

Case report**Cushing's syndrome in pregnancy:
Report of a case and review of the literature**

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Cushing's syndrome (CS) during pregnancy is a rare nosology with only a few cases reported in the literature. Misdiagnosis is common, as the syndrome may be easily confused with pre-eclampsia or gestational diabetes. CS during pregnancy is usually associated with severe maternal and fetal complications. A high degree of clinical awareness is therefore required to avoid miscarriage or premature delivery. We report an 18-year old female referred to our institution with amenorrhea and truncal obesity. Physical examination revealed cushingoid characteristics, including mild hypertension (130/100 mmHg). She was also found to be 8 weeks pregnant. A provisional diagnosis of CS was made based on plasma cortisol and adrenocorticotropin hormone (ACTH) measurements but the patient did not receive any relevant therapy. She eventually gave birth to a healthy full-term infant via vaginal delivery. A right adrenal adenoma was diagnosed post-labor and was subsequently treated with surgical resection. The patient's condition remained stable and 19 months after the adrenalectomy she gave birth to a second healthy full-term infant. Hydrocortisone (30 mg/day) was administered throughout the second gestation. Six months post-labor the treatment was discontinued after a normal hypothalamic-pituitary-adrenal (HPA) axis was ascertained.

Key words: Adrenal Adenoma, Cushing's syndrome, Pregnancy

PATIENT'S DESCRIPTION

An 18-year old female was admitted to our institution (July 1997) with secondary amenorrhea, hirsutism and truncal obesity. She was also found to be 8 weeks pregnant. Physical examination revealed moon face, purple striae throughout the abdomen, forearms and the inner thighs, bruising over pressure areas, a dorsocervical fat pad, acne and mild hypertension

(130/100mmHg). The Body Mass Index (BMI) was 29.5kg/m². The biochemical screening was largely consistent with Cushing's (CS). The daily serum cortisol variation was abnormal; the serum cortisol level was 860nmol/L at 08:00 (normal: 138-690nmol/L) and 530nmol/L at midnight (normal 138-414nmol/L). The plasma adrenocorticotropin hormone (ACTH) value was 2pmol/L at 08:00 (normal: 2-11pmol/L). Basal urine free cortisol (UFC) was 990nmol/24h (normal: 55-275nmol/24h). A pathology of the pituitary gland to which the CS could be attributed was unlikely owing to the relatively low plasma ACTH levels. An adrenal adenoma was considered to be the most likely cause

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of her condition. An ultrasound (US) of the adrenal glands was obtained, but on account of her obesity no special findings were depicted. Adrenal computed tomography (CT) scans could not be obtained due to gestation. The patient refused a magnetic resonance (MRI) scan because of gestation. No further intervention was thus possible. The patient also refused to receive any pharmacological treatment but remained under close surveillance throughout her gestation. Definitive diagnosis and treatment would be feasible post-labor. She eventually delivered a healthy full-term infant without any maternal or fetal complications. Three months post-labor she was clinically and biochemically re-assessed. All cushingoid characteristics were still present. Serum cortisol value was 758nmol/L at 08:00 (normal: 137-690nmol/L) and 728nmol/L (normal: 138-414nmol/L) at midnight. The plasma ACTH value was 2pmol/L at 08:00 (normal: 2-11pmol/L). The 24-hour UFC value was 785nmol/24h (normal 55-275nmol/24h). The serum cortisol levels were not suppressed with the low dose dexamethasone suppression test (0.5mg of dexamethasone per os every 6h for 2 days). Blood was drawn for cortisol at 08:00, before and 48 hours after the low dexamethasone dose. The daily urine collections were also carried out throughout the test period. An abdominal CT scan disclosed a 2.6cm x 2.2cm right adrenal mass, while pituitary MRI scan was normal. Fifteen months after her initial admission to



Figure 1. An abdominal CT after the patient's first labor depicted a 2.6 cm x 2.2 cm right adrenal mass. It was eventually identified as an adrenocortical adenoma, after a laparoscopic adrenalectomy.

our department, she underwent a laparoscopic right adrenalectomy. The mass was eventually identified as an adrenocortical adenoma. A Synacthen test was obtained and Hydrocortisone (30mg daily) was administered, followed by Prednisolone (5mg daily). Ten months post-operatively she had lost 18kg of weight, her blood pressure was normal and her menstrual cycle had normalized until she had become pregnant for a second time a few weeks earlier. She delivered a full-term infant without any maternal or fetal complications during gestation or delivery. Throughout the second gestation she was on Hydrocortisone 30 mg daily. This was continued for a further six months, and was subsequently discontinued when a Synacthen test demonstrated adequate function of her hypothalamic-pituitary-adrenal (HPA) axis.

DISCUSSION

Pregnancy is uncommon in women with CS, as hyperandrogenism and hypercortisolism suppress gonadotrophin secretion.¹ Oligomenorrhea and amenorrhea, which are directly associated with infertility, are also reported in approximately 75% of women of reproductive age diagnosed with CS.¹⁻³ Hunt et al⁴ first reported in 1953 cases of pregnancy in women with CS, and Buescher et al³ in the early 1990s reviewed a total of 58 patients and 65 pregnancies associated with CS. Half of the pregnant women with CS in this series were eventually diagnosed with an adrenal adenoma. Murakami et al in 1998⁵ reported that benign adrenal adenoma was the commonest cause of CS in pregnant women, in contrast to non-pregnant women where pituitary-dependent hyperplasia is the most common cause of CS. This may be attributed to the fact that patients with an adrenal adenoma are most likely to be purely Cortisol-producing, thus their ovulatory function remains unaffected.^{3,5,6} The patient in this report was eventually diagnosed as having an adrenal adenoma.

Misdiagnosis of CS in pregnant women is common. The syndrome may easily be confused with complications of pregnancy such as gestational diabetes and pre-eclampsia, which usually present the same symptoms as gestational CS. The rarity of this nosology has also led to a low degree of clinical suspicion, especially among obstetricians.^{7,8} Normal changes

during pregnancy include an increase in serum Cortisol, plasma ACTH and UFC levels, which further complicate the biochemical screening process for CS.⁹⁻¹¹ Pregnancy dramatically affects the HPA axis and the endogenous secretion of cortisol and ACTH, and therefore the definitive diagnosis for CS cannot be based solely on those two parameters.¹² Total and free serum cortisol concentrations have been reported to rise in parallel throughout gestation with total serum cortisol being 2- to 3-fold higher compared to non-pregnant controls.¹² However, the circadian rhythm of cortisol¹² and ACTH¹³ secretion is preserved. Plasma ACTH levels during pregnancy reach maximal levels during labor and delivery.¹² In a study by Carr et al the levels of serum ACTH increased almost 3-fold from the end of the first to the third trimester of pregnancy (23–59pg/ml measured by radioimmunoassay; 5–13pmol/liter) in normal women.⁹ Compared with healthy non-pregnant women, the plasma ACTH levels in pregnancy have been reported as either low⁹ or high.³⁷ The cause(s) for rising ACTH during pregnancy include placental synthesis and release of Corticotropin Releasing Hormone (CRH) and ACTH, pituitary desensitization to cortisol feedback or enhanced pituitary responses to corticotrophin-releasing factors. The high levels of placental CRH in plasma during the latter half of pregnancy are the main cause of rising cortisol during pregnancy.¹³ Lindsay et al have proposed that, during the second and third trimesters of gestation, UFC levels greater than 3 times the upper normal limit should be taken as a credible primary indication of CS.⁸ Ultrasound

adrenal imaging and plasma ACTH levels should be considered as the primary diagnostic tools in the differential diagnosis of gestational CS.⁸ Night-time salivary Cortisol (NSC) has also been suggested as a useful first-line screening test for CS,¹⁴ but its efficacy has not yet been proven in pregnant women. Pituitary MRI with gadolinium enhancement should be obtained in all non-pregnant patients with ACTH-dependent CS, as it provides a definitive diagnosis in most cases of pituitary adenomas.¹⁵ During pregnancy, however, the administration of gadolinium has not been proven to be safe and MRI is contraindicated, at least during the first trimester, due to the potential for teratogenicity.¹⁶ However, there have been many reports on the use of MRI during pregnancy for the management of other acute pathologies and no adverse effects were observed.¹⁷ Therefore, until imaging issues during pregnancy have been fully resolved, diagnosis of gestational CS is mainly dependent upon a high index of suspicion, clinical examination and relevant biochemical tests and ultrasonography of the adrenals. Abdominal CT and pituitary MRI should be performed as soon as possible post-labor to secure the diagnosis of CS and verify the existence of adrenal or pituitary gland pathologies.

CS in pregnancy is usually associated with an increased incidence of abortion, premature labor, gestational diabetes and glucose intolerance, cardiac failure, pulmonary edema, hypertension, myopathy, pre-eclampsia, poor wound healing and higher maternal and fetal morbidity rates.^{1,3,5,7,18,19} Viaordot et al reported two cases of pregnancy in patients

Table 1. The patient's pertinent data.

Biochemical Results	Morning serum cortisol (08:00) [nmol/L]	Evening serum cortisol (midnight) [nmol/L]	Plasma ACTH (08:00) [pmol/L]	Basal Free Urine Cortisol [nmol/24h]	Leukocyte Count	Blood Glucose [mmol/L]
1st admission	860 (normal: 138 - 690)	530 (normal: 138 - 414)	2 (normal: 2 - 11)	990 (normal: 55 - 275)	15600	5.5 (normal: 3.9 - 6.1)
Re-evaluation 3 months post labor	758	728	2	785	11900	5.4
Re-evaluation post adrenalectomy	68	72	1	42	9900	4
Re-evaluation during the 2nd gestation	91	58	3.5	–	10300	4.5
Final re-evaluation	502	201	11	187	5400	4.2

with CS, who developed a severe, sudden and early HELLP syndrome (Hemolytic anemia, Elevated Liver Enzymes, Low Platelet count), which eventually progressed to fetal death.¹⁴ Fetal complications, such as intra-uterine growth retardation, are also common.^{1,5} Fayol et al presented a case of transient hypertrophic obstructive cardiomyopathy in a newborn whose mother had hypercortisolism due to a primary adrenal lesion.²⁰ Perinatal death rates are generally reported to be higher in women with gestational CS compared to normal women.⁸ The rates of premature labor and fetal loss are reported to decrease in women with CS surgically treated during pregnancy. Consequently, a pregnancy complicated by CS is a high-risk obstetric condition. A high degree of clinical suspicion is required for the early identification and appropriate management.

As mentioned above, CS during pregnancy may be a cause for major maternal and fetal complications. A series of cases of live births after pharmaceutical or conservative management of CS during gestation have been reported.^{21-23,12} However, no author suggests that medical treatment alone could eliminate the risk for major complications during pregnancy. So far medical therapy during pregnancy has been reported in 20 women.²⁴⁻²⁶ Metyrapone, Ketoconazole, Cyproheptadine and Aminoglutethimide have all been used in the treatment of gestational CS with inconclusive results. Metyrapone, a steroidogenesis inhibitor, seems to be well tolerated and no congenital abnormalities have yet been reported. Ketoconazole has also been successfully used without any major adverse events.^{27-29,36} It should however be reserved for individuals who need emergency medical therapy and cannot tolerate metyrapone.²⁵ Cyproheptadine and aminoglutethimide are contraindicated due to lack of efficacy and fetal masculinization, respectively.³⁰ Some authors have reported successful non-complicated pregnancies in women with CS without any conventional or surgical treatment⁶. Surgical treatment is reported to be the most successful treatment option in gestational CS. Live birth rate may be up to 87% following trans-sphenoidal surgery or adrenalectomy.^{2,3,29,31,34,35} A total of 5 cases of successful trans-sphenoidal pituitary adenomatectomies during gestation, followed by an uneventful delivery, have been reported.³² The best outcome is achieved by a multidisciplinary approach

consisting of endocrinology, obstetric, anesthesiology and endocrine surgery specialists.³³ Lindsay et al suggested that surgical treatment is the mainstay of therapy of CS in pregnancy, with medical treatments constituting the second choice.⁸ Due to the rarity of the pathology, however, no generally accepted treatment guidelines are available. The treatment plan in each case is dependent upon the clinician's experience and the patient's general condition.

In our case, the patient did not receive any medication during her first pregnancy. No major or minor complications were reported and she eventually gave birth to a full-term healthy infant via vaginal delivery. Definitive diagnosis was only possible post-labor, once an abdominal CT could be performed. During her second uneventful pregnancy she was on therapy with a Hydrocortisone 30 mg daily, because of unilateral adrenalectomy and a Synacthen test, which indicated adrenal insufficiency.

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