MANAGEMENT OF ENDOCRINE DISEASE

Management of pregnant patients with Cushing's syndrome

M D Bronstein¹, M C Machado¹ and M C B V Fragoso^{1,2}

¹Neuroendocrine Unit and ²Adrenal Unit, Division of Endocrinology and Metabolism, Hospital das Clínicas, University of São Paulo Medical School, Avenida Enéas de Carvalho Aguiar, 155 8º andar Bloco 03, São Paulo, São Paulo 05403-000, Brazil

Correspondence should be addressed to M D Bronstein
Email
mdbronstein@uol.com.br

Abstract

Progress in the diagnosis and treatment of endocrine diseases has turned pregnancy into a possibility for women with such medical disorders, including Cushing's syndrome (CS). Nevertheless, despite its rarity, pregnancy in patients with CS can be troublesome because of the risk of 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, because many laboratory assessments suggestive of CS may be present in normal pregnancy, with clinical features mimicking those seen in patients with CS. The aim of the present 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.

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Introduction

Progress in the diagnosis and treatment of endocrine diseases has led to an increase in ovulation rates and has consequently turned pregnancy into a possibility for women with such medical disorders. These achievements include patients with Cushing's syndrome (CS), a condition in which high serum cortisol and androgen levels usually impair the gonadotropic axis. Nevertheless, pregnancy in a setting of hypercortisolism brings risks for both the mother and the fetus, and it is therefore a concern

for endocrinologists, gynecologists, and pediatricians. The present review intends: i) to describe the changes in the hypothalamic–pituitary–adrenal (HPA) axis during normal pregnancy, which may mislead the diagnosis of CS during normal pregnancy; ii) to update the diagnostic approach to this medical condition, mainly for pregnant women without a previous diagnosis of CS; and iii) to describe the therapeutic strategies for CS during pregnancy in order to minimize complications for both mother and fetus.

Invited Author's profile:

Marcello D Bronstein, MD, PhD, is Professor of Endocrinology at the University of São Paulo Medical School and Chief of the Neuroendocrine Unit, Division of Endocrinology and Metabolism, Department of Internal Medicine at the Hospital das Clínicas at the same institution. From 2011 to 2012, he was president of the International Pituitary Society. He has published extensively in various international peer-reviewed journals and has written 20 textbook chapters. His main fields of interest and research are the diagnosis and treatment of pituitary tumors and pituitary tumorigenesis.

Figure 1

Hypothalamic–pituitary–adrenal axis during normal pregnancy. The production of cortisol linked to corticosteroid-binding globulin is increased, as is the free fraction. The concentration of ACTH is high, and the adrenal cortex is responsible for stimulus. 16 α -OH-4A, 16 α -hydroxyandrostenedione; CRH, corticotropin-releasing hormone. Reproduced with permission from Bronstein MD, Paraiba DB & Jallad RS. Management of pituitary tumors in pregnancy. *Nature Reviews. Endocrinology* 2011 **7** 301–310. © Macmillan Publishers limited.

HPA axis of binary complex maternal–fetus

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

The corticotropin-releasing hormone (CRH), one the most important modulators of the HPA, is not only produced in the hypothalamus but has also 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 been shown to have specific CRH receptors (2, 3). This peptide has effects on the maturation of the fetal adrenal, on fetal-placental unit circulation, and also on paracrine effects on the placenta. Its molecular structure is identical to the hypothalamic form (4).

During pregnancy, CRH and adrenocorticotropin (ACTH) plasma levels increase exponentially in the first trimester of gestation as a result of CRH and ACTH placenta production (Fig. 2). Nevertheless, the HPA axis is protected by a physiological concurrent increase in CRH-binding protein (5). The physiological increase in

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 during the third trimester when cortisol attains maximal levels (6).

Another aspect to be considered concerns the increase in corticosteroid-binding globulin (CBG) production secondary to high levels of estradiol during pregnancy. The increase in CBG reaches its highest levels at the end of pregnancy and leads to a serum cortisol overestimation by commercial assays that generally measure total serum cortisol levels, which mainly represent the bound fraction with CBG (7). Nevertheless, serum-free cortisol levels also rise around 1.6-fold by the 11th week of pregnancy because of the pregnancy-induced HPA activation (6). Consequently, urinary free cortisol increases up to threefold the normal range (8). Interestingly, the placenta expresses 11- β hydroxysteroid dehydrogenase 2, which

Figure 2

Serial increases in serum cortisol (B) and ACTH (C) during pregnancy in normal controls. Reproduced with permission from Carr BP, Parker CR Jr, Madden JD, MacDonald PC & Porter JC. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *American Journal of Obstetrics and Gynecology* 1981 **139** 416-422. © Mosby Inc.

converts cortisol to cortisone and therefore protects the fetus from the high maternal cortisol levels (9). As a consequence of the HPA changes, the stimulation test with exogenous CRH during pregnancy fails to increase ACTH and cortisol, which recover in few weeks after delivery (10). However, higher doses of CRH can produce an increase in ACTH and cortisol starting during the third trimester (11). Moreover, the suppression of cortisol after a dexamethasone suppression test is attenuated as compared to non-pregnant state (9).

Because of 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 detected in fetal plasma at 12 weeks gestation (10). The CRH-binding protein is elevated during the first two trimesters of pregnancy, but it decreases considerably in the final trimester, and bioavailable plasmatic CRH is consequently elevated. The increase in CRH plays a role in the labor process and in fetal lung maturation (12). Fetal adrenals are very large compared to the adult adrenal glands, and the major steroid they produce is DHEAS, in contrast to the preponderance of cortisol detected in the fetal circulation, which appears to come from the maternal source (13). In addition, the fetal adrenal converts placental progesterone into cortisol. Another origin of cortisol is the amniotic fluid, where cortisone is converted into cortisol by choriondecidua.

Around the 4th day *postpartum*, maternal plasma CRH, ACTH, and cortisol gradually decline to basal levels. The adrenal glands are slightly suppressed, similarly to those in the early stages after successful operation in patients with Cushing's disease (CD), and they normalize at 12 weeks (13). This transient period of CRH suppression might be related to the mood disorders and autoimmune diseases that are frequently observed in *postpartum* women.

Pregnancy with CS

Pregnancy is considered a transient physiologic state of 'hypercortisolism'; however, it lacks specific clinical manifestations of CS. Despite its higher prevalence in women of reproductive age, pregnancy with CS is extremely rare because infertility is associated with hypogonadotrophic hypogonadism secondary to cortisol and androgens excess (14).

There is a significant difference between the frequency of etiologies of CS in pregnant and in non-pregnant women. During 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 CD (1). This preponderance is probably related to the exclusive cortisol production from adrenal adenomas as compared to CD, which exhibits a mixed secretion of cortisol and androgens (15). Lindsay *et al.* (1), upon 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 ($n=4$), possibly resulting from aberrant receptor stimulation.

Diagnosis

The diagnosis of CS during pregnancy is often a challenge, because we need to cope with three situations: i) patients who become pregnant with previously diagnosed CS (the most straightforward scenario); ii) patients who develop CS during pregnancy; and iii) women who exhibit clinical features of CS, such 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 the abdomen) (Fig. 3), and osteoporosis are clues that point to CS instead of normal pregnancy. Hirsutism, resulting from hyperandrogenism, is not a common sign of CS associated with pregnancy, because most cases are pure benign adrenal adenomas that usually feature isolated cortisol secretion (16). Nevertheless, differential diagnosis on a 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, because high serum and urinary cortisol levels and abnormal cortisol dexamethasone suppression tests occur frequently in normal pregnancies (4, 17). Thus, high urinary free cortisol, particularly if it is less than three times the upper limit normal range, usually cannot differentiate normal pregnancy from CS, especially during the second and third trimesters. The absence of circadian rhythm is probably the best test, seeing as the circadian rhythm is preserved during normal pregnancy, and this points to salivary cortisol as one of the best tools for detection. Nevertheless, to date, threshold values for the diagnosis of CS during 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,

Figure 3

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

probably because pituitary ACTH can be stimulated by placental CRH or by placental ACTH itself (17, 18). Patients with CD diagnosed during pregnancy present ACTH levels in the upper half of the normal range or even higher (17).

A high-dose dexamethasone suppression test could be a clue for differential diagnosis, because, if the results are positive, an adrenal tumor would be unlikely. Nevertheless, a lack of suppression does not rule out ACTH-dependent Cushing's because of the elevated levels of bound cortisol (18).

A distinctive feature of adrenal CS caused by aberrant luteinizing hormone (LH) receptor is the disappearance of hypercortisolism after delivery in conjunction with the cessation of human chorionic gonadotrophin placental production. Of course, this feature is not a diagnostic aid during pregnancy (19) (Fig. 4).

Concerning the distinction between pituitary and EAS, pituitary etiology can be safely confirmed by either of the commonly used tests. In fact, the high-dose dexamethasone suppression test has been shown to correctly identify almost all reported cases using the 50% cortisol decrease threshold, and stimulation with 100 µg CRH has been shown to evoke marked ACTH and cortisol responses in patients with CD (20). Inferior petrosal sinus sampling has been carried out in a few pregnant women with suspected CD (21), but it should be employed sparingly in order to avoid unnecessary radiation and possible thrombotic events (17). Non-gadolinium-enhanced magnetic resonance imaging (MRI) itself may not be informative for microadenomas (1, 22), and furthermore, the physiological enlargement of the pituitary gland during pregnancy may mask a small tumor (1). Imaging should be performed only if surgery is planned before 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.

Figure 4

Illustration of aberrant receptor expression (LH/hCGR) in adrenal cortex causing bilateral macronodular adrenal hyperplasia in a patient with Cushing's syndrome developed during pregnancy. Reproduced with permission from Lacroix A, Ndiaye N, Tremblay J & Hamet P. Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. *Endocrine Reviews* 2001 22 75–110. © The Endocrine Society.

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Table 1 Reports of medications used to treat patients with Cushing's syndrome during pregnancy.

Medication	n=26	%	Dose (g/day)	Comments
Metyrapone (17, 26, 27, 30, 33, 34)	16	61	0.5–3.0	Systemic hypertension and preeclampsia risk
Ketoconazole (17, 30, 31)	4	15	0.6–1.0	Teratogenicity (only in animal studies)
Cyproheptadine (17)	3	11		Lack of efficacy
Aminoglutethimide (17)	1	4	2.5	Fetal masculinization
Mitotane (17)	1	4		Teratogenic
Cabergoline (31, 32)	1	4		

n, number of patients; %, percentage of total of patients treated.

Treatment of pregnancies with CS

Approximately 150 cases of pregnancy and endogenous CS have been 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 by 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 (17). Even in treated cases, some patients develop complications, such as preeclampsia and premature delivery.

The most commonly described maternal morbidities include: 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%) (17).

Concerning newborns, a tendency for a higher live birth rate was observed in women who were treated during pregnancy. The more frequent fetal morbidity is prematurity, which occurs in about 43% of pregnancies. Other described complications include: intrauterine growth retardation (21%), stillbirths (6%), spontaneous abortion or intrauterine death (5%), and hypoadrenalism (2%) (17).

Similarly to non-pregnant women, surgery is usually the first treatment option in pregnant CS patients (1, 17, 23, 24). On the other hand, further options to treat hypercortisolism, such as radiotherapy and mitotane, are contraindicated in this period because of their potential harmful or teratogenic effects and their delayed outcomes (25).

In patients with CD during pregnancy, 42.5% were not submitted to specific treatment of hypercortisolism (17). The treated patients were submitted equally to transsphenoidal surgery, medical treatment, or bilateral adrenalectomy. Surgical treatment was performed on ACTH-secreting pituitary adenomas between the end of the first trimester and the early second trimester (12–29 weeks gestation), a period associated with a lower rate of maternal and fetal complications. Several factors can

influence the decision to perform surgery, including the etiology, severity, stage of gestation, and therapeutic risk–benefit for the maternal–fetal outcomes (24).

Adrenalectomy for adrenal etiologies of CS, such as adrenal adenomas and carcinomas, was performed with positive results both for hypercortisolism resolution and birth rate (87%) (23). Additionally, bilateral adrenalectomy can be performed in other situations, especially in non-controlled CD or severe EAS.

Medical therapy, which was generally initiated during the second or third trimesters, is a second treatment option. Of these, treatment with steroidogenesis inhibitors, particularly with metyrapone, was the option used most often (26) (Table 1). This drug was used in 69% of cases and showed good control of hypercortisolism in most of them, with one report of adrenal insufficiency (17, 27). The most worrisome side effects of metyrapone are an increase in precursors such as 11-deoxycorticosterone, worsened hypertension, and an increase in preeclampsia frequency. Although it crosses the placental membrane in animal studies, no neonatal abnormalities have been reported in human patients (28, 29). Ketoconazole, the steroidogenesis inhibitor used most often in non-pregnant CS patients, has been utilized less during pregnancy because of its potential side effects, which include an anti-androgenic effect and teratogenicity (only shown in animal studies) (17, 30, 31). Other adrenal steroidogenesis blockers, such as aminoglutethimide and mitotane, were rarely used, because they were contraindicated as a result of fetal masculinization and teratogenicity respectively (16). Concerning pituitary tumor-directed drugs, in spite of the increasing use of cabergoline for CD, only one patient has reportedly been treated with this dopamine agonist during pregnancy to date (32).

In conclusion, despite its rarity, pregnancy in patients with CS can be troublesome because of maternal–fetal complications. Achievements in the physiology of the corticotrophic axis during pregnancy applied to

laboratorial assays, improvements in imaging methods, and advancements in pituitary and adrenal surgical approaches have all favorably contributed to the differential diagnosis with normal pregnancy as well as to the reduction of maternal and fetal morbidity and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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