses the placenta to reach the fetus. Glucocorticoid treatment is known to accelerate organ maturation at the expense of organ size, so it was also reassuring to find no difference in birth weight and head circumference [14].

Growth retardation also complicated our case despite additional mineralocorticoid replacement. Although the patient underwent physiological prednisolone replacement therapy, steroid replacement may cause growth retardation. The patient was not married and was not considering pregnancy just before the operation and an unexpected fracture of the femoral neck necessitated definitive curative treatment before she got married and pregnant.

Signs of both inadequate and excessive steroid treatment such as lethargy and hypotension during pregnancy must be monitored in these patients because plasma renin activity and plasma cortisol level are not used for dose titration of prednisolone and fludrocortisone in pregnancy [15]. Our case was normotensive and developed no electrolyte imbalance throughout pregnancy under both glucocorticoid and mineralocorticoid therapy. In spite of the absence of signs of lethargy in our case, the dose of prednisolone was increased 1.5 times at the third trimester in order to catch up with normally increasing serum cortisol levels as pregnancy progresses. Addisonian crisis is a life-threatening event in pregnant women and usually accompanies stressful conditions such as hyperemesis gravidarum, infection and labour. A stress dose of hydrocortisone, owing to its glucocorticoid and mineralocorticoid activities, should be administered in such situations. Following the stress dose and three-day hydrocortisone weaning in the postoperative period, the dose regimen prior to pregnancy was resumed in our case.

Maternal and fetal successful outcomes could also be obtained with meticulous multidisciplinary management in cases which have undergone bilateral adrenalectomy secondary to PPNAD.

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