Management of the pregnant patient with Cushing’s syndrome

Bronstein MD¹, Machado MC¹, Fragoso MCBV¹,²

Neuroendocrine Unit¹, Adrenal Unit², Division of Endocrinology and Metabolism
Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil

Corresponding authors: Marcello D. Bronstein MD, PhD¹
Sao Paulo Medical School, Av Enéas de Carvalho Aguiar, 155 8° andar bloco 03, São Paulo, SP, 05403-000, Brazil
Email: mdbronstein@uol.com.br

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Abstract: The progress in diagnosis and treatment of endocrine diseases turned pregnancy into reality for women with such medical disorders, including Cushing’s syndrome (CS). Nevertheless, despite its rarity, pregnancy in patients with CS can be troublesome due to maternal-fetal complications. Therefore hypercortisolism, if present, should be surgically or medically controlled in most cases. Moreover, changes in the hypothalamic-pituitary-adrenal axis during normal pregnancy may mislead the diagnosis of CS during this period, as many laboratory assessments suggestive of CS may be present in normal pregnancy, in a setting of clinical features mimicking those seen in patients with CS. The aim of this review is to update the diagnostic approach to this medical condition, mainly for pregnant women without previous diagnosis of CS, and to describe the therapeutic strategies for CS during pregnancy in order to minimize complications for both mother and fetus.

Introduction

The progress in diagnosis and treatment of endocrine diseases has led to an increase in the ovulation rate and consequently turned pregnancy into reality for women with such medical disorders. These achievements include patients with Cushing’s syndrome (CS), a condition where high serum cortisol and androgen levels usually impair the gonadotropic axis. Nevertheless, pregnancy in a setting of hypercortisolism
brings risk for both mother and fetus, becoming a concern for endocrinologists, gynecologists and pediatricians. This review intends: 1) To describe the changes in the hypothalamic-pituitary-adrenal axis during normal pregnancy, which may mislead the diagnosis of CS during this period; 2) To update the diagnostic approach to this medical condition, mainly for pregnant women without previous diagnosis of CS; 3) To describe the therapeutic strategies for CS during pregnancy in order to minimize complications for both mother and fetus.

I. Hypothalamic-pituitary-adrenal axis of binary complex maternal-fetus

The physiological activation of the hypothalamic-pituitary-adrenal axis (HPA) during pregnancy has been proposed to act as a biological clock that times labor and delivery (Figure 1).

The corticotropin-releasing hormone (CRH), one the most important modulators of the HPA, is not only produced in the hypothalamus but has been detected in theca and in stromal cells as well as in cells of the ovarian corpora lutea\(^1\). In addition, the epithelial cells of the endometrium encompass CRH and have shown specific CRH receptors\(^2,3\). This peptide has effects on maturation of fetal adrenal, on fetal-placental unit circulation and also paracrine effects on the placenta. Its molecular structure is identical to the hypothalamic form\(^4\).

During pregnancy, CRH and ACTH plasma levels exponentially increase in the first trimester of gestation due to CRH and ACTH placenta production (Figure 2). Nevertheless, the HPA axis is protected by a physiological concurrent increase of CRH-binding protein\(^5\). The physiological increase of CRH/ACTH during pregnancy causes a slight elevation of cortisol levels (serum, salivary and urinary). Nonetheless, the cortisol
secretion maintains a pulsatile and circadian rhythm even in the third trimester when cortisol attains maximal levels. Another aspect to be considered concerns the increase of corticosteroid-binding globulin (CBG) production secondary to high levels of estradiol in pregnancy. The CBG’s increase reaches its highest levels at the end of pregnancy, leading to a serum cortisol overestimation by commercial assays that generally measure total serum cortisol levels, which mainly represent the bound fraction with CBG. Nevertheless, serum-free cortisol levels also rise around 1.6 fold by the eleventh week of pregnancy due to the pregnancy-induced HPA activation. Consequently, urinary free cortisol increases up to threefold the normal range. Interestingly enough, the placenta expresses 11ß hydroxysteroid dehydrogenase 2, which converts cortisol to cortisone, therefore protecting the fetus from the high maternal cortisol levels. As a consequence of the HPA changes, the stimulation test with exogenous CRH in pregnancy fail to increase ACTH and cortisol which recovers in few weeks after delivery. However, higher doses of CRH can produce an increase of ACTH and cortisol starting from the third trimester. Moreover the suppression of cortisol after dexamethasone suppression test is attenuated compared to non-pregnant state.

Due to ACTH-induced cell proliferation during pregnancy, maternal adrenal glands gradually become hypertrophic. The circulating fetal CRH is almost exclusively of placental origin and ACTH can be detectable in fetal plasma at 12 weeks of gestation. The CRH-binding protein is elevated in the first two trimesters of pregnancy and decreases considerably in the last trimester with consequent elevation of bioavailable plasmatic CRH. The increase of CRH plays a role in the labor process and in fetal lung maturation. Fetal adrenals are huge compared to the adult adrenal glands and the major steroid produced is DHEAS, in contrast to the preponderance of cortisol detected
in the fetal circulation, which appears to come from maternal source. In addition, the fetal adrenal converts placental progesterone to cortisol. Another origin of cortisol is the amniotic fluid where cortisone is converted into cortisol by choriodecidua.

Around the fourth day postpartum, maternal plasma CRH, ACTH, and cortisol gradually decline to basal levels. The adrenal glands are slightly suppressed similarly to early stages of successfully operated patients with Cushing disease (CD), normalizing at 12 weeks. This transient period of CRH suppression might be related to mood disorders and autoimmune diseases frequently observed in postpartum women.

II. Pregnancy in Cushing’s syndrome

Pregnancy is considered a transient physiologic state of “hypercortisolism”, however lacking specific clinical manifestations of CS. Despite its higher prevalence in women of reproductive age, pregnancy in CS is extremely rare due to infertility associated with hypogonadotrophic hypogonadism secondary to cortisol and androgens excess.

There is a significant difference between the frequency of etiologies of CS in pregnancy and in non-pregnant women. In pregnancy the incidence of adrenal disorders (particularly adenomas) and CD is 60% and 33% respectively, in contrast to non-pregnant patients where the incidence is 15% for adrenal adenoma and 70% for Cushing’s disease. This preponderance is probably related to the exclusive cortisol production from adrenal adenomas, as compared to CD with its mixed secretion of cortisol and androgens. Lindsay et al., reviewing 136 pregnancies in 122 women with CS, described the following etiologies: CD (n = 40); adrenal adenoma (n = 56); adrenal carcinoma (n = 12); ectopic ACTH secretion (EAS) (n = 4), Carney’s complex (n = 1);
and ACTH-independent hyperplasia (AIH) (n = 4) possibly due to aberrant receptor stimulation.

**III. Diagnosis**

The diagnosis of CS during pregnancy is often a challenge, as we need to cope with three situations: 1) Patients who become pregnant with previously diagnosed CS (the easiest scenario); 2) Patients who develop CS during pregnancy, and 3) Women with clinical features of CS, as striae, hypertension and diabetes, which are prevalent in normal pregnancy. Concerning clinical differential diagnosis, features such as muscular weakness, larger purple striae (mainly in regions outside of abdomen) (Figure 3), and osteoporosis are clues that point to CS instead of normal pregnancy. Hirsutism, resulting from hyperandrogenism, is not a common sign in CS associated to pregnancy since most cases are pure benign adrenal adenomas usually with isolated cortisol secretion. Nevertheless, differential diagnosis on clinical basis is often misleading and therefore needs the additional support of laboratory and imaging procedures.

Hormonal diagnosis of CS during pregnancy may also be a challenge, as high serum and urinary cortisol levels and an abnormal cortisol dexamethasone suppression test frequently occur in normal pregnancy. Thus, high urinary free cortisol, mainly if lower than 3 times the upper limit normal range, usually cannot differentiate normal pregnancy from CS, especially during the second and third trimester. The absence of circadian rhythm is probably the best test as it is preserved during normal pregnancy, pointing to salivary cortisol as one of the best tools. Nevertheless, to date, threshold values for the diagnosis of CS in pregnancy are not well validated.

Once the diagnosis of CS is confirmed or highly suspected, we must proceed to discover its etiology. Although adrenal adenomas account for 60% of cases of
Cushing’s pregnancy, the expected ACTH suppression of this condition, albeit confirmatory, is often not observed, probably due to pituitary ACTH stimulation by placental CRH or by placental ACTH itself. Patients with CD diagnosed during pregnancy present ACTH levels in the upper half of the normal range or even higher.

High-dose dexamethasone suppression test could be a clue for differential diagnosis, since, if positive, an adrenal tumor should be unlikely. Nevertheless, lack of suppression does not rule-out ACTH-dependent Cushing’s, due to the elevated levels of bound cortisol.

A distinctive feature of adrenal Cushing’s syndrome caused by aberrant LH receptor is the disappearance of hypercortisolism after delivery in coincidence with cessation of HCG placental production. Of course, this feature is of no diagnostic aid while pregnancy is in course (Figure 4).

Concerning the distinction between pituitary and ectopic ACTH secretion, pituitary etiology can be safely confirmed by either of the commonly used tests. In fact, high dose dexamethasone suppression test correctly identified almost all reported cases using the 50% cortisol decrease threshold, and stimulation with 100 μg CRH evoked marked ACTH and cortisol responses in patients with CD. Inferior petrosal sinus sampling has been carried out in a few pregnant women with suspected CD but should be employed sparingly in order to avoid unnecessary radiation and possible thrombotic events. Non-gadolinium enhanced MRI itself may not be informative for microadenomas, and, further, the physiological enlargement of the pituitary gland during pregnancy may mask a small tumor. Imaging should be performed only if surgery is planned prior to birth and, obviously, adrenal CT scans should be avoided.

Therefore adrenal imaging should be initially performed by ultrasound, leaving non-
gadolinium contrasted MRI for non-diagnosed cases. Nonetheless, the issue of adrenal incidentalomas should be taken into account for the differential diagnosis.

IV. Treatment of pregnancies with Cushing’s syndrome

Approximately 150 cases of pregnancy and endogenous CS were reported in the literature. Of those, treatment was performed in a subset of patients but many cases, especially when discovered late in pregnancy, were managed conservatively, just trying to control comorbidities such as hypertension and diabetes mellitus.

Nonetheless, uncontrolled CS during pregnancy is associated with a high rate of maternal complications. Even in treated cases some patients develop complications such as preeclampsia and premature delivery.

The most common described maternal morbidities are: hypertension (68%), diabetes or glucose intolerance (25%), preeclampsia (14%), osteoporosis and fractures (5%), cardiac failure (3%), psychiatric disorders (4%), wound infections (2%) and maternal death (2%).

Concerning newborns, a tendency for higher live birth rate was observed in women treated during pregnancy. The more frequent fetal morbidity is prematurity occurring in about 43% of pregnancies. Other described complications are: intrauterine growth retardation (21%), stillbirths (6%), spontaneous abortion or intrauterine death (5%) and hypoadrenalism (2%).

Similarly to non-pregnant women, surgery usually is the first treatment option in pregnant CS patients. On the other hand, further options to treat hypercortisolism as radiotherapy and mitotane are contraindicated in this period due to the potential harmful or teratogenic effect and delayed outcome.
In patients with CD and pregnancy, 42.5% were not submitted to specific treatment of hypercortisolism. The treated ones were equally submitted to transsphenoidal surgery, medical treatment or bilateral adrenalectomy. Surgical treatment has been done in ACTH secreting pituitary adenomas ideally between the end of first trimester and early second trimester (12-29 weeks of gestation), a period associated with a lower rate of maternal and fetal complications. Several factors influence surgical decision as the etiology, severity, stage of gestation and therapeutic risk-benefit for the maternal-fetal outcomes.

Adrenalectomy for adrenal etiologies of CS, such as adrenal adenomas and carcinomas, was performed with good results both for hypercortisolism resolution and birth rate (87%) Additionally, bilateral adrenalectomy can be performed in other situations, especially in non-controlled CD or severe ectopic ACTH syndrome.

Medical therapy, generally initiated during the second or third trimesters, is the second treatment option. Of these, treatment with steroidogenesis inhibitors was the most used option, particularly with metyrapone (Table 1). This drug was used in 69% of cases showing good control of hypercortisolism in most of them, with one report of adrenal insufficiency. The most worrisome side effect of metyrapone is the increase of precursors such as 11-deoxycorticosterone, worsening hypertension and increasing preeclampsia frequency. Although it crosses the placental membrane in animal studies, no neonatal abnormalities have been reported in human patients. Ketoconazole, the most used steroidogenesis inhibitor in non-pregnant CS patients, has been less utilized in pregnancy due to potential side effects such as anti-androgenic effect and teratogenicity (only in animal studies). Other adrenal steroidogenesis blockers as aminoglutethimide and mitotane, were rarely used, being contraindicated due to fetal masculinization and teratogenicity, respectively. Concerning pituitary tumor directed
drugs, in spite of the increasing use of cabergoline for CD, only one patient treated with
this dopamine agonist during pregnancy was reported, to date\textsuperscript{32}.

In conclusion, despite its rarity, pregnancy in patients with CS can be
troublesome due to maternal-fetal complications. The achievements in the physiology of
the corticotrophic axis during pregnancy applied to laboratorial assays, the improvement
of imaging methods and of pituitary and adrenal surgical approaches, favorably
contributed for the differential diagnosis with normal pregnancy as well as for the
reduction of maternal and fetal morbidity and mortality.

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interest.

References:


**Figure 1.** Hypothalamic-pituitary-adrenal axis in normal pregnancy. The production of cortisol linked of corticosteroid-binding globulin is increased as well as the free fraction. The concentration of ACTH is high and the adrenal cortex is responsible to stimulus. Abbreviations: 16 alpha-OH-4A, 16 alpha – hydroxyandrostenedione; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate.

Figure 2. Serial increases in serum cortisol (B) and ACTH (C) during pregnancy in normal controls throughout pregnancy.


Figure 3. Non-pregnant woman with Cushing’s disease exhibiting large striae in the abdomen and arm (HC/FMUSP).

Figure 4. Illustration of aberrant receptors expression (LH/hCGR) in adrenal cortex causing bilateral macronodular adrenal hyperplasia in patient with Cushing’s syndrome developed during pregnancy.

Table 1. Reports of medications used to treat patients with Cushing’s syndrome and pregnancy.

<table>
<thead>
<tr>
<th>Medication</th>
<th>n=26</th>
<th>%</th>
<th>Dose</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Metyrapone</td>
<td>16</td>
<td>61%</td>
<td>0.5-3.0 g/day</td>
<td>Systemic hypertension and preeclampsia risk</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>4</td>
<td>15%</td>
<td>0.6-1.0 g/day</td>
<td>Teratogenicity (only in animal studies)</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>3</td>
<td>11%</td>
<td>-</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Aminoglutethimide</td>
<td>1</td>
<td>4%</td>
<td>2.5 g/day</td>
<td>Fetal masculinization</td>
</tr>
<tr>
<td>Mitotane</td>
<td>1</td>
<td>4%</td>
<td>-</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>1</td>
<td>4%</td>
<td>-</td>
<td>-</td>
</tr>
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n (number of patients); % percentage of total of patients treated
Figure 1. Hypothalamic-pituitary-adrenal axis in normal pregnancy. The production of cortisol linked of corticosteroid-binding globulin is increased as well as the free fraction. The concentration of ACTH is high and the adrenal cortex is responsible to stimulus. Abbreviations: 16 alpha-OH-4A, 16 alpha – hydroxyandrostenedione; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate.


251x208mm (72 x 72 DPI)
Figure 2. Serial increases in serum cortisol (B) and ACTH (C) during pregnancy in normal controls throughout pregnancy.

Figure 3. Non-pregnant woman with Cushing’s disease exhibiting large striae in the abdomen and arm (HC/FMUSP)  
136x102mm (220 x 220 DPI)
Figure 3. Non-pregnant woman with Cushing’s disease exhibiting large striae in the abdomen and arm (HC/FMUSP)
451x338mm (72 x 72 DPI)
Figure 4. Illustration of aberrant receptors expression (LH/hCGR) in adrenal cortex causing bilateral macronodular adrenal hyperplasia in patient with Cushing’s syndrome developed during pregnancy. From Ref 19: Lacroix A, Ndiaye N, Tremblay J, Hamet P. Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. Endocrine reviews. Feb 2001;22(1):75-110.