

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)

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 $\mu\text{g/dl}$ (~ 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 $\mu\text{g/dl}$ (~ 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 $\mu\text{g/dl}$, 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 $\mu\text{g/dl}$ (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 $\mu\text{g/24 h}$ (55 nmol/24 h) suggest remission, whereas values in the normal range (20–100 $\mu\text{g/24 h}$; 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 sst₁, sst₂, and sst₅, although expression of sst₅ predominates (73, 74). The commercially available somatostatin analogs octreotide and lanreotide are predominantly sst₂-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 sst₅, 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 D₂ 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 D₂ 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/m² (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/m²) 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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References

1. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M 2003 Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 88:5593–5602
2. Boscaro M, Barzon L, Fallo F, Sonino N 2001 Cushing's syndrome. *Lancet* 357:783–791
3. Makras P, Toloumis G, Papadogias D, Kaltsas GA, Besser M 2006 The diagnosis and differential diagnosis of endogenous Cushing's syndrome. *Hormones (Athens)* 5:231–250
4. Newell-Price J, Trainer P, Besser M, Grossman A 1998 The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev* 19:647–672
5. Findling JW, Raff H 2006 Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab* 91:3746–3753
6. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B 2005 Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clin Endocrinol (Oxf)* 63:549–559
7. Chee GH, Mathias DB, James RA, Kendall-Taylor P 2001 Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? *Clin Endocrinol (Oxf)* 54:617–626
8. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH 2003 Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. *J Neurosurg* 98:967–973
9. Esposito F, Dusick JR, Cohan P, Moftakhar P, McArthur D, Wang C, Swerdloff RS, Kelly DF 2006 Clinical review: early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab* 91:7–13
10. Estrada J, Garcia-Uria J, Lamas C, Alfaro J, Lucas T, Diez S, Salto L, Barcelo B 2001 The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab* 86:5695–5699
11. Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A, Wilson CB 2004 Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J Clin Endocrinol Metab* 89:6348–6357
12. Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, Roelfsema F, Romijn JA 2003 Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. *J Clin Endocrinol Metab* 88:5858–5864
13. Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF 2002 Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. *Clin Endocrinol (Oxf)* 56:541–551
14. Yap LB, Turner HE, Adams CB, Wass JA 2002 Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. *Clin Endocrinol (Oxf)* 56:25–31
15. Bochicchio D, Losa M, Buchfelder M 1995 Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. *J Clin Endocrinol Metab* 80:3114–3120
16. Fahlbusch R, Buchfelder M, Muller OA 1986 Transsphenoidal surgery for Cushing's disease. *J R Soc Med* 79:262–269
17. Hofmann BM, Fahlbusch R 2006 Treatment of Cushing's disease: a retrospective clinical study of the latest 100 cases. *Front Horm Res* 34:158–184
18. Knappe UJ, Ludecke DK 1996 Persistent and recurrent hypercortisolism after transsphenoidal surgery for Cushing's disease. *Acta Neurochir Suppl* 65:31–34
19. Stevenaert A, Perrin G, Martin D, Beckers A 2002 [Cushing's disease and corticotrophic adenoma: results of pituitary microsurgery]. *Neurochirurgie* 48:234–265 (French)
20. Shimon I, Ram Z, Cohen ZR, Hadani M 2002 Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. *Neurosurgery* 51:57–61
21. Swearingen B, Biller BM, Barker FG, Katznelson L, Grinspoon S, Klibanski A, Zervas NT 1999 Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med* 130:821–824
22. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M 1996 Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *J Clin Endocrinol Metab* 81:2647–2652
23. Woo YS, Isidori AM, Wat WZ, Kaltsas GA, Afshar F, Sabin I, Jenkins PJ, Monson JP, Besser GM, Grossman AB 2005 Clinical and biochemical characteristics of adrenocorticotropin-secreting macroadenomas. *J Clin Endocrinol Metab* 90:4963–4969
24. De Tommasi C, Vance ML, Okonkwo DO, Diallo A, Laws Jr ER 2005 Surgical management of adrenocorticotrophic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. *J Neurosurg* 103:825–830
25. Blevins Jr LS, Christy JH, Khajavi M, Tindall GT 1998 Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. *J Clin Endocrinol Metab* 83:63–67
26. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, Savage MO, Afshar F, Besser GM 1993 Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clin Endocrinol (Oxf)* 38:73–78
27. Pouratian N, Prevedello DM, Jagannathan J, Lopes MB, Vance ML, Laws Jr ER 2007 Outcomes and management of patients with Cushing's disease with-

- out pathological confirmation of tumor resection after transsphenoidal surgery. *J Clin Endocrinol Metab*
28. Mampalam TJ, Tyrrell JB, Wilson CB 1988 Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. *Ann Intern Med* 109:487–493
 29. Robert F, Hardy J 1991 Cushing's disease: a correlation of radiological, surgical and pathological findings with therapeutic results. *Pathol Res Pract* 187:617–621
 30. Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN, Post KD 2005 Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *J Neurosurg* 102:1004–1012
 31. Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler Jr GB, Loriaux DL 1989 Repeat transsphenoidal surgery for Cushing's disease. *J Neurosurg* 71:520–527
 32. Hofmann BM, Hlavac M, Kreutzer J, Grabenbauer G, Fahlbusch R 2006 Surgical treatment of recurrent Cushing's disease. *Neurosurgery* 58:1108–1118
 33. Castinetti F, Nagai M, Dufour H, Kuhn JM, Morange I, Jaquet P, Conte-Devolx B, Regis J, Brue T 2007 Gamma knife radiosurgery is a successful adjuvant treatment in Cushing's disease. *Eur J Endocrinol* 156:91–98
 34. Devin JK, Allen GS, Cmelak AJ, Duggan DM, Blevins LS 2004 The efficacy of linear accelerator radiosurgery in the management of patients with Cushing's disease. *Stereotact Funct Neurosurg* 82:254–262
 35. Estrada J, Boronat M, Mielgo M, Magallon R, Millan I, Diez S, Lucas T, Barcelo B 1997 The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* 336:172–177
 36. Little MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML 1990 Long-term follow-up of low-dose external pituitary irradiation for Cushing's disease. *Clin Endocrinol (Oxf)* 33:445–455
 37. Petit JH, Biller BM, Yock TI, Swearingen B, Coen JJ, Chapman P, Ancukiewicz M, Bussiere M, Klibanski A, Loeffler JS 2008 Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. *J Clin Endocrinol Metab* 93:393–399
 38. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML 2007 γ knife surgery for Cushing's disease. *J Neurosurg* 106:980–987
 39. Brada M, Ford D, Ashley S, Bliss JM, Crowley S, Mason M, Rajan B, Traish D 1992 Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 304:1343–1346
 40. Gumbs AA, Gagner M 2006 Laparoscopic adrenalectomy. *Best Pract Res Clin Endocrinol Metab* 20:483–499
 41. Walz MK, Alesina PF, Wenger FA, Deligiannis A, Szuczik E, Petersenn S, Ommer A, Groeben H, Peitgen K, Janssen OE, Philipp T, Neumann HP, Schmid KW, Mann K 2006 Posterior retroperitoneoscopic adrenalectomy: results of 560 procedures in 520 patients. *Surgery* 140:943–948
 42. Chow JT, Thompson GB, Grant CS, Farley DR, Richards ML, Young Jr WF 2008 Bilateral laparoscopic adrenalectomy for corticotrophin-dependent Cushing's syndrome: a review of the Mayo Clinic experience. *Clin Endocrinol (Oxf)* 68:513–519
 43. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC 2007 Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience. *Ann Surg* 245:790–794
 44. Assie G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X 2004 The Nelson's syndrome. . . revisited. *Pituitary* 7:209–215
 45. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X 2007 Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. *J Clin Endocrinol Metab* 92:172–179
 46. Beardwell CG, Adamson AR, Shalet SM 1981 Prolonged remission in florid Cushing's syndrome following metyrapone treatment. *Clin Endocrinol (Oxf)* 14:485–492
 47. Boscaro M, Sonino N, Rampazzo A, Mantero F 1987 Response of pituitary-adrenal axis to corticotrophin releasing hormone in patients with Cushing's disease before and after ketoconazole treatment. *Clin Endocrinol (Oxf)* 27:461–467
 48. Burrin JM, Yeo TH, Ashby MJ, Bloom SR 1986 Effect of ketoconazole on adrenocorticotrophic hormone secretion in vitro and in vivo. *J Endocrinol* 108:37–41
 49. Gartner R, Albrecht M, Muller OA 1986 Effect of etomidate on hypercortisolism due to ectopic ACTH production. *Lancet* 1:275
 50. Loli P, Berselli ME, Tagliaferri M 1986 Use of ketoconazole in the treatment of Cushing's syndrome. *J Clin Endocrinol Metab* 63:1365–1371
 51. Schteingart DE, Tsao HS, Taylor CI, McKenzie A, Victoria R, Therrien BA 1980 Sustained remission of Cushing's disease with mitotane and pituitary irradiation. *Ann Intern Med* 92:613–619
 52. Sonino N, Boscaro M, Ambrosio G, Merola G, Mantero F 1986 Prolonged treatment of Cushing's disease with metyrapone and aminoglutethimide. *IRCS Med Sci* 14:485–486
 53. Sonino N, Boscaro M, Paoletta A, Mantero F, Ziliotto D 1991 Ketoconazole treatment in Cushing's syndrome: experience in 34 patients. *Clin Endocrinol (Oxf)* 35:347–352
 54. Sonino N, Boscaro M, Fallo F 2005 Pharmacologic management of Cushing syndrome: new targets for therapy. *Treat Endocrinol* 4:87–94
 55. Sonino N 1987 The use of ketoconazole as an inhibitor of steroid production. *N Engl J Med* 317:812–818
 56. Sonino N, Boscaro M 1999 Medical therapy for Cushing's disease. *Endocrinol Metab Clin North Am* 28:211–222
 57. Jimenez Reina L, Leal-Cerro A, Garcia J, Garcia-Luna PP, Astorga R, Bernal G 1989 In vitro effects of ketoconazole on corticotrope cell morphology and ACTH secretion of two pituitary adenomas removed from patients with Nelson's syndrome. *Acta Endocrinol (Copenh)* 121:185–190
 58. Luton JP, Mahoudeau JA, Bouchard P, Thieblot P, Hauteceuvre M, Simon D, Laudat MH, Touitou Y, Bricaire H 1979 Treatment of Cushing's disease by O,p'DDD: survey of 62 cases. *N Engl J Med* 300:459–464
 59. Krakoff J, Koch CA, Calis KA, Alexander RH, Nieman LK 2001 Use of a parenteral propylene glycol-containing etomidate preparation for the long-term management of ectopic Cushing's syndrome. *J Clin Endocrinol Metab* 86:4104–4108
 60. Johnson TN, Canada TW 2007 Etomidate use for Cushing's syndrome caused by an ectopic adrenocorticotrophic hormone-producing tumor. *Ann Pharmacother* 41:350–353
 61. Greening JE, Brain CE, Perry LA, Mushtaq I, Sales MJ, Grossman AB, Savage MO 2005 Efficient short-term control of hypercortisolemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm Res* 64:140–143
 62. Johanssen S, Allolio B 2007 Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol* 157:561–569
 63. Trainer PJ, Eastment C, Grossman AB, Wheeler MJ, Perry L, Besser GM 1993 The relationship between cortisol production rate and serial serum cortisol estimation in patients on medical therapy for Cushing's syndrome. *Clin Endocrinol (Oxf)* 39:441–443
 64. Emery MN, Leontiou C, Bonner SE, Merulli C, Nanzer AM, Musat M, Galloway M, Powell M, Nikooskam K, Korbonits M, Grossman AB 2006 PPAR- γ expression in pituitary tumours and the functional activity of the glitazones: evidence that any anti-proliferative effect of the glitazones is independent of the PPAR- γ receptor. *Clin Endocrinol (Oxf)* 65:389–395
 65. Heaney AP, Fernando M, Yong WH, Melmed S 2002 Functional PPAR- γ receptor is a novel therapeutic target for ACTH-secreting pituitary adenomas. *Nat Med* 8:1281–1287
 66. Heaney AP, Fernando M, Melmed S 2003 PPAR- γ receptor ligands: novel therapy for pituitary adenomas. *J Clin Invest* 111:1381–1388
 67. Mullan KR, Leslie H, McCance DR, Sheridan B, Atkinson AB 2006 The PPAR- γ activator rosiglitazone fails to lower plasma ACTH levels in patients with Nelson's syndrome. *Clin Endocrinol (Oxf)* 64:519–522
 68. Munir A, Song F, Ince P, Walters SJ, Ross R, Newell-Price J 2007 Ineffectiveness of rosiglitazone therapy in Nelson's syndrome. *J Clin Endocrinol Metab* 92:1758–1763
 69. Pecori GF, Scaroni C, Arvat E, Martin M, Giordano R, Albiger N, Leao AA, Picu A, Mantero F, Cavagnini F 2006 Effect of protracted treatment with rosiglitazone, a PPAR- γ agonist, in patients with Cushing's disease. *Clin Endocrinol (Oxf)* 64:219–224
 70. Suri D, Weiss RE 2005 Effect of pioglitazone on adrenocorticotrophic hormone and cortisol secretion in Cushing's disease. *J Clin Endocrinol Metab* 90:1340–1346
 71. Paez-Pereda M, Kovalovsky D, Hopfner U, Theodoropoulou M, Pagotto U, Uhl E, Lusa M, Stalla J, Grubler Y, Missale C, Arzt E, Stalla GK 2001 Retinoic acid prevents experimental Cushing syndrome. *J Clin Invest* 108:1123–1131
 72. Castillo V, Giacomini D, Paez-Pereda M, Stalla J, Labeur M, Theodoropoulou M, Holsboer F, Grossman AB, Stalla GK, Arzt E 2006 Retinoic acid as a novel medical therapy for Cushing's disease in dogs. *Endocrinology* 147:4438–4444
 73. Batista DL, Zhang X, Gejman R, Ansell PJ, Zhou Y, Johnson SA, Swearingen B, Hedley-Whyte ET, Stratakis CA, Klibanski A 2006 The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. *J Clin Endocrinol Metab* 91:4482–4488
 74. Hofland LJ, Van Der Hoek J, Felders R, van Aken MO, van Koetsveld PM, Waaijers M, Spruij-Mooij D, Bruns C, Weckbecker G, de Herder WW, Beckers A, Lamberts SWJ 2005 The multi-ligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. *Eur J Endocrinol* 152:645–654
 75. Ambrosi B, Boccicchio D, Fadin C, Colombo P, Faglia G 1990 Failure of somatostatin and octreotide to acutely affect the hypothalamic-pituitary-

- adrenal function in patients with corticotropin hypersecretion. *J Endocrinol Invest* 13:257–261
76. Lamberts SW, Uitterlinden P, Klijn JM 1989 The effect of the long-acting somatostatin analogue SMS 201–995 on ACTH secretion in Nelson's syndrome and Cushing's disease. *Acta Endocrinol (Copenh)* 120:760–766
77. Invitti C, de Martin M, Brunani A, Piolini M, Cavagnini F 1990 Treatment of Cushing's syndrome with the long-acting somatostatin analogue SMS 201–995 (sandostatin). *Clin Endocrinol (Oxf)* 32:275–281
78. Van Der Hoek J, Waaijers M, van Koetsveld PM, Sprij-Mooij D, Feelders RA, Schmid HA, Schoeffter P, Hoyer D, Cervia D, Taylor JE, Culler MD, Lamberts SW, Hofland LJ 2005 Distinct functional properties of native somatostatin receptor subtype 5 compared with subtype 2 in the regulation of ACTH release by corticotroph tumour cells. *Am J Physiol Endocrinol Metab* 289:E278–E287
79. Silva AP, Schoeffter P, Weckbecker G, Bruns C, Schmid HA 2005 Regulation of CRH-induced secretion of ACTH and corticosterone by SOM230 in rats. *Eur J Endocrinol* 153:R7–R10
80. Schmid HA 2007 Pasireotide (SOM230): development, mechanism of action and potential applications. *Mol Cell Endocrinol* 286:69–74
81. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G 2002 SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *Eur J Endocrinol* 146:707–716
82. Pivonello R, Ferone D, de Herder WW, Kros JM, De Caro ML, Arvigo M, Annunziato L, Lombardi G, Colao A, Hofland LJ, Lamberts SW 2004 Dopamine receptor expression and function in corticotroph pituitary tumors. *J Clin Endocrinol Metab* 89:2452–2462
83. Miller JW, Crapo L 1993 The medical treatment of Cushing's syndrome. *Endocr Rev* 14:443–458
84. Zanettini R, Antonini A, Gatto G, Gentile R, Tesi S, Pezzoli G 2007 Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 356:39–46
85. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E 2007 Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 356:29–38
86. Sonino N, Fava GA, Fallo F, Franceschetto A, Belluardo P, Boscaro M 2000 Effect of the serotonin antagonists ritanserin and ketanserin in Cushing's disease. *Pituitary* 3:55–59
87. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK 2005 Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *J Clin Endocrinol Metab* 90:4955–4962
88. Aniszewski JP, Young Jr WF, Thompson GB, Grant CS, van Heerden JA 2001 Cushing syndrome due to ectopic adrenocorticotrophic hormone secretion. *World J Surg* 25:934–940
89. Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, Reznek RH, Jenkins PJ, Monson JP, Grossman AB, Besser GM 2006 The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. *J Clin Endocrinol Metab* 91:371–377
90. Mansi L, Rambaldi PF, Panza N, Esposito D, Esposito V, Pastore V 1997 Diagnosis and radioguided surgery with ¹¹¹In-pentetreotide in a patient with paraneoplastic Cushing's syndrome due to a bronchial carcinoid. *Eur J Endocrinol* 137:688–690
91. von Werder K, Muller OA, Stalla GK 1996 Somatostatin analogs in ectopic corticotropin production. *Metabolism* 45:129–131
92. Pivonello R, Ferone D, Lamberts SW, Colao A 2005 Cabergoline plus lanreotide for ectopic Cushing's syndrome. *N Engl J Med* 352:2457–2458
93. Winquist EW, Laskey J, Crump M, Khamis F, Shepherd FA 1995 Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. *J Clin Oncol* 13:157–164
94. Schteingart DE 1989 Cushing's syndrome. *Endocrinol Metab Clin North Am* 18:311–338
95. Storr HL, Chan LF, Grossman AB, Savage MO 2007 Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. *Trends Endocrinol Metab* 18:167–174
96. Storr HL, Afshar F, Matson M, Sabin I, Davies KM, Evanson J, Plowman PN, Besser GM, Monson JP, Grossman AB, Savage MO 2005 Factors influencing cure by transphenoidal selective adenomectomy in paediatric Cushing's disease. *Eur J Endocrinol* 152:825–833
97. Storr HL, Plowman PN, Carroll PV, Francois I, Krassas GE, Afshar F, Besser GM, Grossman AB, Savage MO 2003 Clinical and endocrine responses to pituitary radiotherapy in pediatric Cushing's disease: an effective second-line treatment. *J Clin Endocrinol Metab* 88:34–37
98. Magiakou MA, Mastorakos G, Gomez MT, Rose SR, Chrousos GP 1994 Suppressed spontaneous and stimulated growth hormone secretion in patients with Cushing's disease before and after surgical cure. *J Clin Endocrinol Metab* 78:131–137
99. Carroll PV, Monson JP, Grossman AB, Besser GM, Plowman PN, Afshar F, Savage MO 2004 Successful treatment of childhood-onset Cushing's disease is associated with persistent reduction in growth hormone secretion. *Clin Endocrinol (Oxf)* 60:169–174
100. Davies JH, Storr HL, Davies K, Monson JP, Besser GM, Afshar F, Plowman PN, Grossman AB, Savage MO 2005 Final adult height and body mass index after cure of paediatric Cushing's disease. *Clin Endocrinol (Oxf)* 62:466–472
101. Lindsay JR, Nieman LK 2005 The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. *Endocr Rev* 26:775–799
102. Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK 2005 Cushing's syndrome during pregnancy: personal experience and review of the literature. *J Clin Endocrinol Metab* 90:3077–3083
103. Lindsay JR, Nieman LK 2006 Adrenal disorders in pregnancy. *Endocrinol Metab Clin North Am* 35:1–20, v
104. Hana V, Dokoupilova M, Marek J, Plavka R 2001 Recurrent ACTH-independent Cushing's syndrome in multiple pregnancies and its treatment with metyrapone. *Clin Endocrinol (Oxf)* 54:277–281
105. Blanco C, Maqueda E, Rubio JA, Rodriguez A 2006 Cushing's syndrome during pregnancy secondary to adrenal adenoma: metyrapone treatment and laparoscopic adrenalectomy. *J Endocrinol Invest* 29:164–167
106. Bronstein MD, Salgado LR, de Castro Musolino NR 2002 Medical management of pituitary adenomas: the special case of management of the pregnant woman. *Pituitary* 5:99–107
107. Trainer PJ 2002 Corticosteroids and pregnancy. *Semin Reprod Med* 20:375–380