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MANAGEMENT OF ENDOCRINE DISEASE

Management of Cushing's syndrome during pregnancy: solved and unsolved questions

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Abstract

With fewer than 200 reported cases, Cushing's syndrome (CS) in pregnancy remains a diagnostic and therapeutic challenge. In normal pregnancies, misleading signs may be observed such as striae or hypokalemia, while plasma cortisol and urinary free cortisol may rise up to 2- to 3-fold. While the dexamethasone suppression test is difficult to use, reference values for salivary cortisol appear valid. Apart from gestational hypertension, differential diagnosis includes pheochromocytoma and primary aldosteronism. The predominant cause is adrenal adenoma (sometimes without decreased ACTH), rather than Cushing's disease. There are considerable imaging pitfalls in Cushing's disease. Aberrant receptors may, in rare cases, lead to increased cortisol production during pregnancy in response to HCG, LHRH, glucagon, vasopressin or after a meal. Adrenocortical carcinoma (ACC) is rare and has poor prognosis. Active CS during pregnancy is associated with a high rate of maternal complications: hypertension or preeclampsia, diabetes, fractures; more rarely, cardiac failure, psychiatric disorders, infection and maternal death. Increased fetal morbidity includes prematurity, intrauterine growth retardation and less prevalently stillbirth, spontaneous abortion, intrauterine death and hypoadrenalism. Therapy is also challenging. Milder cases can be managed conservatively by controlling comorbidities. Pituitary or adrenal surgery should ideally be performed during the second trimester and patients should then be treated for adrenal insufficiency. Experience with anticortisol drugs is limited. Metyrapone was found to allow control of hypercortisolism, with a risk of worsening hypertension. Cabergoline may be an alternative option. The use of other drugs is not advised because of potential teratogenicity and/or lack of information. Non-hormonal (mechanical) contraception is recommended until sustained biological remission is obtained.

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Invited author's profile

Thierry Brue is Prof. of Endocrinology at Aix-Marseille University (AMU, Marseille, France), and Endocrinologist at Conception University hospital, where he is also Head of the Department, Head of the division of Endocrinology, Nutrition, Diabetes and Obesity and coordinator of the national and European (ERN) rare disease reference center for pituitary disorders (HYPO). Prof. Brue's main clinical interests are in Neuroendocrinology. His research activities include: clinical research in pituitary disorders, especially participation as investigator in international multicenter clinical trials; experimental research as leader of the research team on the 'Differentiation and Proliferation of Neuroendocrine Tissues' (DIPNET) in the Marseille Medical Genetics AMU-INSERM Laboratory of Nicolas Lévy; coordination of a research network on genetically determined pituitary hormone deficiency (GENHYPOPIT).



Cushing's syndrome (CS) denotes various causes of endogenous overproduction of glucocorticoids that may be due to cortisol hypersecretion by a pituitary adenoma, an adrenal tumor or a neuroendocrine tumor (1, 2). It represents a severe medical condition that preferentially affects women of childbearing age (3, 4). This is why, despite possible deleterious effects of the disease on fertility, the occurrence of pregnancy in women with this condition is not unusual. Due to the overall severity of the disease, endocrinologists and gynecologists should be aware of this possibility and informed on how best to manage this difficult therapeutic challenge. A PubMed search performed in November 2017, combining the terms 'Cushing' and 'pregnancy', limited to the last 5 years, yielded only 52 results, confirming that it is a rare condition. However, as such an occurrence represents a high-risk pregnancy with potentially severe consequences for mother and child alike, endocrinologists should be aware of the specificities and traps in diagnosis and treatment. The management of CS during pregnancy is indeed highly challenging both for diagnosis, due to technical caveats or to the possibility of pregnancy-induced CS (5) and for therapy due to limited information on drug safety. This topic has previously been reviewed in recent years by Bronstein and colleagues (6) and by others (7, 8, 9, 10). We will thus, in this present review, summarize in the form of a number of open questions, the main challenges clinicians face when managing a woman with CS who is pregnant or seeking to become pregnant.

What is the epidemiology of hypercortisolism diagnosed during pregnancy?

Hypercortisolism is a rare condition. Moreover, the diagnosis of CS is rarely made during pregnancy and altered fertility is also frequent in patients with active hypercortisolism. Altogether, this explains why, to date, fewer than 200 cases of CS during pregnancy have been reported in the literature (6, 7, 11). The main atypical characteristic is the fact that the predominant etiology is adrenal adenoma, reported in 40–60% cases, in contrast to non-pregnant women for whom the most frequent cause is Cushing's disease, and adrenal adenomas only account for 10–15% of cases. Pituitary adenomas represent 15–40% cases, while adrenal carcinomas are reported in less than 10% of cases. This may be explained by the fact that ovulation could be more effective in patients with

adrenal rather than pituitary disease (especially in women with normal androgen secretion) (12, 13, 14).

How to diagnose CS during pregnancy?

Clinical diagnosis is more difficult than in non-pregnant women: indeed, some of the clinical signs of hypercortisolism overlap with classical signs observed during pregnancy, such as fatigue, weight gain, hirsutism, acne and emotional instability. Striae can also be seen, even if the classical purple color and the thickness of Cushing's striae are usually different from the thin whitish striae of a classical pregnancy (15). However, purple striae can also be seen during pregnancy. It has been advocated that when a triad of hypertension, ecchymosis and muscle weakness is observed in pregnant women, CS should be considered (11). While hypokalemia can be observed during pregnancy because of vomiting, pathological fractures, though rare, should lead to examination for hypercortisolism. Finally, hypertension and hyperglycemia, other hallmarks of exposure to hypercortisolism, are frequent complications of pregnancy. Etiologies of hypertension during pregnancy will be detailed in the next paragraph.

The biochemical diagnosis is at least as difficult as the clinical diagnosis. Pregnancy is indeed characterized by several endocrine biochemical changes (Fig. 1) including activation of both the hypothalamic–pituitary–adrenal axis and the renin–angiotensin–aldosterone system (4,

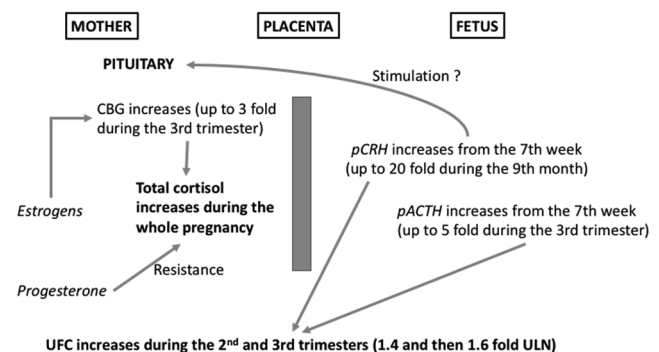


Figure 1

Biochemical characteristics of the hypothalamo–pituitary axis during pregnancy. The increase of total cortisol begins early during pregnancy while the increase in urinary free cortisol usually begins during the 2nd trimester. These biological changes can also lead to the loss of nycthemeral rhythm during the 3rd trimester. CBG, cortisol-binding globulin; pACTH, placental ACTH; pCRH, placental CRH. UFC, urinary free cortisol. ULN, upper limit normal.

16). This conveys an additional challenge, as the majority of the classical biochemical characteristics used to diagnose hypercortisolism in non-pregnant women will be biased during pregnancy.

- Firstly, there is an increase in total plasma cortisol beginning during the first trimester, and lasting for the whole of pregnancy. This is due to the elevated concentration of its transport protein, i.e. corticosteroid-binding globulin (CBG), consecutive to the increase in plasma estrogens (16) and to an increase in CRH produced by the placenta (14). The rise in CBG can be up to 3 times the normal value during the third trimester, leading to 2- to 3-fold increase of plasma cortisol levels (17). The placenta also plays a main role in the changes to cortisol levels: placental CRH and ACTH increase progressively from the 7th week until the end of pregnancy (18). Of note, the parallel increase of CRH-binding protein protects the HPA axis. Usually, the circadian rhythm of cortisol is maintained, but it can be blunted during the third trimester. High levels of total cortisol make the dexamethasone suppression test very difficult to interpret during pregnancy: it is reported that less than 40% of women without CS during pregnancy have a so-called normal low-dose dexamethasone suppression test with a cortisol level <50 nmol/L (14).
- Secondly, urinary free cortisol (UFC) also increases during the second trimester (1.4- to 1.6-fold increase in the 2nd and 3rd trimester, respectively). UFC should thus not be considered a reliable marker after the first trimester, unless levels are clearly increased (up to 2- to 3-fold the upper limit of normal values, as suggested by the Endocrine Society guidelines) (19).
- Interestingly, in contrast, Ambroziak and coworkers did not show any obvious change in salivary cortisol during pregnancy (Fig. 2). These authors suggested that reference values for salivary cortisol established for a healthy adult population could be used for pregnant women and women on oral contraceptives in the initial diagnostic testing for CS (20). Of note, some pregnant women from this group had higher values than expected, despite the fact that they were not hypercortisolic. More recently, Lopes and coworkers addressed this issue by defining normal threshold values of salivary cortisol in each trimester of pregnancy: <6.9 nmol/L for the first, <7.2 nmol/L for the second and <9.1 nmol/L for the third trimester. Of note, despite the overlap between patients with Cushing's disease and eucortisolic pregnant women in

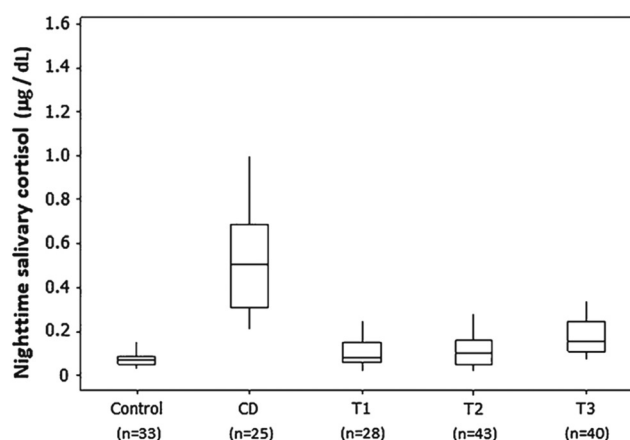


Figure 2

Nighttime salivary cortisol ($\mu\text{g}/\text{dL}$) in the control and CD groups, and in the first (T1), second (T2) and third trimesters (T3) in the pregnancy group. *P* values for T3 vs controls < 0.001. All *P* values in the CD group compared with the control group and with each pregnancy group were *P* < 0.001. To convert salivary cortisol from $\mu\text{g}/\text{dL}$ to nmol/L, multiply by 27.6. From Lopes *et al.* (21).

each trimester, the specificity ranged from 80 to 92% (21). Despite the low number of women evaluated, we thus think that salivary cortisol level should be considered the most robust criterion for positive diagnosis of hypercortisolism during pregnancy (at least during the first 2 trimesters).

Of note, pregnancy also leads to stimulation of the renin-angiotensin-aldosterone system, due to both increase in estrogens and placental renin. This leads to increased aldosterone and deoxycorticosterone levels (that is also due to increased progesterone levels, leading to resistance to aldosterone) and can account for hypokalemia (18). Wilson and coworkers evaluated the renin-aldosterone system in greater detail in 106 pregnant women through the first trimester to delivery. They showed that plasma renin was increased twofold by the eighth week of pregnancy, doubled again by the 20th week, and then remained stable until term. In parallel, aldosterone increased progressively during pregnancy, to reach an 8- to 10-fold increase by the third trimester (22).

The diagnosis of etiology can also prove to be an equally challenging issue. Indeed, the placental secretion of ACTH and CRH can lead to non-decreased ACTH levels in 50% of women with adrenal CS (13). The following diagnostic steps, i.e. CRH test, desmopressin test and high-dose dexamethasone suppression test have not been performed in a sufficient number of patients to draw any

firm conclusion on their reliability. Imaging should be focused on ultrasound (adrenal) and then MRI (pituitary or adrenal), without contrast (13). While adrenal tumors are usually obvious, the ACTH-dependent etiologies are mostly difficult to diagnose on imaging.

What are the differential diagnoses of hypertension during pregnancy?

Newly diagnosed hypertension is usually considered as pre-existing before pregnancy when diagnosed in the first trimester, and at the beginning of the second trimester (in contrast to preeclampsia and gestational hypertension). Secondary forms of hypertension occur in 0.24% of all pregnancies: the most frequent cause being chronic kidney disease, which will not be discussed in this review. Other endocrine etiologies include pheochromocytoma and primary aldosteronism, while non-endocrine etiologies are mainly represented by renal artery stenosis and obstructive sleep apnea (23).

Pheochromocytoma is the most common tumoral cause of hypertension during pregnancy. It induces a 10% mortality rate for the mother and 20% for the fetus, when the diagnosis is made early during pregnancy, and superior to 50% for the mother and the fetus, when the diagnosis is made later during pregnancy. Usually, there is no weight gain in contrast with CS. Proteinuria can be seen in both cases depending on the level of hypertension. Urinary free metanephrines can be used during pregnancy to confirm the diagnosis (24).

Primary aldosteronism can be diagnosed during pregnancy. It usually leads to varying degrees of severe hypertension and hypokalemia. Interestingly, increased progesterone levels lead to resistance to aldosterone, and this can lead to a spontaneous improvement of the symptoms during pregnancy. As previously detailed, biochemical diagnosis proves to be challenging as aldosterone levels increase up to 8-fold, compared to normal values, during pregnancy. This would make aldosterone renin ratio difficult to evaluate: an additional evidence could be given by low renin levels. When the diagnosis is made, spironolactone should be avoided during the first trimester, as it is an androgen antagonist. Primary aldosteronism is not associated with classical clinical signs of hypercortisolism such as weight gain, purple striae, ecchymosis and muscle weakness (25).

In conclusion, the diagnosis of CS during pregnancy is difficult as no clinical sign is sufficiently specific to allow

certainty of the diagnosis. Several differential diagnoses can be made in case of hypertension: however, none of them is associated with some of the clinical signs found in patients with hypercortisolism.

What are the risks for the mother?

Uncontrolled CS during pregnancy is associated with a high rate of maternal complications (6): 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%).

In a systematic review of 168 manuscripts published in the literature from January 1952 to April 2015 (7), the authors analyzed published reports on 263 pregnancies in 220 women with active CS during pregnancy or with a history of CS, which was controlled during gestation. Women with active CS had more gestational diabetes mellitus (36.9 vs 2.3%, $P=0.003$), gestational hypertension (40.5 vs 2.3%, $P<0.001$) and preeclampsia (26.3 vs 2.3%, $P=0.001$) than those with cured disease.

What are the risks for the fetus?

Before outlining the consequences of fetal exposure to hypercortisolism, a brief summary of the way the fetus reacts when the mother's cortisol levels increase during pregnancy is necessary: upregulation of placental 11 β -hydroxy-steroid-dehydrogenase type 2 (11 β HSD2) allows conversion of glucocorticoids to inactive metabolites, thereby leading to a fetal protection (18). Recent studies suggested that endocrine disruptors or mental health disease of the mother could decrease the activity of 11 β HSD2 (26). Increased fetal morbidity was underlined in previous reviews (6): prematurity (43% of pregnancies), intrauterine growth retardation (21%), stillbirths (6%), spontaneous abortion or intrauterine death (5%) and hypoadrenalism (2%). In the previously cited study by Caimari and colleagues (7), the proportion of fetal loss in active CS was higher than in cured CS (23.6 vs 8.5%, $P=0.021$), as well as increased global fetal morbidity (33.3 vs 4.9%, $P<0.001$). Diagnosis during pregnancy was associated with the poorest outcome compared to diagnosis before or after pregnancy. Both medical and surgical treatments during pregnancy appeared to reduce the risk of fetal loss.

Although in some experimental models high cortisol levels in the mother have been associated with increased

risk of obesity and adiposity in the next generation, a study on normal human pregnancies showed that higher maternal cortisol was independently associated only with marginally higher fat mass index in girls and not in boys (27). To the best of our knowledge, such data on children born from mothers with pathological hypercortisolism are lacking.

When should aberrant receptors be suspected in hypercortisolism during pregnancy?

Patients with active CS in pregnancy-induced CS, experienced more problems in pregnancy and had the worst fetal prognosis in comparison to other causes (7). Andreescu *et al.* (28) recently reported the rare cases of 3 patients with hypercortisolism and adrenal adenoma during pregnancy: 1 of them showed *in vivo* response of cortisol production to HCG, LHRH, glucagon, vasopressin and a standard mixed meal. In these 3 patients, pregnancy led to overt hypercortisolism. Before pregnancy, it is likely that these patients had mild hypercortisolism due to glucocorticoid stimulation by LH and that increased HCG levels during pregnancy led to overt hypercortisolism. The outcome in such patients is difficult to predict: autonomous cortisol secretion can happen only during pregnancy or can be maintained, usually at lower levels of cortisol, after delivery (28).

What is the optimal timing of surgery in hypercortisolism during pregnancy?

Whatever the type of surgery (pituitary or adrenal), it should be ideally performed during the second trimester, before the 24th week of gestation (29). Some case reports showed the possibility of surgery during the third trimester, with a higher risk of prematurity (6, 8, 9). For instance, laparoscopic adrenalectomy for CS in pregnancy was found to be a safe and efficacious procedure up to 32 weeks of gestation (30), leading to a reduction in perinatal mortality and maternal morbidity rates, but with little effect on the occurrence of preterm birth and intrauterine growth restriction (30, 31). There are very limited data on the efficacy and the risks induced by bilateral adrenalectomy for hypercortisolism during pregnancy: if this option is chosen, the ideal time frame is the same as for unilateral adrenalectomy.

Physicians should keep in mind that patients treated surgically for hypercortisolism will likely have adrenal insufficiency for the rest of the pregnancy. The dose of hydrocortisone to administer is identical to the dose in non-pregnant woman in the first 2 trimesters while some authors recommended to slightly increase the dose during the third trimester. Of note, extreme caution must be taken during delivery with a drastic increase of the dose of hydrocortisone to avoid the risk of adrenal insufficiency (32).

Is the use of anticortisol drugs possible during pregnancy?

Importantly, a subset of patients, especially those discovered late in pregnancy, can be managed conservatively by trying to control comorbidities such as hypertension and diabetes mellitus without necessarily using specific anticortisol drugs (6). In some cases, however, the use of inhibitors of steroidogenesis or centrally acting drugs has been reported. The experience reported in the literature is however poor (33).

Metyrapone was found to allow good control of hypercortisolism, including one report of adrenal insufficiency, but may worsen hypertension because of deoxycorticosterone accumulation, and thus, increase the frequency of preeclampsia (6). Metyrapone also passes through the placental barrier and may thus affect fetal adrenal steroid synthesis (34, 35).

Medical treatment of CS with ketoconazole in pregnant women may permit good control of hypercortisolism and in a limited number of cases was found to be well tolerated both by the mother and the fetus (36). However, it was less frequently used because of potential teratogenicity and increased rate of abortion observed in animal studies (6).

Cabergoline may be an effective and safe therapeutic option for the treatment of Cushing's disease during pregnancy (37, 38). Indeed in two reported cases, a pregnancy was obtained while on high-dose cabergoline and maintained throughout pregnancy with complete remission (37, 38).

Mitotane is classically contraindicated due to a risk of teratogenicity (6). To our knowledge, published data are lacking for pasireotide.

In conclusion, medical treatments should be reserved for specific cases, where surgery could be life-threatening. If necessary, the safest option appears to be metyrapone, though due to the very low number of patients reported in the literature it should be used with caution.

How should follow-up of hypercortisolism be done after delivery?

Patient follow-up is mainly dependent on the treatment performed during pregnancy. In case of adrenal insufficiency due to pituitary surgery or unilateral adrenal surgery, regular cortisol evaluations should be performed to look for recovery of the HPA axis. In untreated Cushing's disease, biological evaluations and a new pituitary MRI should be performed 3–6 months after delivery. Interestingly, Owens *et al.* reported that a period of up to 5 weeks after delivery would be necessary to obtain a normal response to dexamethasone (39).

Jornayvaz and coworkers evaluated the risk of Nelson's syndrome during pregnancy in 17 patients (20 pregnancies in total) treated by bilateral adrenalectomy for Cushing's disease before pregnancy. While the majority of the patients presented pituitary progression and ACTH increase during pregnancy, it was not significantly different with the progression observed before the pregnancy: pregnancy *per se* thus does not increase the risk of Nelson's syndrome (40).

What are the diagnostic and therapeutic challenges of adrenocortical carcinoma diagnosed during pregnancy?

Adrenocortical carcinoma (ACC) accounts for less than 10% of the etiologies of CS during pregnancy. The diagnosis is usually made on clinical signs of hypersecretion and/or clinical signs of compression of local structures. Of note, the levels of testosterone can be difficult to analyze, because of the increase in testosterone-binding globulin, leading to artificially increased total testosterone. Usually, initial European Network for the Study of Adrenal Tumors (ENSAT) staging is more severe than for ACC diagnosed in non-pregnant women due both to a delayed diagnosis, and possibly to increased adrenal cell proliferation due to increased sex hormone levels (41). The diagnosis is based first on ultrasound and then MRI, when necessary, to avoid the risk of radiation exposure for the fetus. Cortisol-lowering drugs may be given over a very short-term period, while waiting for urgent surgery. However, mitotane has been shown to be a teratogen in mouse models, and use during pregnancy does not therefore appear to be safe even if rare cases have been reported in the literature with no short-term damage to the fetus (42). In contrast to the

results of surgery for non-malignant tumors, the few cases of patients operated on during pregnancy for adrenal carcinoma showed incomplete resection in the majority of cases, and prematurity with use of cesarean section in 25–50% cases. The overall prognosis after pregnancy was worse than that for non-pregnant women of the same age and ENSAT grade (43, 44).

A recent ENSAT study reported the outcome of pregnancy in 17 women operated for an ACC, at least 3 months prior to the pregnancy. The authors showed that there was no increased risk of recurrence in this group of patients, however, interpretation of these results needs to be tempered due to the low number of patients (in this rare disease and rare situation), and the fact that the majority of patients had ACC with a good prognosis (ENSAT Grades 1 and 2). These authors recommended a 5-year period after remission before considering falling pregnant (45).

How to handle contraception in a young woman with CS?

Pregnancy in CS is extremely rare due to the influence of hypercortisolism and hyperandrogenism on the reproductive axis, resulting in suppression of gonadotropin secretion. This leads to abnormal menses evolving to amenorrhea in the majority of patients with CS, and consequent infertility. One study reported smaller ovaries with inconsistent fibrosis, a lower number of primordial follicles and decreased follicular activity in women with CS (12). Though the possibility of pregnancy is low in patients with active hypercortisolism, physicians should consider contraceptive methods in these young patients at high risk. However, the state of hypercoagulability observed in patients with hypercortisolism, and consequently, the increased risk of deep venous thrombosis, contraindicates the use of classical estrogen-progestin pills (46). After remission, data are contradictory on the time needed to return to a normal coagulation status: it is clearly improved one year after surgery, but slight anomalies persist (47). A complete coagulation workup is advisable at this stage to look for persistent contra-indications to estrogens. Given the risks of exposure to hypercortisolism during pregnancy for the mother and the fetus, we consider that pregnancy should not be recommended, even in patients controlled by cortisol-lowering drugs on a long-term basis, and that non-hormonal methods of contraception should be advised.

Conclusion

Pregnancy is a rare event in patients presenting with CS. However, the consequences of maternal and fetal exposure to hypercortisolism can be life threatening. This is why proper diagnosis and management of such patients is crucial. When a clinician considers the diagnosis of CS, it should then lead to repeated biochemical evaluations, as cortisol levels are usually difficult to analyze during pregnancy. To this end, salivary cortisol should be looked at carefully, as it appears to be the most reliable marker in this situation. The management is then based on the treatment of comorbidities, and surgery, after considering the ratio of risk to benefit. The complex issues raised by the management of such patients leads us to consider that pregnancy should be contra-indicated, unless a biochemical remission is obtained for at least one year.

Declaration of interest

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

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