Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

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Objective: Our objective was to evaluate the published literature and reach a consensus on the treatment of patients with ACTH-dependent Cushing's syndrome, because there is no recent consensus on the management of this rare disorder.

Participants: Thirty-two leading endocrinologists, clinicians, and neurosurgeons with specific expertise in the management of ACTH-dependent Cushing's syndrome representing nine countries were chosen to address 1) criteria for cure and remission of this disorder, 2) surgical treatment of Cushing's disease, 3) therapeutic options in the event of persistent disease after transsphenoidal surgery, 4) medical therapy of Cushing's disease, and 5) management of ectopic ACTH syndrome, Nelson's syndrome, and special patient populations.

Evidence: Participants presented published scientific data, which formed the basis of the recommendations. Opinion shared by a majority of experts was used where strong evidence was lacking.

Consensus Process: Participants met for 2 d, during which there were four chaired sessions of presentations, followed by general discussion where a consensus was reached. The consensus statement was prepared by a steering committee and was then reviewed by all authors, with suggestions incorporated if agreed upon by the majority.

Conclusions: ACTH-dependent Cushing's syndrome is a heterogeneous disorder requiring a multidisciplinary and individualized approach to patient management. Generally, the treatment of choice for ACTH-dependent Cushing's syndrome is curative surgery with selective pituitary or ectopic corticotroph tumor resection. Second-line treatments include more radical surgery, radiation therapy (for Cushing's disease), medical therapy, and bilateral adrenalectomy. Because of the significant morbidity of Cushing's syndrome, early diagnosis and prompt therapy are warranted. **(*J Clin Endocrinol Metab* 93: 2454–2462, 2008)**

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Abbreviations: HPA, Hypothalamo-pituitary-adrenal; MRI, magnetic resonance imaging; UFC, urinary free cortisol.

Endogenous Cushing's syndrome is an endocrine disease caused by excessive secretion of ACTH in approximately 80% of cases, usually by a pituitary corticotroph adenoma (Cushing's disease), less often by an extrapituitary tumor (ectopic ACTH syndrome), and very rarely by an ectopic CRH-secreting tumor. About 20% of patients have ACTH-independent Cushing's syndrome, *i.e.* excess cortisol secretion by unilateral adrenocortical tumors or by bilateral adrenal hyperplasia or dysplasia (1).

In ACTH-dependent Cushing's syndrome, elevated corticotroph tumor-derived ACTH secretion results in excess adrenal gland cortisol secretion. The normal cortisol feedback mechanism of the hypothalamo-pituitary-adrenal (HPA) axis is disturbed, with loss of circadian rhythm and excess cortisol production, resulting in hypercortisolism (2). Features of hypercortisolism include weight gain, severe fatigue and muscle weakness, high blood pressure, depression, cognitive impairment, purplish skin striae, easy bruising, hyperpigmentation, loss of libido, diabetes, hirsutism, acne, and menstrual disorders (1–5). In adults, muscular atrophy and purple striae can be important diagnostic features, whereas growth retardation is often present in children. The diagnosis of Cushing's syndrome is complicated by the nonspecificity and high prevalence of clinical symptoms in patients without the disorder and involves a variety of biochemical tests of variable sensitivity and specificity. Efficient screening and confirmatory procedures are therefore essential before considering therapy. Treatment decisions should be weighed carefully in patients with only mild or intermittent hypercortisolism, because the benefits of surgery have not been established definitively in this population.

In 2003, a consensus statement was published on the diagnosis and complications of Cushing's syndrome (1). In April 2007, a workshop was held in Budapest, Hungary, to reach a consensus on the treatment of ACTH-dependent Cushing's syndrome. Participants included leading endocrinologists, clinicians, and neurosurgeons with specific expertise in the management of ACTH-dependent Cushing's syndrome, and the workshop was endorsed by the European Neuroendocrine Association and The Pituitary Society. This paper is a summary of the consensus reached on the treatment of ACTH-dependent Cushing's syndrome.

Part I: Criteria for Cure and Remission of ACTH-Dependent Cushing's Syndrome

The goals of treatment in ACTH-dependent Cushing's syndrome include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence.

In general, the initial treatment of choice for Cushing's disease is selective pituitary adenomectomy by a surgeon with extensive demonstrated experience in pituitary surgery. Tumor resection leads to corticosteroid deficiency because the remaining normal corticotroph cells have been suppressed by longstanding hypercortisolism. As a result, hypocortisolism provides an index of surgical success. However, patients with minimal preoperative hypercortisolism, because of medical treatment or mild disease, may be eucortisolemic and not require additional therapy. Thus, the decision to treat a patient with cortisol-lowering medications before surgery should be undertaken with the realization that the ability to assess cure may be compromised. Glucocorticoid withdrawal symptoms (*e.g.* fatigue, nausea, and joint aches) should be anticipated in all patients; hypocortisolism and symptoms are managed with physiological glucocorticoid therapy until the axis recovers. Some patients with severe withdrawal symptoms require transient treatment with supraphysiological doses of glucocorticoids (see below: *Postoperative treatment of secondary adrenal insufficiency*).

We recommend assessment of remission by measurement of morning serum cortisol during the first postoperative week, either by withholding treatment with glucocorticoids or by using low doses of dexamethasone (*i.e.* below the standard low-dose test amount). If glucocorticoid treatment is withheld, it is essential that the patient be monitored closely for signs of hypoadrenalism, preferably in-hospital; in centers where patients are routinely discharged to home within 36 h, this approach may not be feasible. Because glucocorticoids may suppress any remaining tumor tissue and mask persistent disease, their use should be avoided, or the dosage minimized, when cure is assessed.

The literature suggests that persistent postoperative morning serum cortisol levels of less than 2 μg/dl (~50 nmol/liter) are associated with remission and a low recurrence rate of approximately 10% at 10 yr (6–14). A persistent serum cortisol level above 5 μg/dl (~140 nmol/liter) for up to 6 wk requires further evaluation. If persistent hypercortisolism is excluded, the recurrence rate is higher in these patients than in those with lower values. When serum cortisol levels are between 2 and 5 μg/dl, the patient can be considered in remission and can be observed without additional treatment for Cushing's disease, as the recurrence rate appears to be no greater than that seen in patients with serum cortisol levels less than 2 μg/dl (6–14). Occasionally the serum cortisol level falls more gradually, possibly reflecting transient adrenal autonomy, and it is important to ensure that the cortisol level has reached a nadir before considering further therapy. Measurement of urinary free cortisol (UFC) can provide additional useful information when the serum cortisol level is equivocal. UFC values below 20 μg/24 h (55 nmol/24 h) suggest remission, whereas values in the normal range (20–100 μg/24 h; 55–276 nmol/24 h) are equivocal. Values above the normal range indicate persistent tumor.

Part II: Surgical Treatment of Cushing's Disease

Transsphenoidal pituitary resection: adenomectomy *vs.* hypophysectomy

Cushing's disease is caused by a discrete ACTH-secreting tumor in the majority of cases (1); diffuse corticotroph hyperplasia is rarely encountered. As a result, optimal treatment is surgical resection by selective adenomectomy, performed by an experienced surgeon, as long as the tumor can be identified. Careful sectioning through the pituitary gland may be required to locate

the tumor, because some tumors have an identifiable pseudocapsule, whereas others do not exhibit a discrete border between the tumor and normal pituitary tissue. If the tumor was pathologically identified at initial surgery, the probability of subsequent successful resection is higher than if no tumor was found initially. Remission rates in patients with a microadenoma undergoing selective adenomectomy by an expert pituitary surgeon are in the range of 65–90%. The recurrence rate in these patients is 5–10% at 5 yr and 10–20% at 10 yr (6, 11, 15–22), with young age (25 yr or younger) being a significant risk factor for relapse (22). Surgical success rates are lower in patients harboring macroadenomas and in patients with tumors that have invaded the dura (23). In patients with a macroadenoma, remission rates are lower (<65% in most series), and not only are recurrence rates higher (12–45%) but recurrence also occurs sooner than in those with a microadenoma (mean of 16 *vs.* 49 months) (21, 24, 25). Transsphenoidal microsurgery is still the most widely used technique, and because there are limited data available on outcome in entirely endoscopic operations, a comparison on outcome between microscopic and endoscopic pituitary surgery cannot be made.

Favorable prognostic factors associated with successful adenomectomy include detection of the microadenoma by magnetic resonance imaging (MRI), a well-defined tumor that is not invading either the basal dura or cavernous sinus, histological confirmation of an ACTH-secreting tumor, low postoperative serum cortisol levels, and long-lasting adrenal insufficiency (6, 11, 15–20, 22, 26, 27).

For patients in whom a discrete microadenoma cannot be located by sellar exploration, total or partial (central core or hemi-) hypophysectomy may be indicated. However, total or partial hypophysectomy induces remission less often (approximately 70% of patients) than selective tumor resection (11, 19, 26, 28, 29) and is associated with a higher rate of complications and hypopituitarism than selective adenomectomy.

Postsurgical recurrence of Cushing's disease may be higher than that associated with other types of pituitary tumors, but more data are needed to establish this observation.

Part III: Persistent Disease after Transsphenoidal Surgery

The criteria for cure after transsphenoidal surgery are discussed in *Part I: Criteria for Cure and Remission of ACTH-dependent Cushing's Syndrome*. In the event of failure after initial pituitary surgery or relapse after a period of remission, a choice of second-line therapeutic options needs to be discussed with the patient, including repeat pituitary surgery, radiotherapy, or bilateral adrenalectomy.

Pituitary surgery for persistent or recurrent disease

Repeat pituitary surgery may be undertaken if disease persists after initial surgery, although there is an overall lower rate of success than that seen after the first operation (30–32). It has been shown to be efficacious in approximately two thirds (50–70%) of patients in a limited number of specialized centers (18, 30–32), although remission rates are higher if an adenoma is located. However, reoperation carries a significant risk of pituitary insufficiency, particularly in patients undergoing hypophysectomy *vs.* selective adenomectomy (50 *vs.* 5%) (31). Improved success rates are achieved in patients with radiologically detectable tumors.

The ideal time for repeat transsphenoidal surgery for residual disease is as soon as active, persistent disease is evident. A delay of 4–6 wk may be required to confirm the need for reoperating because of continued partial improvement in cortisol levels after the initial surgery.

Radiotherapy

Fractionated external beam radiotherapy or stereotactic radiosurgery achieves control of hypercortisolemia in approximately 50–60% of patients within 3–5 yr (22, 33–36). It remains to be determined whether stereotactic radiosurgery will result in more rapid biochemical control than conventional radiation (35, 37, 38). Long-term follow-up is necessary to detect relapse, which can occur after an initial response to both types of radiotherapy.

The incidence of therapy-induced pituitary failure appears to be similar with radiotherapy or radiosurgery. Insufficient studies are available to evaluate the effects of radiotherapy on cerebrovascular and neurocognitive functions. The risk of second tumor formation after pituitary radiation is considered to be in the range of 1–2% (39), but this may not be due to the radiotherapy *per se*.

Bilateral adrenalectomy

Bilateral adrenalectomy is a definitive treatment that provides immediate control of hypercortisolism. Furthermore, employing minimally invasive adrenalectomy decreases the immediate morbidity of this procedure (40–43). However, the resultant permanent hypoadrenalism requires careful education and evaluation of patients because of the need for lifelong glucocorticoid and mineralocorticoid replacement therapy. Performing regular pituitary-directed MRI scans and evaluation of plasma ACTH levels is mandatory in these patients to ascertain whether there is corticotroph tumor progression because of the risk of developing Nelson's syndrome (22, 44, 45).

The final treatment recommendation may in part depend on the treatment options available, as well as the acceptability of the relative risks. Both repeat transsphenoidal surgery and radiation therapy carry significant risks of hypopituitarism; the advantage of surgery is that, if successful, the response is immediate. Radiation therapy can eliminate tumors invading the dura or cavernous sinus, both of which are frequent causes of surgical failure, which repeat surgery cannot do. Adrenalectomy is generally a more morbid procedure than either transsphenoidal surgery or radiation therapy, carries the risk of Nelson's syndrome, and requires lifelong glucocorticoid and mineralocorticoid replacement therapy. Nonetheless, the response is immediate and the morbidity can be minimized by the use of endoscopic approaches. In general, we favor repeat transsphenoidal surgery as the initial therapy for persistent or recurrent disease, with radiosurgery or conventional radiotherapy if unsuccessful, but any

treatment recommendation needs to be individualized. If remission is not achieved with reoperation, the choice between pituitary-directed radiotherapy and bilateral adrenalectomy requires consideration of pituitary status after pituitary surgery as well as the capacity of the patient to tolerate medical therapy while awaiting the effects of radiotherapy. Bilateral adrenalectomy may be indicated in patients with persistent hypercortisolism despite treatment with adrenal enzyme inhibitors or with intolerance to these agents or as an alternative to long-term medical treatment after pituitary radiotherapy and in women who wish to maintain fertility without the need for ovulation induction.

Additional studies on the quality of life of patients treated with either radiotherapy or bilateral adrenalectomy will be important.

Part IV: Medical Therapy of Cushing's Disease

Adrenal-directed therapy: steroidogenesis inhibitors

Adrenal-directed therapy (steroidogenesis inhibitors) may be highly effective but does not treat the underlying tumor or restore normal HPA secretory dynamics. Most experience with steroidogenesis inhibitors has been acquired with metyrapone and ketoconazole, which appear to be more effective and better tolerated than aminoglutethimide (46–55). Metyrapone treatment leads to marked inhibition of aldosterone biosynthesis and accumulation of aldosterone precursors with weak mineralocorticoid activity. Electrolyte balance and blood pressure levels vary individually with the degree of aldosterone inhibition and 11-deoxycorticosterone stimulation. Adverse effects due to increased 11-deoxycorticosterone levels (hypokalemia, edema, and hypertension) are infrequent (56). At present, metyrapone is not commercially available in the United States, but it can be provided for compassionate use by contacting the manufacturer (Novartis) directly, whereas aminoglutethimide is no longer available worldwide. Mild elevations in liver enzymes (up to 3-fold normal), which are transient, are not a contraindication to medical therapy with ketoconazole, but liver function should be monitored carefully because of the rare complication of liver failure. The possibility of the development of hypogonadism in men during ketoconazole therapy may favor the initial use of metyrapone in this population. Conversely, the association of hirsutism with metyrapone treatment in women may make ketoconazole a better choice in this population.

Interestingly, in contrast to subjects with an intact HPA axis, patients with pituitary-dependent Cushing's disease show no compensatory rise, or decrease, in ACTH levels upon prolonged administration of ketoconazole. According to human and animal studies, however, this phenomenon does not seem to involve a direct effect on ACTH secretion but rather an adjustment in the sensitivity of the HPA axis (47, 48, 50, 53, 54). Moreover, the ACTH response to CRH in patients with Cushing's disease was enhanced (47) or unchanged (50) during ketoconazole treatment compared with the pretreatment response. Taken together, these findings argue against an additional site of inhibition at the pituitary level, although it was suggested by *in vitro* studies of pituitary corticotrophs (57).

Mitotane (o,p'-DDD) may prove highly effective in the long-term suppression of hypercortisolism in the majority of patients with ACTH-dependent Cushing's syndrome because of its specific adrenolytic action. Its mechanism of action also prevents the risk of escape phenomenon in response to the ACTH rise that occurs in Cushing's disease when plasma cortisol is decreased (58). However, its onset of action is slow (weeks or months), and the adverse effects associated with mitotane therapy (mainly digestive and neurological) require careful monitoring of drug levels, and it is routinely used in only a few centers.

In situations where rapid control of cortisol levels is required and oral therapy is problematic, iv etomidate therapy may be considered (59–61).

Treatment with the glucocorticoid receptor antagonist mifepristone (RU486) has been reported in fewer than 20 patients with ectopic ACTH secretion, and its use for this indication is currently investigational (62). There is no significant experience reported yet with this agent in patients with Cushing's disease, and assessment of its efficacy in the absence of a biochemical marker is challenging.

The initial dose and escalation of the drugs used (Table 1) depend on the severity of the presenting symptoms and biochemical features. There are regional differences in regulatory approvals; local prescribing information should be consulted.

Follow-up evaluations should include the examination of clinical features and 24-h UFC levels, aiming for normalization of both. A few centers use a cortisol day curve with five measurements of serum cortisol over 12 h, with a goal of maintaining the mean level within normal limits. Blood samples are taken at 0900, 1200, 1500, 1800, and 2100 h, and the mean cortisol levels are calculated; previous studies using an isotopic dilution production rate technique have established that a mean level of 150–300 nmol/liter (~5–10 μg/dl) is equivalent to a normal production rate (63). Several assessments may be advisable, because control may be variable with cyclical disease.

TABLE 1. Dosages of steroidogenesis inhibitors used in patients with Cushing's disease

Drug	Initial dosage	Maximal dosage	Total daily dose
Ketoconazole	200 mg bid	400 mg tid	1200 mg
Metyrapone	250 mg qid	1500 mg qid	6000 mg
Mitotane	500 mg tid	3000 mg tid	9000 mg
Etomidate	Bolus of 0.03 mg/kg iv followed by infusion 0.1 mg/kg·h	0.3 mg/kg·h	

These recommendations are from the international consensus panel. Local prescribing information should be consulted because of regional differences in regulatory approvals. bid, Twice daily; qid, four times daily; tid, three times daily.

The choice of UFC assay should be considered carefully, with tandem mass spectrometry considered most specific, and it is important to note that normal ranges vary greatly depending on the assay method. Although salivary cortisol measurements may be an important endpoint in establishing efficacy and restoration of normal cortisol levels, validation data in patients treated for Cushing's disease are needed. Whichever technique is used, the aim is to restore a 24-h production rate of cortisol within the normal range, although circadian rhythmicity may not necessarily be restored. However, the clinical impact of these abnormal rhythms remains unclear.

Adrenal-directed medical therapy is effective in the majority of patients in a dose-dependent manner. Its indications might include the preoperative preparation of patients to correct severe complications of the disease quickly. In this context, the possibility of avoiding hypoadrenalism immediately after surgery by normalization of cortisol production for a sufficient length of time preoperatively pertains to clinical observation rather than randomized clinical trials and should be better explored. Drug control of hypercortisolism is also suitable for patients awaiting a response to radiation therapy and whenever a palliative treatment is needed. In general, definitive therapy, either surgery or radiotherapy, should be considered for all patients, and long-term medical therapy alone is rarely indicated.

Tumor-directed medical therapy

Pituitary-directed therapy targets the underlying cause of the disease, and therefore, several investigational agents are under evaluation. Despite initial promise (54, 64–66), subsequent studies do not support a routine clinical role for the use of peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, such as rosiglitazone and pioglitazone (67–70). Although retinoic acid is effective at reducing ACTH in animal models (71) and in dogs with Cushing's disease (72), the effective dose used is high and human clinical trial results are not currently available.

Current medical therapies targeted to the corticotroph tumor itself have not been uniformly successful. However, a medical therapy that acts directly on the pituitary tumor to normalize ACTH secretion and inhibit tumor growth would represent a major nonsurgical advance in the treatment of this disease. Molecular studies provide a rationale for the use of somatostatin receptor ligands for the treatment of corticotroph adenomas, because these tumors express somatostatin receptor subtypes sst_1, sst_2, and sst_5, although expression of sst_5 predominates (73, 74). The commercially available somatostatin analogs octreotide and lanreotide are predominantly sst_2-selective ligands and are mostly ineffective in treating Cushing's disease (75–77). Somatostatin analogs with a broader somatostatin receptor subtype affinity might be more effective. Pasireotide (SOM230; Novartis, Basel, Switzerland), which has high affinity for sst_{1-3} and especially sst_5, shows promise as a tumor-directed medical therapy in patients with Cushing's disease (74, 78–81). Longer-term trials are needed to determine the safety and efficacy of pasireotide.

The dopamine D_2 receptor is expressed in more than 75% of corticotroph pituitary adenomas (82). In long-term studies with bromocriptine, disease remission was confirmed in only a small minority of patients (83). A small, short-term study suggests that cabergoline at dosages of 2–3.5 mg/wk may be effective in treating a subset of patients with Cushing's disease (82). However, more data are required not only for efficacy but also to address the long-term safety of cabergoline in these patients (84, 85). The use of combination pituitary-directed drug therapy (*e.g.* a dopamine D_2 receptor agonist plus a sst receptor ligand) is an exciting concept that has not been evaluated to date.

Previous studies have shown that serotonin antagonists and γ-aminobutyric acid (GABA) agonists are generally ineffective and are not routinely recommended (86).

Part V: Management of Ectopic ACTH Syndrome, Nelson's Syndrome, Special Patient Populations, and the Patient after Successful Surgical Treatment

Ectopic ACTH syndrome

Ectopic ACTH syndrome is a heterogeneous disease. Ectopic ACTH-secreting tumors include small-cell lung cancer, thymic, pulmonary, appendiceal, and pancreatic carcinoid tumors, gastrinomas pheochromocytomas, medullary thyroid cancer, and other neuroendocrine tumors (87–89). The choice of treatment for ectopic ACTH syndrome depends on tumor identification, localization, and classification. The most effective treatment option is surgical resection and cure, although this is not always possible, *e.g.* in metastatic disease or in the case of occult tumors.

Tumor-directed therapy involves a multidisciplinary, individualized approach and can include somatostatin analogs, systemic chemotherapy, interferon-α, chemoembolization, radiofrequency ablation, and radiation therapy (88–91). Adrenal-directed therapy, *i.e.* medical therapy to block cortisol production or bilateral adrenalectomy, is warranted in patients with ectopic ACTH syndrome who have failed primary surgical therapy. It is also used in patients with occult ectopic ACTH syndrome or patients with malignant disease with metastases or very severe symptoms of Cushing's syndrome (92, 93).

Although some ectopic ACTH-producing tumors, such as carcinoid tumors, may be indolent, others may be rapidly progressive, in which case prompt control of the hypercortisolemia and related biochemical dysfunction, especially hypokalemia, using an aggressive treatment regimen is important. Potassium-sparing diuretics are valuable and, *in extremis*, iv etomidate can be very useful (59, 94).

Nelson's syndrome

Nelson's syndrome comprises growth of a pituitary corticotroph adenoma after bilateral adrenalectomy and is associated with symptoms due to physical compression of neurological structures and increased ACTH secretion. Reported rates of Nelson's syndrome range from 8–29% (45). Rather than wait for the development of Nelson's syndrome after bilateral adrenalectomy, close monitoring by regular MRI scans and plasma ACTH levels should be undertaken to detect the occurrence of corticotroph tumor progression. Pituitary MRI and ACTH plasma level measurements are advised 3–6 months after bilat-

eral adrenalectomy and then at regular intervals thereafter. There is no validated predictive factor for Nelson's syndrome before surgery; however, a high plasma ACTH level (>1000 ng/liter) in the year after bilateral adrenalectomy may be a predictive factor for corticotroph tumor progression (45).

The early detection of corticotroph tumor progression offers the possibility of cure by surgery, particularly with microadenomas. Alternatively, an invasive adenoma might require radiotherapy, especially when repeated imaging shows a tumor progression. Fractionated external beam radiotherapy or stereotactic radiosurgery can be used depending on tumor size and location. Routine preventive radiotherapy after bilateral adrenalectomy is not generally warranted, and there is no proven efficacious medical treatment for corticotroph tumor progression after bilateral adrenalectomy.

Pediatric/adolescent Cushing's syndrome

The etiology of pediatric Cushing's syndrome varies with age. Adrenal hyperplasia secondary to McCune-Albright syndrome tends to occur in infants (mean age 1.2 yr), adrenocortical tumors are found in young children (mean age 4.5 yr), and ectopic ACTH syndrome is seen, albeit rarely, in older children (mean age 10.1 yr). By contrast, primary pigmented nodular adrenocortical disease (mean age 13.0 yr) and Cushing's disease (mean age 14.1 yr) are most often seen in adolescents (95).

Transsphenoidal surgery by an experienced surgeon is the preferred primary therapy of pediatric Cushing's disease, with cure rates similar to those seen in adult patients (96). If surgery is unsuccessful, radiotherapy may be more effective than it is in adult patients, with effective cure often occurring within 1 yr (97). There is disagreement as to the utility of bilateral petrosal sinus sampling in this age group to locate the tumor. However, it is agreed that MRI is less useful in children than in adults, because the tumor is often not visualized.

Many pediatric patients will have persistent GH deficiency after successful transsphenoidal surgery (98, 99). It is important to treat GH deficiency aggressively with GH replacement therapy and to avoid supraphysiological glucocorticoid doses to achieve the patient's adult height potential. Early diagnosis and treatment of GH deficiency is recommended to achieve optimal long-term growth (100). In addition, although normalization of decreased bone mineral density generally occurs in the long term, other metabolic abnormalities, particularly obesity, may remain problematic (100).

Pregnancy and Cushing's syndrome

Cushing's syndrome in pregnancy occurs rarely but has a significant effect on maternal and fetal morbidity. Detection of Cushing's syndrome usually occurs late in gestation, and the diagnosis is complicated by the signs of normal pregnancy, such as central weight gain, facial plethora, and pigmentation (101) and the normal physiological changes in the maternal HPA axis.

The etiology of Cushing's disease in pregnant patients varies. Pituitary-dependent Cushing's syndrome occurs in 33% of patients compared with 58–70% in nonpregnant groups. Adrenal causes account for 40–50% of pregnant patients (adrenal adenoma 46%, adrenal carcinoma 10%) compared with 15% in nonpregnant groups. ACTH-independent adrenal hyperplasia is seen in 3% of patients and ectopic Cushing's syndrome in 3% of patients (102, 103). Recurrent ACTH-dependent Cushing's syndrome during pregnancy has been described with the presence of LH/human chorionic gonadotropin receptors in the adrenal cortex (104). Maternal morbidity includes hypertension (68%), glucose intolerance (25%), and preeclampsia (14%), whereas fetal morbidity includes prematurity (43%), intrauterine growth restriction (21%), and stillbirth (6%) (102).

The treatment of choice for Cushing's disease in pregnancy is pituitary surgery, which should be undertaken as soon as possible or before the late third trimester. Although bilateral adrenalectomy is technically possible during gestation for patients with tumor remnant after transsphenoidal pituitary surgery, it is best reserved until the postpartum period. Second-line therapy with steroidogenesis inhibitors carries a potential risk to the fetus due to adverse effects from the medications. As a result, regulatory authorities in the United States and Europe consider ketoconazole, metyrapone, and mitotane either to be contraindicated in pregnancy or indicated only if the risk to the fetus is outweighed by the risks of nontreatment. If treatment is considered, metyrapone is recommended rather than ketoconazole, because of its effects of inhibition of androgen inhibition. It is also recommended over mitotane, because of its potential teratogenicity (105–107).

Postoperative treatment of secondary adrenal insufficiency

As noted above, successful surgery unmasks secondary adrenal insufficiency, so that nearly all patients require glucocorticoid replacement therapy. During the first postoperative year, the HPA axis recovers in most patients, allowing for discontinuation of these medications (all patients require glucocorticoid and mineralocorticoid replacement therapy after bilateral adrenalectomy, and this is not considered further here).

Ideally, the dosage of glucocorticoids after surgery should be equivalent to replacement dosages, *e.g.* hydrocortisone 12–15 mg/m^2 (or an equivalent) in a single morning dose or a divided dose with the majority given in the morning. This dosage avoids the continued suppression of the HPA axis and the prolongation of Cushingoid features associated with higher dosages. However, some patients have prominent features of glucocorticoid withdrawal that overlap with classical symptoms of adrenal insufficiency. These features include fatigue, depression, joint aches, nausea, and anorexia. If possible, we suggest that these patients receive hydrocortisone replacement therapy at the upper end of normal (*i.e.* 15 mg/m^2) in a split-dose regimen and be encouraged that these symptoms will improve in the first postoperative month. If the symptoms are intolerable, the glucocorticoid dose may be raised slightly above replacement, but supraphysiological doses should be tapered to replacement doses as soon as possible, ideally within the first month after surgery. Replacement therapy can be stopped when the morning cortisol level or the cortisol response to cosyntropin (Cortrosyn) is greater than 18 μg/dl (500 nmol/liter).

Conclusions

ACTH-dependent Cushing's syndrome is a heterogeneous disorder and requires a multidisciplinary and individualized approach to patient management. In general, the treatment of choice for ACTH-dependent Cushing's syndrome is curative surgery with selective pituitary or ectopic corticotroph tumor resection, although this is not always possible. Second-line treatments include more radical surgery, radiation therapy (for Cushing's disease), medical therapy, and bilateral adrenalectomy. Because of the significant morbidity of Cushing's syndrome, early diagnosis and prompt therapy are warranted.

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