

# Cushing Syndrome in Pregnancy – Review of the Literature and Case Report

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## Abstract

Cushing syndrome rarely occurs in pregnancy and even more rarely is thought of, due to overlapping features with normal pregnancy. Yet left untreated, this condition can impair the normal course of pregnancy and may lead to maternal and fetal complications.

To illustrate the condition, we present the case of a 33-year-old woman who was diagnosed with adrenal Cushing's syndrome at 30 weeks of gestation, despite having had red striae since 1<sup>st</sup> trimester and hyperten-

sion and gestational diabetes since the 2<sup>nd</sup> trimester. Due to late diagnosis, this case could only be treated conservatively before delivery which was performed at 34 weeks of gestation.

We reviewed the literature with respect to alterations of the pituitary-adrenal function in normal pregnancy, addressing the difficulties of diagnosis and management of Cushing's syndrome in this state.

**Keywords:** Cushing's syndrome, pregnancy

## Introduction

Cushing syndrome rarely occurs in pregnancy as hypercortisolism inhibits pituitary-gonadal axis and thus prevents ovulation in 75% of women. Since 1953, when Hunt and McCohaney had reported the first case, less than 150 pregnancies with Cushing's syndrome have been described<sup>[1]</sup>. Because of fetal and maternal morbidity, both early diagnosis and treatment of Cushing's syndrome in pregnancy are critical. However, the diagnosis is seldom thought of, as signs of hypercortisolism can quite often occur in normal pregnancy. This implies certain delays in diagnosis and

progress to Cushing's related complications with increased maternal and fetal morbidity and mortality.

## Case report

We hereby present the case of a 33-year-old female who was referred to our endocrine unit for Cushing syndrome at 30 weeks of gestation. This woman has had purple abdominal striae, weight gain and facial rounding since the 12<sup>th</sup> week of gestation. She had been diagnosed with hypertension at 20 weeks of gestation and one month later with diabetes mellitus. However, she had been treated for

gestational diabetes (controlled on diet only) and hypertension (controlled on methyldopa 250 mg three times per day) until the 30th week, when her obstetrician suggested that it may be a little problem with her hormones and delivery.

On admission to the National Institute of Endocrinology at 30 weeks of gestation the patient had round face, central adiposity, a body mass index of 30.17 kg/m<sup>2</sup>, very thin skin with purple abdominal, axillary, and inguinal striae (Figure 1a), a blood pressure of 150/80 mmHg, and a gravid uterus with upper limit at 10 cm above umbilicus, and at 5 cm below the ribs.

Biochemical testing was consistent with Cushing syndrome. Full blood count revealed leukocytosis, neutrophilia, lymphopenia, and hormonal screening showed high levels of cortisolemia, with loss of diurnal rhythm and lack of suppression to high dose dexamethasone suppression test (HDST) (Table 1). Suppressed ACTH (<5 pg/mL) was consistent with adrenal Cushing's syndrome.

Indeed, ultrasound imaging confirmed a right adrenal mass sized 3.65/2.97 cm, with partial necrosis. No pathologic formations were found in the left adrenal.

Fetal ultrasound examination revealed a single fetus with estimated weight of 1479 g, fetal tachycardia 184/min high resistivity index in both uterine arteries and umbilical artery and increased S/D ratio. Hematological screening revealed hypercoagulability status (APC-R 47.3s, positive LA, PC97%, PSF 58%, AT 98%).

At 31 week of gestation a mixed team of obstetricians and endocrinologists decided to monitor the patient for fetal growth and fetal heart rate, with the plan of controlled early delivery as soon as possible, in order to prevent maternal and fetal complications. Patient was continued on methyldopa (250 mg tds), low molecular weight heparin and hypoglycemic diet (180 g of carbohydrates/day), with controlled hypertension and glycemia and within the therapeutic limits of AFX.

Labor was induced at 34 week of gestation due to intrauterine growth retardation of the fetus and a healthy male infant of 43.5 cm length and 2250 g weight was delivered via cesarean section.

The patient returned for preoperative evaluation one month after delivery. She presented with purple abdominal, inguinal and axillaries striae, truncal adiposity and also muscular hypotrophy of the limbs. Biochemical testing confirmed Cushing's syndrome (Table 2) and impaired glucose tolerance.

Abdominal CT scan demonstrated a right adrenal tumor of 4.4/2.7 cm (Figure 2).

Bone mass densitometry revealed low BMD al lumbar spine (0.917 g/cm<sup>2</sup>) with an age-matched Z score of -2.2 SD, consistent with BMD below the expected value for age.

While waiting for surgical intervention, the patient was commenced on methyrapone 250 mg tds, titrated on a cortisol day curve. Right adrenalectomy was per-



Figure 1: a. Clinical features of Cushing's syndrome at 30 weeks of gestation; b. Clinical features at 3 months postoperative

Table 1

#### Plasma cortisol and ACTH levels at 30 week of gestation

	Morning (8a.m.)	Midnight	HDST (8 mg dexamethasone for 48 hours)
Cortisol	51.25 µg/dL (1419.62 nmol/L)	57.00 µg/dL (1578.9 nmol/L)	45.96 µg/dL (1273.09 nmol/L)
ACTH	<5 pg/mL		

Table 2

#### Plasma cortisol and ACTH levels at 1 month postpartum

	Morning (8a.m.)	LDST (2mg dexamethasone for 48 hours)
Cortisol	15.49 µg/dL (429.07 nmol/L)	14.67 µg/dL (406.36 nmol/L)
ACTH	5.11 pg/mL	

formed via laparoscopy 6 weeks later. The adrenal tumor was 4.5 cm in diameter with red-orange cut surface. Microscopical examination revealed adrenal cortex hyperplasia of zona fasciculata (cells with lipid-rich, clear cytoplasm, with small nuclei and no mitoses) and zona reticularis, with no microscopical evidence of vascular or capsular invasion, or atypical mitotic cells.

Postoperative at 8 am the plasma cortisol was very low (0.36 µg/dl) and the patient was discharged on prednisone, 7.5 mg/day.

At 3 months postoperative the patient was well, with regression of cushingoid features (Figure 1 b) while she remained adrenal insufficient with a morning plasma cortisol of 1.15 µg/dl and is still on prednisone therapy.

## Discussions

### Alterations of HPA axis in normal pregnancy

Pregnancy is associated with increased hypothalamic-pituitary-adrenal (HPA) axis function, leading to increased circulating and urinary cortisol and ACTH levels. Increased placental production of estrogens stimulates hepatic corticosteroid-binding globulin (CBG) production thus increasing circulating levels of bound cortisol. However both circulating and urinary free cortisol (UFC) levels, as well as 17hydroxycorticosteroids (17OHCS) increase. The increase in plasma cortisol can be seen as early as 11 week of gestation with a 2 to 5 fold increment between the first trimester and delivery<sup>[1]</sup>.

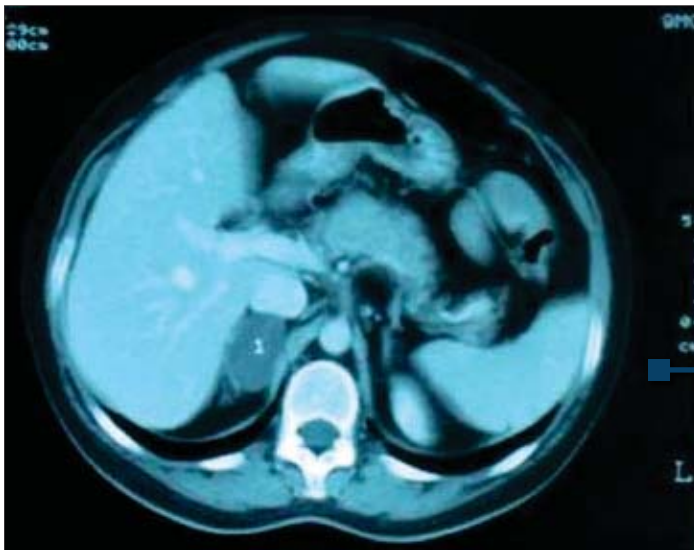


Figure 2.  
Abdominal  
CT scan: right  
adrenal tumor  
causing Cushing's  
syndrome<sup>(1)</sup>

The diurnal rhythm and stress response of plasma cortisol is preserved during pregnancy albeit with a higher nighttime nadir<sup>[2]</sup>.

Plasma ACTH levels rise through pregnancy reaching maximal levels during labour and delivery. The reason for this may include placental synthesis and release of CRH and ACTH or enhanced pituitary response to vasopressin and CRH. Plasma CRH levels rise exponentially by around 1000-fold as gestation progresses, with a peak at 40 weeks of gestation and normalizes to non-pregnant values within 24 h of delivery. The source of this overproduction is more likely to be the placenta, as CRH levels in the umbilical cord plasma are significantly lower than those in maternal circulation<sup>[1]</sup>. The reproductive roles of CRH include decidualization, blastocyst implantation and early maternal tolerance, fetal adrenal steroidogenesis and onset of parturition<sup>[1]</sup>. In the immediate postpartum period plasma CRH, ACTH and cortisol levels fall rapidly toward the non-pregnant range, with more rapid normalization of CRH and ACTH (within 2 h from delivery)<sup>[3]</sup>.

The fetus is protected from the effects of maternal hypercortisolism by placental 11 $\beta$ -hydroxysteroid dehydrogenase 2 (11 $\beta$ -HSD 2) which converts active glucocorticoids, cortisol and corticosterone in their inactive 11 $\beta$ -ketometabolites.

In normal pregnancy plasma and urinary aldosterone does indeed increase, but the potassium level remains constant, because of mineralocorticoid antagonist

effects of progesterone. Aldosterone levels are reduced in pregnancy-associated hypertension as compared to primary hyperaldosteronism<sup>[4]</sup>.

The HPA axis response to exogenous glucocorticoids during pregnancy is blunted. This abnormality may persist for up to 2-3 weeks in a significant proportion of women<sup>[5]</sup>. Thus, screening for hypercortisolism is more difficult in pregnancy, particularly in the second and third trimesters.

#### Cushing's Syndrome in Pregnancy

Hypercortisolism inhibits hypothalamic-pituitary-ovarian axis, therefore pregnancy is rare in women with untreated Cushing's syndrome. The diagnosis of Cushing's syndrome is difficult to establish during pregnancy, as fatigue, hypertension and glucose intolerance may be features of pregnancy alone. However the presence of red striae and proximal myopathy should alert the physician to the diagnosis of Cushing syndrome, as the condition is associated with significant maternal and fetal morbidity and mortality. The most common maternal complications are hypertension (68%), diabetes mellitus or impaired glucose tolerance (25%), followed by preeclampsia (14%), cardiac failure, osteoporosis and fracture, psychiatric disorders, wound infection<sup>[1]</sup>. Maternal death is rare (2%). Fetal morbidity comprises prematurity (43%), intrauterine growth retardation (21%), stillbirths (6%), and spontaneous abortion. Hypoadrenalism in the neonate is rare.

Unlike the general population, the

etiology of Cushing's syndrome in pregnancy is mainly due to adrenal disease, responsible for over 50% of the reported cases, compared with about 15% in non-pregnant women<sup>[6,7]</sup>. Cushing's disease (pituitary ACTH-secreting adenoma) comes second accounting for 33% of causes in pregnant women, as compared with 60-70% in non-pregnant population. Ectopic ACTH-producing tumors are very rare in pregnancy.

Screening and diagnosis for Cushing's syndrome in pregnancy is complicated by the increased HPA axis function with blunted response on exogenous glucocorticoids and the lack of pregnancy-specific criteria.

It seems that the most appropriate initial approach would be the assessment of morning (8-9 a.m.) and midnight plasma/salivary cortisol levels combined with 24-h UFC (the latter measured with the gold standard assay as mass spectroscopy, not RIA). Diurnal rhythm loss of plasma cortisol and UFC values in the second and third trimester greater than 3 times the upper limit of normal can be taken to indicate Cushing's syndrome. For differential diagnosis between ACTH-dependent and ACTH independent Cushing's syndrome a two site IRMA assay discriminates low (<10pg/ml), or suppressed (<5 pg/ml) ACTH level to identify a primary adrenal cause of Cushing's syndrome. In this setting no further biochemical testing is needed, just imaging of the adrenal glands to localize the lesion (unilateral adrenal adenoma/carcinoma or bilateral adrenal nodular hyperplasia)<sup>[1]</sup>.

However, pregnant patients with Cushing's syndrome of any cause may not exhibit ACTH suppression. In this case a combination of high dose dexamethasone suppression test (HDST 8 mg/day, for 48h) and CRH stimulation test is needed to establish the presence of and distinguish between ACTH-dependent forms of Cushing syndrome. In non-pregnant individuals HDST distinguishes Cushing's disease from ectopic ACTH secretion with a sensitivity of 60-80% and specificity above 80%. In pregnant women with Cushing's syndrome the specificity of this test is unknown. Inferior petrosal sinus sampling (IPSS) - for detection of pituitary ACTH and its response to CRH - should only be considered in centers with special expertise of this technique and only if the noninvasive testing is ambiguous.



Adrenal ultrasound imaging is safe and effective in most of the women with adrenal Cushing's syndrome. Magnetic resonance imaging (MRI) of the pituitary or adrenals is contraindicated in the first trimester of pregnancy because of potential (yet unproven) teratogenic effects, but is considered safe after 32 weeks of gestation. The use of gadolinium is contraindicated in pregnancy. A pituitary adenoma greater than 6 mm in the presence of biochemical testing consistent with Cushing's disease is considered a definitive diagnosis in non-pregnant population. However as the normal pituitary increases up to 2-3 fold in the 3<sup>rd</sup> trimester of gestation, there may be an increased number of incidentalomas identified in pregnancy using this criterion<sup>[1]</sup>.

Nieman et al. recommend adrenal imaging with US, HDST, and plasma ACTH levels as an initial step in the differential diagnosis of pregnant patients with Cushing's syndrome. Patients with borderline or low plasma ACTH or without suppression on HDST are likely to have an adrenal etiology. Whereas US imaging identified adrenal lesions in 73% of these cases, second-line imaging with MRI may be needed in the event of a negative US scan<sup>[2]</sup>.

#### Treatment of Cushing's syndrome in pregnancy

Untreated Cushing's syndrome is associated with significant maternal morbidity including diabetes, hypertension, heart failure, and preeclampsia<sup>[2]</sup>. How-

ever, medical treatment may be hazardous to the fetus and mother.

Primary medical therapy was reported in 20 women<sup>[8-10]</sup>. There is most experience with metyrapone, which seems generally well tolerated, but hypertension and progression to preeclampsia have been reported. Apart from this, the drug is not licensed in Romania. In rats, ketoconazole crosses the placenta and is teratogenic and abortifacient so that the drug should be reserved for individuals who need urgent medical therapy, but cannot tolerate metyrapone<sup>[9]</sup>. Cyproheptadine is not recommended due to lack of efficacy<sup>[11]</sup>. Fetal masculinization precludes the use of aminoglutethimide<sup>[12]</sup>. Mitotane should also be contraindicated because it crosses the placenta and is teratogenic<sup>[13]</sup>.

In contrast to medical therapy, surgery is more successful, except late in the third trimester, when baby delivery should be done as soon as possible, followed by treatment for Cushing's syndrome<sup>[2]</sup>.

Though there is no consensus for Cushing's management in pregnancy, it has been advocated that mild Cushing's syndrome should be treated conservatively, while severe Cushing's syndrome, when diagnosed in the 1<sup>st</sup> trimester of pregnancy, should be followed by termination of pregnancy and specific treatment<sup>[14]</sup>. Alternatively, surgical treatment (adrenalectomy or pituitary adenectomy) could be performed early in

the second trimester, with minimal risk to the fetus. Laparoscopic adrenalectomy can also be performed up to 29 weeks of pregnancy in the third trimester.

Lindsay & Nieman reviewed 136 pregnancies with Cushing's syndrome for treatment outcomes. When no active treatment was given, there were 59 (76%) live births compared with 50 (89%) in women in whom treatment was instituted at a mean gestational age of 20 weeks. The authors recommend surgical treatment for Cushing's syndrome (with the exception of late third trimester) with medical treatment being a second choice<sup>[11]</sup>.

#### Conclusion

Cushing's syndrome is a rare disorder to be diagnosed in pregnancy, which may impair the pregnancy outcome. To prevent its maternal and fetal complications, it should be thought more often in the presence of red striae, myopathy, hypertension or gestational diabetes and treated actively ideally before the third trimester. ■

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