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Perioperative Management of the Pituitary Patient

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Managing a patient requiring pituitary surgery involves a multidisciplinary approach that includes the neurosurgeon, ENT surgeon, anesthesiologist, ophthalmologist, and endocrinologist. This issue of *Endocrinology Rounds* discusses the perioperative management of these patients from an endocrinology point of view, with particular emphasis on indications for surgery, evaluation of the need for perioperative glucocorticoid replacement, and postoperative assessment of water balance disorders.

Patients with pituitary disease may present with findings in 3 broad categories:

- hypersecretion of pituitary hormone
- hypopituitarism
- mass effect from the tumour.

Each category needs to be addressed when considering whether surgery is required for patients, in deciding how to best prepare them for surgery, and how to follow them post-operatively.

Preoperative issues

In addition to a history and physical examination, the initial work-up of the patient suspected of having pituitary disease includes magnetic resonance imaging (MRI) of the sella, ideally with gadolinium contrast. It has been recently recognized that patients with advanced renal disease (glomerular filtration rate [GFR] <30 mL/min/1.73m²) can develop nephrogenic systemic fibrosis following gadolinium; therefore, it should not be used in this condition.¹ Patients also require visual field assessment (Humphrey 24-2 and Goldman).^{2,3} The following baseline pituitary blood tests should be measured to screen for hyper- or hypofunction: prolactin, sensitive thyroid-stimulating hormone (sTSH), free thyroxine (T₄), cortisol at 0800 h, adrenocorticotropic hormone (ACTH), 24-hour urine-free cortisol or overnight 1 mg dexamethasone suppression testing if Cushing's disease is possible, luteinizing hormone (LH), follicular-stimulating hormone (FSH), estradiol, or bioavailable testosterone, growth hormone (GH), insulin-like growth factor (IGF-1). The plasma sample for prolactin levels should be serially diluted to rule-out a falsely reduced value due to assay interference. This is seen in some patients with macroprolactinomas that secrete very high prolactin levels (the "hook effect"). Finally, α -subunit can be checked since, if it is elevated, it can be subsequently used for postoperative tumour surveillance.

Indications for surgery

The major indications for pituitary surgery include the following:

Mass effect

Clinical evidence of a mass effect includes any of the following: headache, decreased visual acuity, visual field defects, diplopia, or facial numbness in a V1 or V2 distribution. There is no characteristic headache with pituitary masses, but a pattern of new or a change in the type of headache tended to be associated with the prediction of an advanced sellar mass (P=0.063) in one study.⁴ It is important to rule-out other causes of headache, such as migraine. Another type of headache not directly related to the tumour is the sinus pain that can accompany acromegaly. Patients whose tumour results in a mass effect require surgery, except in special circumstances. With prolactinomas, the optimal initial therapy is medical management with a dopamine agonist even when there is a significant mass effect, since these tumours usually respond promptly to medical therapy. In one study, pretreatment visual field abnormalities normalized in 70% of patients after therapy with a dopamine agonist and tumour shrinkage was seen in 67% of cases.⁵ In a study of patients with giant adenomas (>4 cm diameter), 90% of patients had significant tumour shrinkage.⁶ Another study of giant adenomas demonstrated that there was a 50% reduction in tumour diameter and improved vision in 90% of patients (33% normalized) with medical therapy.⁷



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Table 1: Primary therapy for sellar masses

Condition	Indication for surgery	Indication for medical therapy	Medical therapy	Indication for radiation
Symptoms of a mass effect Growth of tumour on serial imaging	Primary therapy unless prolactinoma	Primary therapy for prolactinoma	DA	Growing tumour and if not a surgical candidate (will not work fast enough for acute symptomatic improvement)
Prolactinoma	Symptomatic with failed medical therapy	Primary therapy	DA	
Acromegaly	– Mass effect or – For cure	– Poor surgical candidate – Unable to cure with surgery	Octreotide DA Pegvisomant	Reduces GH production if failed medical and surgical therapy
Cushing's disease	– Primary therapy is transsphenoidal surgery – Bilateral adrenalectomy if transsphenoidal surgery fails	If poor surgical candidate	Ketoconazole	Nelson syndrome post-bilateral adrenalectomy for Cushing's disease
Hypofunction	Primary therapy if recovery predicted		Replace any ongoing hormonal deficiencies	
Pituitary apoplexy	Visual compromise	If clinical status is improving and vision is unaffected	Replace hormone deficiencies	
Other masses	For mass effect Craniopharyngiomas and cystic lesions	Hyperplasia due to longstanding primary hypothyroidism	L-T ₄	
		Hypophysitis	Glucocorticoids	

DA = dopamine agonist, GH = growth hormone

Pituitary apoplexy should be suspected in the patient with sudden severe headache, often accompanied by acute hormonal deficiencies and other signs of mass effect. Urgent surgery is recommended for apoplexy in patients with decreased vision, including visual field deficits. However, diplopia – in the context of apoplexy – often resolves spontaneously without surgery, as does the headache, so patients without visual compromise can be managed expectantly as long as the improvement in their symptoms continues.⁸

Hyperfunction

Prolactinomas: As noted above, the primary therapy for a prolactinoma is medical with a dopamine agonist. Patients whose tumour is >1 cm in diameter will typically have a plasma prolactin level >200 µg/L, while tumours of >2 cm in diameter usually cause a prolactin level of >1000 µg/L. If the prolactin level is only modestly elevated – out of keeping with tumour size – the elevation is likely due to stalk effect and the tumour size will not respond to a dopamine agonist. In this case, surgery should be offered if there is a significant mass effect.⁹

Acromegaly: Surgery is recommended for both microadenomas and noninvasive macroadenomas, the goal being a cure, which can be achieved in 60%-80% of cases. As well, surgery is used in the treatment of invasive macroadenomas when there is evidence of a mass effect.¹⁰

Cushing's disease: As there is no satisfactory long-term medical therapy, surgery is first-line therapy for Cushing's disease. Pituitary re-operation or bilateral adrenalectomy will be required if the patient is not cured postoperatively.¹¹

Hypofunction

Pituitary function improves or returns to normal after transsphenoidal surgery in a significant percentage of

patients. Overall, 46%-65% of patients had recovery of between 1 to 3 hormonal axes after surgery.¹²⁻¹⁴ It has been hypothesized that this improvement is due to a reduction in stalk compression and restoration of normal hormonal signals from the hypothalamus.¹⁵ Conversely, if there is destruction of the normal gland by the tumour, this improvement is not seen postoperatively. A low preoperative prolactin level suggests the gland is destroyed and predicts a lack of response to surgery. A subnormal response of thyroid-stimulating hormone (TSH) to administered thyrotropin-releasing hormone (TRH) also suggests a poor surgical outcome.^{12,13} In the setting of apoplexy, hormonal deficiencies usually do not resolve whether surgery is performed or not,⁸ although one small study showed improvement following surgery.¹⁶

Preparation for surgery

Once the decision is made to proceed with surgery, the following issues need to be addressed:

Replace critical deficiencies, starting preoperatively, based on clinical examination and baseline pituitary testing (free T₄, 8 AM cortisol). If there is clear evidence of a cortisol deficiency (see Intraoperative section below for detailed discussion), maintenance glucocorticoid therapy should be started immediately, especially if the patient is symptomatic. The need for ongoing replacement needs to be readdressed after surgery, as recovery of pituitary function is possible.

Address comorbid conditions: In patients with acromegaly or Cushing's disease, it is important to control hypertension and hyperglycemia, and the possibility of cardiac disease should be excluded. Consider the use of somatostatin preoperatively for acromegaly to optimize cardiovascular, respiratory, and metabolic parameters,¹⁷ although this is not universally done.

Table 2: Postoperative testing of hormonal deficiencies				
Hormone	When to initially test	Test to use	Triple bolus testing	How to replace
Cortisol	Every 12 hours post-op if not on glucocorticoid replacement	Plasma cortisol	Week 4-6, if post-op 8 AM cortisol is 100-300 nmol/L (if <100, treat as deficient, if >300, treat as no deficiency)	Hydrocortisone 20 mg/day or cortisone acetate 25 mg/day in divided doses
T4	Day 7	Free T4	TSH as part of triple bolus	L-thyroxine 1.6 µg/kg (start with 25 µg/day if older, or has cardiac disease)
Sex hormones	1-2 months post-op	Women: Menstrual history ± LH,FSH, estradiol, day 21 progesterone	LH, FSH can be done as part of triple bolus	Estrogen/progesterone
		Men: History (sexual function) LH, FSH, bioavailable testosterone		Androgen (IM, transdermal, p.o.)
GH			GH response to hypoglycemia	Consider replacement with GH SC if symptomatic after other hormonal deficiencies corrected
ADH	Monitor fluid balance, plasma and urine electrolytes and osmolality, fluid balance post-op	<ul style="list-style-type: none"> - Urine output > 400 cc/h for more than 2 hours - Urine dilute (spec gravity < 1.005, urine osmolality < plasma osmolality) - Negative fluid balance - Hypernatremia 		DDAVP 1 ug SC prn, switch to intranasal 10 ug qhs on discharge. Reassess need in 2 weeks

GH = growth hormone, ADH = antidiuretic hormone, LH = luteinizing hormone, DDAVP = desmopressin acetate

In Cushing's disease, consider reducing cortisol production with ketoconazole if surgery will be delayed or if the patient is very ill with metabolic decompensation due to hypercortisolemia. It is best to avoid ketoconazole, if possible, as it may mask the fall in cortisol seen postoperatively in cases with successful resection.

Intraoperative care

Steroid coverage: Some centres administer stress-dose glucocorticoids to all patients undergoing transsphenoidal surgery.^{18,19} In the past, there were theoretical concerns that even transsphenoidal selective adenoma resection could blunt the normal rise in cortisol during stress; however, this has been shown to be untrue. During the perioperative period, in patients with no exogenous steroid administration, cortisol rises on average to 1110 nmol/L at 6 hours, and falls to around 450 by days 4-7.²⁰ When Hout followed these patients postoperatively, only 2/83 acutely developed secondary hypocortisolemia. Therefore, it is felt by many that steroid coverage should be offered only to individuals with evidence of a deficient hypothalamic-pituitary-adrenal (HPA) axis.²⁰

Most groups assess the HPA axis preoperatively with basal cortisol and ACTH stimulation testing.²¹ However, it is well-recognized that the latter can be falsely normal in new-onset secondary hypoadrenalism if the adrenals have not had time to atrophy. If 8 AM basal cortisol levels are used to rule-out hypoadrenalism, a cutoff above 500 nmol/L is certainly safe. This was shown by Jones²² in a review of insulin tolerance tests (ITTs) done at his institute over 1 year. He found that all patients above this cutoff had normal ITT. Furthermore, Inder noted that, "<4% of patients with morning plasma cortisol levels of >350 nmol/L fail the ITT and that these are usually associated with peak cortisol levels close to or >500 nmol/L,

based on retrospective reviews of ITT series."^{22,23} Inder argues that the cutoff of 350 nmol/L can be used postoperatively to avoid the need for testing with an ITT.²¹ One can also argue it can be used to make a decision preoperatively about the need for stress dose steroid coverage for surgery. In Hout's study, the 5 patients identified with secondary hypoadrenalism, based on preoperative ITT or metyrapone testing, all had baseline morning cortisol levels of <250 nmol/L (ranging from 14 to 215 nmol/L).²⁰

In the case of the patient with Cushing's disease, intraoperative glucocorticoid therapy is administered at some centres, but not at others.²⁴ The rationale for not using it perioperatively is 2-fold: First, cortisol levels are already high during surgery from endogenous production²⁴ and, second, falling plasma cortisol levels postoperatively can be viewed as a prognostic factor indicating remission or cure.²⁵

When steroid coverage is required, it is reasonable to use the regimen proposed by Inder: solucortef 50 mg IV q 8 hours on the day of surgery (day 0), 25 mg q 8 hour on day 1, and 25 mg at 0800 hours on day 2 and onwards, until reassessed.²¹

Postoperative care

Addressing hormonal deficiencies (Table 2): Many deficiencies improve or resolve entirely, so it is important to reassess the pituitary hormonal axes after surgery.

Cortisol: A high risk of glucocorticoid deficiency is more likely if there has been extensive surgery, if there is a low prolactin level, or if there are multiple deficiencies in other hormones. Patients not on glucocorticoid replacement require daily clinical assessment plus 8 AM plasma cortisol levels from days 1-3 postoperatively to screen for glucocorticoid deficiency. In those requiring steroid coverage for surgery, an 8 AM value can be obtained on days 3-5, at least 24 hours after the last dose of hydrocortisone.

A final decision about the HPA axis should never be based on a single plasma cortisol value.²⁶ If the 8 AM cortisol is <100 nmol/L, permanent glucocorticoid therapy should be initiated, along with counselling for future sick day management. If it is >500 nmol/L, the patient can be presumed to have a normal HPA axis and this is probably true even if the cortisol is >350 nmol/L. Inder²¹ suggests a cutoff even as low as 250 nmol/L can be used to decide the need for definitive testing.²⁶⁻²⁸ If the 8 AM plasma cortisol is between 100-250 nmol/L, daily steroid coverage should be given until definitive testing is done. ACTH stimulation testing (1 µg or 250 µg) is not appropriate after surgery to detect acute secondary hypoadrenalism.²⁷ ITT is the gold standard and is usually done 4-6 weeks after surgery. There is conflicting evidence about the best timing for this test; one study suggests that performing an ITT at 5-8 days post-surgery is reliable,²⁶ while another suggests that early dysfunction may normalize when checked by ITT between 1-3 months after surgery.²⁹

Which glucocorticoid should be used to replace cortisol? Multiple forms of glucocorticoid hormones are commercially available, ranging from cortisone acetate (converted to hydrocortisone [cortisol] in the body by 11-β-OH dehydrogenase), hydrocortisone, prednisone, methylprednisolone, and dexamethasone. The advantage of the latter three drugs is that they can be given once daily; however, most studies use hydrocortisone or cortisone acetate. These are typically given at least twice daily, but their advantage is that plasma cortisol levels can be tracked throughout the day in an attempt to reproduce the normal circadian rhythm and, in addition, 24-hour urine-free cortisol levels can be followed.^{30,31}

A nonrandomized trial compared metabolic parameters for patients on different glucocorticoids with parameters for patients with an intact HPA axis. Patients on glucocorticoid therapy had worse metabolic parameters (lipids and body mass index [BMI]) than those with an intact HPA axis. This deterioration appeared to be dose-related; ie, the use of low-dose hydrocortisone (<20 mg/day) was associated with the same metabolic parameters seen in patients with an intact HPA axis. Patients on cortisone acetate had the best metabolic profiles (lipids, waist circumference).³²

Studies examining normal glucocorticoid production rates indicate that, in the past, doses of replacement glucocorticoids may have been too high. The recommended starting dose is 10-12 mg/m² po of hydrocortisone, then monitoring for symptoms of adrenal hormone excess or deficiency should occur.³² There are concerns that the usual doses (20-30 mg/day) are associated with increased bone turnover and bone loss.³³ One study examined serial plasma cortisol levels throughout the day and urine-free cortisol levels to determine which dose and frequency of administration of glucocorticoid was best. Low-dose cortisone acetate given 3 times a day (12.5 mg at breakfast, 6.25 mg at lunch, and 6.25 mg at supper)

best achieves target plasma and urine-free cortisol levels; this dose is equivalent to hydrocortisone 20 mg total daily dose.³⁴

Antidiuretic hormone (ADH): Diabetes insipidus (DI) occurs commonly after transsphenoidal surgery,¹⁹ ranging in frequency from 0.5% to 25% of cases. In one study, early DI occurred in 31% of 1,571 post-operative patients; 17% still had it on day 3, while only 6% still had DI on day 7.³⁵ It is important to rule-out other causes of polyuria, since the excretion of fluids administered intraoperatively and osmotic diuresis due to hyperglycemia or mannitol therapy will result in a higher urine osmolality than that seen in DI. Nephrogenic DI and psychogenic polydipsia can mimic central DI, but can usually be elucidated by history, a relatively lower plasma sodium [Na⁺] in the case of psychogenic polydipsia, and a lack of response to desmopressin acetate (DDAVP) in the case of nephrogenic DI. It is critical to pay close attention to fluid balance with twice-daily serum and urine electrolytes and osmolality and urine specific gravity in the early post-operative period. As serum Na concentration and osmolality can remain relatively normal in the patient with central DI and a normal thirst mechanism, a water deprivation test may be required to clarify the underlying diagnosis.

When it occurs, central DI can follow several patterns: it may be transient (occurring on post-op day 1-2), permanent or triphasic (low ADH due to nerve shock occurring on day 1-3), followed by an elevated ADH due to release of pre-formed ADH (lasting 1-14 days), then low ADH once reserves are depleted).³⁶

When treating central DI, DDAVP should be given sporadically for the first few days, since ADH deficiency may spontaneously resolve. The water and Na⁺ content of fluids administered *per os* or intravenously should be assessed to ensure that hypernatremia (if present) is corrected at an appropriate rate, depending on symptoms; and hyponatremia does not develop. Two weeks after surgery, the patient should try holding one dose of DDAVP to assess if DI has resolved. Plasma Na⁺ should be checked if there has been any change in the patient's condition while on DDAVP.

Independent of the use of DDAVP, there is also the risk of late hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH), which classically presents 5-10 days after surgery. Serum Na <135 meq/L is seen in up to 25%-40% of post-operative patients, with 7%-9% of all patients having symptomatic hyponatremia.³⁷⁻³⁹ Secondary hypo-adrenalism and hypothyroidism and cerebral salt wasting should be ruled-out. Patients should be educated about seeking medical attention if they develop worsening headache, nausea, or an altered level of consciousness and they should be instructed not to ingest excess water (ie, drinking only when thirsty, provided they have an intact thirst centre).

Free T₄: The free T₄ level at one week post-surgery may give an indication of thyrotroph function. Given

that the half-life of T_4 is 5-7 days, if the free T_4 level has fallen by 50%, it suggests there is no remaining thyrotroph function. One should treat with L-thyroxine if the free T_4 is less than normal and consider therapy if it is in the lower third of the normal range in the presence of symptoms of hypothyroidism. The sick euthyroid state can also present with low free T_4 and normal or low TSH levels. Generally, TRH stimulation is not considered to be essential and does not differentiate between secondary and tertiary hypothyroidism.⁴⁰ If triple bolus testing is conducted, the normal response of TSH is a rise of at least 2.5-fold, or an increase of 5-6 mU/L (females) or 2-3 mU/L (males).⁴¹ It is recommended that free T_4 levels be maintained in the upper half of the normal range as long as the patient does not develop symptoms of thyrotoxicosis. This results in patients with secondary hypothyroidism on slightly higher doses of levothyroxine than patients with primary hypothyroidism.⁴²

Sex hormones: History and physical examination are useful to detect hypogonadism in men, along with baseline laboratory tests (LH, FSH, and bioavailable testosterone) at 1-2 months after surgery. There is a diurnal variation in the levels of testosterone, with the highest levels occurring in the early morning. For women, normal menses in the premenopausal woman and elevated FSH and LH levels in postmenopausal woman indicate normal pituitary function.⁴³ If menses are not regular, measurement of prolactin, LH, FSH, estradiol and mid-luteal progesterone levels are required.

Prolactin: Levels can be measured at 1 and 4 weeks. Elevated levels may indicate stalk damage; alternatively, if the prolactin level is very low, the patient will likely have multiple hormonal deficiencies.

Growth hormone (GH): GH deficiency can be diagnosed in the presence of low IGF-1 levels and multiple hormonal deficiencies or during the ITT. Therapy can be considered if patients are symptomatic with GH deficiency (see Canadian consensus¹⁰).

Cure of the hypersecretory tumour (Table 3)

Prolactinoma: In one study, a prolactin level of $<10 \mu\text{g/L}$ on postoperative day 1 predicted a cure in 100% of microadenomas and 93% of macroadenomas. In contrast, no patients with a macroadenoma and a prolactin level $>10 \mu\text{g/L}$ on postoperative day 1 was cured.

Acromegaly: Oral glucose suppression testing is valid at one week after surgery. If GH levels are suppressed to $<0.5 \mu\text{g/L}$, it is highly predictive of cure. In some patients, IGF-1 levels do not stabilize until 3 months postoperatively.⁴⁵

Cushing's disease: If patients are *not* administered intraoperative glucocorticoid, they will need to be followed closely postoperatively with clinical examination and q 6 hour plasma cortisol levels. Plummeting levels of plasma cortisol indicate disease remission or cure.²⁵ Patients should be placed on glucocorticoid coverage if this deficiency occurs; the dose can be slowly tapered over 6 months as suppressed corticotroph function slowly returns.

Table 3: Postoperative testing of hormonal excess

Condition	When to initially test	Test to use	If cured
Prolactinoma	Day 1	Prolactin	Monitor levels periodically
Acromegaly	Day 7	GH (oral glucose suppression test)	Monitor levels periodically
	3 months	IGF-1	
Cushing's disease	Q 12 hr post-op if not on glucocorticoid replacement	Plasma cortisol	Hydrocortisone 10 mg bid, slowly taper off over 6 months

Deep vein thrombosis (DVT) prophylaxis should be provided especially with the hypercoagulable state associated with Cushing's disease.⁴⁶

Long-term follow-up

It is beyond the scope of this review to describe the long-term follow-up of the postoperative patient in detail. General principles are as follows:

- First, the tumour should be assessed for regrowth using MRI at 3, 6, and 12 months postoperatively, then annually for 5 years, and then less often.⁴⁷ Closer follow-up is required in patients whose pathology shows a high proliferative index (MIB-1).
- If the tumour is close to the chiasm, ophthalmology and visual field assessments should be performed regularly.
- If residual tissue is growing, repeat transsphenoidal surgery or pituitary irradiation should be considered.
- Baseline pituitary function tests and tumour markers (if it is a secretory tumour) should be obtained every 6-12 months.
- Hormonal deficiencies require ongoing replacement, including cortisol, L-thyroxine, sex hormones, with consideration of GH replacement in the symptomatic patient.
- Finally, because of an increased risk of cardiovascular disease in patients with hypopituitarism, any conventional cardiovascular risk factors need to be addressed.

Conclusions

In summary, the endocrinologist must be aware of several unique features about pituitary surgery. The decision to proceed with surgery is usually based on symptoms of mass effect, or hormonal hyper- or hypofunction. Prolactinomas should be treated with DA as primary therapy. Before surgery, hormonal deficiencies should be corrected and the patient should be treated for any co-existent problems such as hypertension, hyperglycemia, and coronary artery disease. A decision is required about the need for intraoperative glucocorticoid therapy. Postoperatively, the patient should be reassessed for hormonal deficiencies and hormonal recoveries and for cure of hypersecretion. Problems with water balance, in particular, need to be vigilantly sought and corrected.

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