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Review article

A suggested protocol for the endocrine postoperative management of patients undergoing pituitary surgery

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A R T I C L E I N F O

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A B S T R A C T

Purpose. – Endocrine disorders are the most frequent postoperative complications in patients undergoing pituitary surgery. Given the absence of recent guidelines on the postoperative care following pituitary surgery, this article summarizes the available evidence on the topic.
Method. – We conducted a systematic search of PubMed up to 2021 and updated the search in December 2022. We retrieved 119 articles and included 53 full-text papers.
Results. – The early postoperative care consists of the assessment for cortisol deficiency and diabetes insipidus (DI). Experts suggest that all patients should receive a glucocorticoid (GC) stress dose followed by a rapid taper. The decision for GC replacement after discharge depends on the morning plasma cortisol level on day 3 after surgery. Experts suggest that patients with a morning plasma cortisol < 10 mcg/dL should receive GC replacement at discharge, and those with 10–18 mcg/dL a morning dose only, with formal assessment of the hypothalamic-pituitary-adrenal axis at week 6 postoperatively. When the cortisol level is > 18 mcg/dL, the patient can be discharged safely without GC, as suggested by observational studies. Postoperative care also includes a close monitoring of water balance. If DI develops, desmopressin is used only in case of uncomfortable polyuria or hypernatremia. The assessment of other hormones is indicated at 3 months postoperatively and beyond.
Conclusion. – The evaluation and treatment of patients following pituitary surgery are based on expert opinion and a few observational studies. Further research is needed to provide additional evidence on the most appropriate approach.

1. Introduction

Pituitary adenoma accounts for approximately 10–15% of surgically-treated primary tumors of the central nervous system [1]. The main indications for surgical management are the presence of hormonal secretion, as in the case of ACTH- and GH-secreting adenoma, visual impairment due to optic nerve or chiasma compression, and pituitary apoplexy with visual field deficit [2]. Endocrine complications are the most common following pituitary surgery, occuring in 11% of patients [3]. In a retrospective analysis of 1,153 consecutive transsphenoidal pituitary adenoma resections performed at the Keck Hospital in the USA (1992–2017), endocrine complications included transient (4.3%) or permanent (0.3%) diabetes insipidus (DI), symptomatic hyponatremia (4.2%), new hormonal deficit affecting any axis (3.6%), and adrenal insufficiency (AI) (0.2%) [3]. Another report from Virginia (1995–2001) reported a higher incidence of DI, reaching 18.3% in the immediate postoperative period, with only 2% of patients having permanent DI [4]. The surgeon's expertise in pituitary surgery largely influences the rate of these complications [5].

Abbreviations: DI, diabetes insipidus; GC, glucocorticoid; AI, adrenal insufficiency; HPA, hypothalamic-pituitary-adrenal axis; HC, hydrocortisone; AACE, American Association of Clinical Endocrinology; IIH, insulin-induced hypoglycemia; LC-MS/MS, liquid chromatography–mass spectrometry; AVP, arginine vasopressin.

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Given the frequency of endocrine complications and in the absence of guidelines on endocrine evaluation of patients undergoing pituitary surgery, the aim of this paper is to review the available literature to date on the topic.

2. Methods

We conducted a search on PubMed in June 2020 and updates in February 2021 and December 2022, without limitations of time or language. We used the following keywords and Mesh terms: postoperative care, pituitary surgery, endocrine evaluation. In addition, we manually screened the citations of previous reviews and ClinicalTrials.Gov for relevant ongoing trials. We included articles on the care of adult patients with pituitary adenoma undergoing transsphenoidal surgery, pituitary adenoma being defined as pituitary gland tumor, classified according to radiological characteristics (microadenoma $\leq$ 10 mm, macroadenoma > 10 mm) or clinical characteristics (functioning versus nonfunctioning) [2]. We retrieved 119 citations and included 35 articles.

3. Results

The postoperative course is divided into an early period up to 3–7 days postoperatively, and a late period after the first week.

3.1. Early postoperative evaluation

The early postoperative endocrine care focuses on the assessment of the most critical axes: the hypothalamic-pituitary-adrenal (HPA) axis, screening for water sodium abnormality in the first 48 hours postoperatively, and the hypothalamic thyroidal axis at the end of the first week [6].

3.1.1. Hypothalamic-pituitary-adrenal axis

To date, trials comparing the various protocols for the evaluation of HPA axis function postoperatively are scarce. We identified 20 articles (1 systematic review, 1 randomized control trial, 2 case reports, 2 guidelines, 3 observational studies, 4 expert opinion papers, 7 study protocols) that we used to derive the suggested approach [7–25].

3.1.1.1. Patients with evidence of preoperative adrenal insufficiency. The history of glucocorticoid (GC) stress dose before pituitary surgery started in the 1950s, following case series of patients with impaired HPA axis secondary to chronic supra-physiologic doses of GC before surgery, and who died shortly after surgery [13,16]. This was followed by universal use of GC stress dose before surgery in patients with impaired HPA axis [18,20]. In 2002, Inder et al. suggested a protocol for perioperative GC management [7] that was evaluated in an Australian retrospective and prospective cohort study. Inder et al.'s protocol was associated with a significant reduction in GC use in comparison with the older protocols [24]. According to Inder et al.'s protocol, if the preoperative evaluation showed evidence of AI, GC stress dose, with hydrocortisone (HC) 50–100 mg, should be given at the time of the surgery, followed by gradual tapering [7]. In the absence of postoperative complications, HC 50 mg is given intravenously every 8 h on day 0, followed by 20 [21] or 25 [7] mg every 8 h on day 1 and then the last dose of 20 [21] or 25 [7] mg at 8.00 a.m. on day 2, also intravenously [7]. Many experts support the use of oral GC on postoperative days 1 and 2, rather than intravenous forms, provided that the patient is able to tolerate oral intake [19]. After GC cessation, morning plasma cortisol level needs to be checked on day 3 postoperatively, along with continuous clinical assessment, to decide on the need for long-term GC replacement [7,17,24]. Another regimen proposed by Feldman et al., in case of preoperative central AI, consisted in administering 100 mg intravenous HC every 8 hours on the day of surgery, 50 mg every 8 hours on day 1, 50 mg every 12 hours on day 2 and then switching to 15 mg orally in the morning and 5 mg in the afternoon on day 3 (or prednisone 5 mg in the morning) [12]. Feldman's protocol advised discharge on prednisone without assessment of the HPA axis [12]. The American Association of Clinical Endocrinology (AACE) experts suggested that all patients with preoperative AI should be treated with GC before (HC 50–100 mg, once) and after surgery (regimen not detailed), with evaluation of the HPA axis only in patients with a high likelihood of recovery [6]. Finally, Ausiello et al. suggested that patients with documented preoperative AI should be treated with a stress dose GC preoperatively (regimen not described), to be tapered to the patient's preoperative replacement dose, which is continued on discharge with assessment of the HPA axis later on [9].

3.1.1.2. Patients without evidence of preoperative adrenal insufficiency. If the preoperative evaluation showed a conserved HPA axis, two approaches have been suggested: steroid sparing or empiric steroid coverage [6,7]. The experts suggested that the empiric GC coverage approach is to be preferred when selective adenomectomy is not possible [7], following the same protocol as for patients with preoperative AI [7]. When the surgeon is confident about the feasibility of selective adenomectomy, the steroid sparing approach is preferable [7]. In a steroid sparing approach, the patient is monitored for any signs and symptoms of AI and, if positive, serum cortisol level is checked and GC replacement is started accordingly [7]. Otherwise, morning cortisol is evaluated (at 8 a.m.) on day 1–3 postoperatively, and the decision on GC replacement is based on this level [7]. The steroid sparing approach is based on findings from an old study in 88 patients without evidence of preoperative AI, undergoing selective pituitary adenomectomy (49 macroadenomas, 15 of which were invasive, and 39 microadenoma); only 1 patient showed transient AI postoperatively, suggesting that this complication is rare in patients with conserved HPA axis preoperatively [14]. However, other studies showed a higher rate of immediate postoperative AI, with variable morning plasma cortisol cutoffs used to define AI, as detailed in Appendix 1 [8,19,23,26]. Only one small pilot trial examined cortisol levels during surgery in ACTH-sufficient and -deficient patients, with or without preoperative HC treatment. Early during surgery, cortisol levels decreased, most likely due to the suppressive effects of the anesthetics, and increased after pituitary manipulation [11].

Although some experts support the steroid sparing approach, others consider that selective adenomectomy does not prevent transient ACTH deficiency in the early postoperative period, and therefore favor systematic use of HC during this period. A cohort of 114 microprolactinomas treated surgically at the Foch Hospital in France showed that, despite the absence of AI preoperatively in all patients with microprolactinoma, as expected, two-thirds had postoperative day-2 cortisol levels < 10 mcg/dL, half of which were < 5 μg/dL [10]. Hence, the authors suggested perioperative GC replacement for all patients, even if this is a typical situation where the surgeon is confident about the feasibility of selective adenomectomy. Notably, all patients showed normalized cortisol levels at 3 months.

We think that the transient adrenal insufficiency observed in the early postoperative period is related to transient alteration of ACTH secretion by corticotroph cells, located in the median and basal part of the pituitary gland secondary to basal drilling of the sellar bone, which typically starts in the median part [10]. Furthermore, the use of HC in the early postoperative period seems to be also necessary in non-functioning macroadenoma, such as fibrous macroadenoma, which requires extracapsular dissection, a procedure at high risk of anterior pituitary insufficiency. Fibrous macroadenoma is difficult to identify preoperatively on MRI [15]. In a new Delphi Survey conducted by the Pituitary Society, 53.1% of panelists agreed that preoperative steroid stress dose is advisable for patients undergoing pituitary surgery, whereas 96% agreed that preoperative stress dose steroid is advisable in patients with AI or suspected AI. [22].

Despite the high risk of AI in the early postoperative period, there is a high rate of HPA axis recovery at 1–3 months' follow-up [8,19,23].

One randomized controlled trial in China, in 436 patients with intact HPA axis undergoing pituitary surgery, compared the impact of HC versus no treatment on the rate of recurrent AI, among other parameters. Postoperatively, the new-onset AI rate was 11.0% (24 out of 218; 95% CI, 6.9–15.2%) in the group without HC replacement and 6.4% (14 out of 218; 95% CI, 3.2–9.7%) in the group who received HC, with a difference of 4.6% (95% CI, −0.7% to 9.9%). The authors considered 10% as a margin for non-inferiority, and concluded that it is safe to withhold HC in patients with intact HPA axis before pituitary surgery [25].

3.1.1.3. Morning serum cortisol level cutoffs to predict or exclude risk of AI post-operatively. We reviewed 14 articles on the use of morning cortisol to estimate the risk of postoperative AI [6–9,19,23,26–33]. There is controversy regarding the plasma cortisol level in the early postoperative period that predicts an impaired HPA axis at follow-up, and regarding the timing of plasma cortisol measurement postoperatively. The AACE guidelines proposed early postoperative assessment and suggested that morning cortisol < 4–5 mcg/dL is associated with a high likelihood of AI, requiring GC replacement, while a level > 10–15 mcg/dL is associated with a low likelihood [6]. The review by Prete et al. advocated checking 8 a.m. cortisol level at 1 week postoperatively in all patients without evidence of preoperative AI; if plasma cortisol is < 15 mcg/dL, patients should continue GC replacement, with definitive reassessment at 6 weeks on cosyntropin stimulation test (CST) [27]. Some experts suggested measuring morning plasma cortisol at 60 or 180 min after surgery, and that a cortisol level > 15 mcg/dL has a positive predictive value of 99%, sensitivity of 98% and accuracy of 97% in predicting normal HPA axis after surgery [28]. Others suggested that clinically stable patients with a postoperative day 2 morning cortisol level > 10 mcg/dL, without evidence of other pituitary hormone deficiency, can be safely discharged without GC replacement, with a prescription for HC to be used in case of symptoms of AI arising [9].

We identified 9 observational studies of patients without evidence of preoperative AI, assessing morning plasma cortisol level in the early postoperative period and performing definitive HPA axis evaluation at 1–6 weeks after surgery, using one of the gold standard tests, either insulin-induced hypoglycemia (IIH) or CST (Appendix 1) [8,19,23,26,28,29,34]. One study ($n = 42$) evaluated the correlation between 9 a.m. cortisol level on day 6–7 following pituitary surgery and the gold-standard IIH test at week 4–6 postoperatively [26]. All patients with cortisol level < 4 mcg/dL ($n = 8$) failed the IIH test, suggesting that this cutoff is diagnostic of AI [20]. Four patients had morning cortisol between 4 and 9 mcg/dL, 3 of whom subsequently passed the IIH test while only 1 failed [26]. Conversely, when morning cortisol was > 9 and > 16 mcg/dL, 93% and 100% of patients passed the IIH test, respectively [26]. Similarly, 2 small studies ($n = 35$ and $n = 17$) showed that morning cortisol ≥ 9 mcg/dL, measured 24 hours after the last HC dose, reflected a preserved HPA axis function, as demonstrated by definitive testing at 1–4 weeks post-surgery [8,23]. Three other studies ($n = 67–139$) demonstrated that morning cortisol ≥ 13–18 mcg/dL was highly specific for intact HPA axis [28,29]. Another study showed that basal postoperative cortisol level ≥ 11.8 mcg/dL ($n = 74$) 18 hours after HC withdrawal reflected a preserved axis in the majority of cases [31]. At postoperative day 1 or 2, basal cortisol > 10.9 mcg/dL had 100% sensitivity and 81% specificity in ruling out AI at 6 months postoperatively [33].

Importantly, the interpretation of results for normal plasma cortisol levels depends largely on the cortisol assay used, and those used nowadays differ from assay used in older studies [7]. The impact of various cortisol assays on the rate of diagnosis of AI was highlighted in a recent paper by Javorsky et al., based on a retrospective analysis of ACTH stimulation tests performed in 110 in- and out-patients with suspected AI [30]. They compared the performance of the newer assays (Elecsys II, Access, and LC-MS/MS) to the older Elecsys I, using the traditional cortisol level of > 18 mcg/dL to rule out AI [30]. While Elecsys I is a polyclonal assay, Elecsys II and Access are monoclonal immunoassays and LC-MS/MS is non-antibody-mediated structural cortisol-specific assay. The newer cortisol assays (Elecsys II, Access, and LC-MS/MS) were more specific, as they cross-reacted less with other steroids, and resulted in lower cortisol concentrations [30]. For the 30-minute values of cortisol after ACTH stimulation test, the cutoff of 18 mcg/dl on the older assay corresponded to 14.6 mcg/dL on Elecsys II immunoassay, 14.8 mcg/dL on Access immunoassay, and 14.5 mcg/dL on LC-MS/MS [30].

The use of the CRH test after pituitary surgery was explored but did not show appropriate predictability of adrenal function status. A retrospective cohort study by Kokshoorn et al. showed that 9 out of 22 patients with cortisol response < 19.9 mcg/dL on CRH test 7 to 10 days after surgery (after withdrawal of HC for 24 h) had evidence of AI on confirmatory testing later on, and 13 out of 75 patients with cortisol level > 19.9 mcg/dL on postoperative CRH test had evidence of AI on later confirmatory test [32]. De Vries et al. also showed that early basal cortisol level performed better than early postoperative CRH test for predicting AI (confirmed by ITT, CRH or basal cortisol at ≥ 6 weeks post-surgery), with a sensitivity of 86% and 78%, respectively [31] (Appendix 1).

3.1.1.4. Comparing different GC coverage doses perioperatively. We identified only 1 study comparing different GC doses. A retrospective study from Karolinska University Hospital compared 38 patients with no preoperative GC treatment and without Cushing disease, who received low-dose GC (total daily HC, 150 mg on day 0, 60 mg on day 1 and 30 mg on day 2 postoperatively) versus 74 patients who received an intermediate dose (total daily HC, 300 mg on day 0, 120 mg on day 1 and 50 mg on day 2) [35]. There was no difference in the rate of AI, defined as cortisol level < 7.25 mcg/dL on day 4 postoperatively [35].

Based on the above literature, we suggest perioperative GC coverage, regardless of the presence or absence of AI preoperatively. Our protocol consists of HC 50–100 mg IV at the time of the surgery, gradual tapering to 50 mg IV every 8 h on day 0, then switch to oral HC 20 to 25 mg every 8 hours on day 1, and 20 to 25 mg at 8 a.m. on day 2 as the last dose (Fig. 1). If there are no postoperative complications, HC is stopped after 48 h, and serum cortisol level is evaluated on day 3 post-surgery (see Fig. 1). The long-term need for cortisol replacement depends on 8 a.m. cortisol level on day 3, and the suggested cutoffs are summarized in Fig. 1. The choice of the timing of cortisol measurement on day 3 postoperatively is based on the fact that most patients are discharged 3 days after surgery in the absence of surgical complications. We suggest definitive testing at 6–12 weeks, using the gold standard ITT or ACTH stimulation test, for all patients with day 3 morning cortisol < 18 mcg/dL.

3.1.2. Hypothalamic-thyroidal axis

We reviewed 5 articles on hypothalamic-thyroidal axis assessment after surgery [6,9,27,36,37]. While the majority of experts agree that the thyroidal axis should be checked at week 6 postoperatively, as there is a low likelihood of detecting insufficiency earlier, given the long half-life of free T4 (fT4) of 1 week [6], others suggest

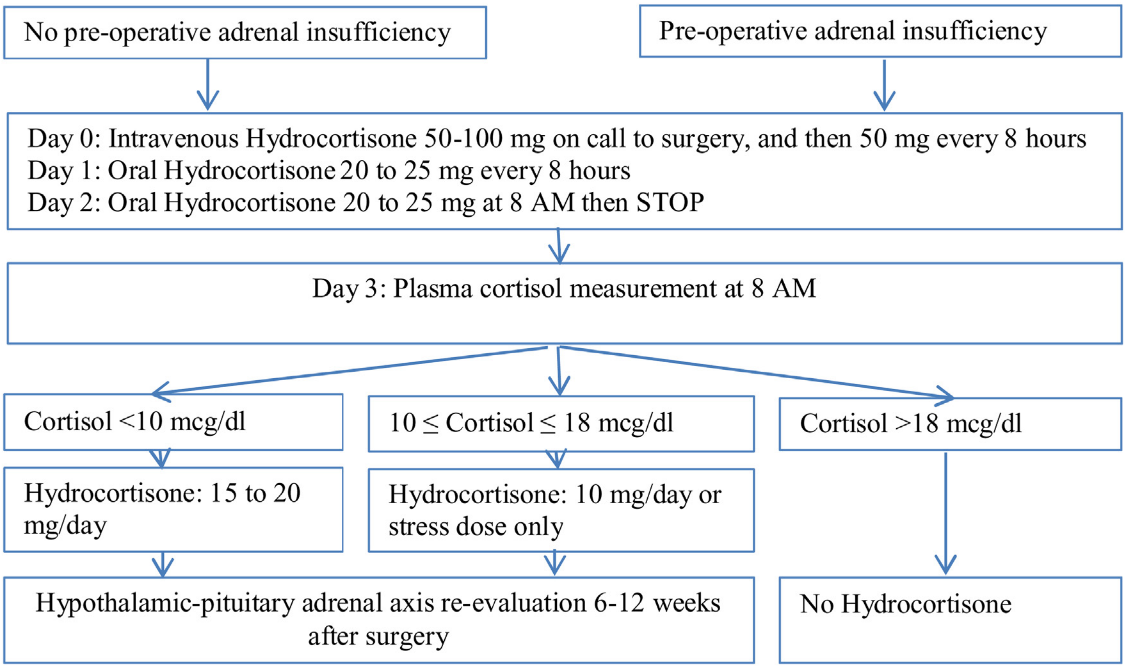

Fig. 1. Suggested approach for the perioperative glucocorticoid replacement in patients undergoing pituitary surgery.

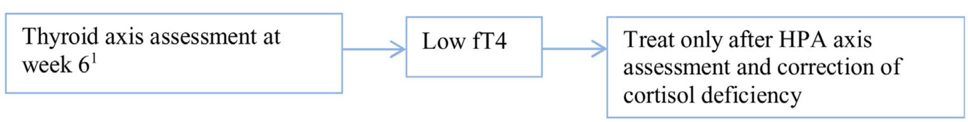

Fig. 2. Suggested approach for the evaluation of the thyroid axis after pituitary surgery. fT4: free T4; HPA: hypothalamic-pituitary-adrenal; [1] fT4 level can be checked on day 7 postoperatively in patients with other pituitary hormone deficiencies, pituitary apoplexy or unknown thyroid status before surgery.

checking fT4 level earlier, on day 7 postoperatively, in patients with other pituitary hormone deficiencies, pituitary apoplexy or unknown thyroidal status before surgery [9]. In patients with low or low-normal fT4, treatment is suggested in case of symptomatic hypothyroidism or if fT4 level drops by ≥ 20% on follow-up [37], as these patients may have mild central hypothyroidism [36,37] (Fig. 2). Experts suggest that, in case of frankly subnormal fT4 levels on day 7, thyroid hormone replacement should be started [9], whereas normal or low-normal values should prompt retesting at week 6, considering the half-life of fT4 [6]. It is always advised to test and replace corticotroph insufficiency before thyroid hormone replacement [27].

3.1.3. Sodium and water balance

3.1.3.1. Diagnosis of DI. We retrieved 11 articles on the diagnosis of DI after pituitary surgery [4,27,38–46]. DI is the most common endocrine complication after pituitary surgery, with an incidence around 10–20%, depending on whether the tumor is confined to the sella or extends beyond it [27]. In a study of 750 patients undergoing transsphenoidal surgery between 1991 and 2001, 20% developed DI after surgery [45]. The onset of polyuria (defined as urine output > 3 liters per day or > 50 mL/kg/24 hours or > 250 mL/h for 2–3 consecutive hours [27]) is usually sudden and within 12–24 hours postoperatively [27]. The triphasic pattern of water balance disorder after pituitary surgery is reported in only 3% of patients. The early polyuric phase starts within 24–48 hours postoperatively, and is due to neurohypophyseal axon shock. The antidiuretic phase starts 5–8 days after surgery, and lasts for 2–5 days, corresponding to a syndrome of inappropriate anti-diuretic hormone (ADH) secretion. The late polyuric phase is often permanent, secondary to irreversible damage to the hypothalamic-hypophyseal tract [27].

Immediately after pituitary surgery, patients should be carefully monitored for polyuria, excessive thirst and craving for cold water [43]. Thirst is a prominent and a consistent symptom of DI [45]. In case of polyuria, it is advised to check vital signs, glucose level, serum sodium, serum and urine osmolality and urine specific gravity. DI is diagnosed in patients with high or borderline-high serum sodium, low urine specific gravity < 1.005) or low urine osmolality (< 300 mosmol/kg) or at least urine osmolality less than serum osmolality [4,43]. Patients with urine osmolality between 300 and 600 mosmol/kg can still have partial DI and should be monitored for thirst, with frequent monitoring of serum sodium every 6 to 12 hours, serum and urine osmolality twice daily, and accurate calculation of fluid and water balance [43]. Given that AI can mask the presence of DI, experts who do not recommend systematic GC preoperatively suggest monitoring for the development of DI after starting GC replacement [41].

Copeptin, the C-terminal segment of the arginine vasopressin (AVP) prohormone, reflects osmo-sensitive circulating AVP concentrations and is considered a promising biomarker for the diagnosis of DI [47]. Direct measurement of hypertonic saline-stimulated plasma copeptin shows good accuracy of 96.5% [95% CI, 92.1–98.6] in diagnosing DI in patients with hypotonic polyuria [39]. An observational study of 50 DI cases after pituitary surgery in 3 referral centers in Canada and Switzerland showed that a copeptin cutoff of < 2.5 pmol/L at ≤ 12 h post-surgery predicted DI with a positive predictive value of 81%, while a level > 30 pmol/L had a negative predictive value of 98% [46].

Kim et al. studied the role of measurement of copeptin level for the diagnosis of DI after pituitary surgery. At 3 months, copeptin level (measured in fasting state except for water) of < 1.9 pmol/L was 81.8% accurate in predicting DI in normonatremic patients

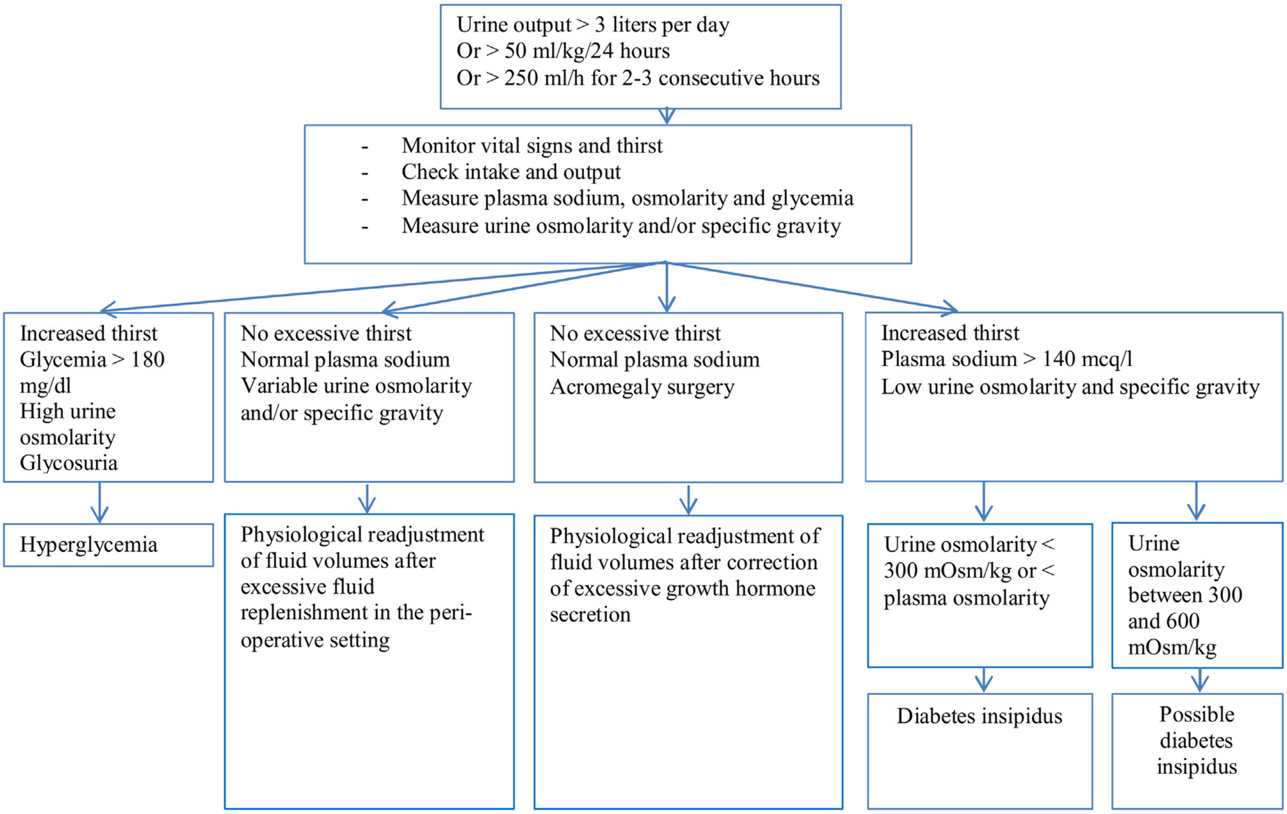

Fig. 3. Differential diagnosis of polyuria in the early period after pituitary surgery.

and a level ≥ 3.5 pmol/L had a negative predictive value of 100% to exclude DI [42].

Similarly, another study examining the role of postoperative copeptin for the diagnosis of DI showed that a copeptin level 1 hour post-extubation of ≤ 12.8 pmol/L was accurate for detecting DI (AUC 0.866, 95% CI 0.751–0.941) [38]. Conversely, another study (n = 47) showed that postoperative day-2 copeptin level was not predictive of postoperative DI [40]. Such findings can be explained by the small sample size, the study design and the relatively late measurement of copeptin, not coinciding with the postoperative stress peak [40]. We identified 2 studies on ClinicalTrials.gov on copeptin measurement for the prediction of DI in patients undergoing resection of sellar (n = 200, Mayo Clinic Rochester) [48] or supra-sellar masses (n = 100, Reims university hospital, France) [49]. These 2 studies have been completed but not yet published.

Several other causes of polyuria should be considered following pituitary surgery. Polyuria can be secondary to glycosuria, typically when glucose level increases above 180 mg/dL, with high urine osmolality and elevated urinary glucose [43]. Fluid mobilization is common after surgery, because of excessive intravenous fluid administration in the perioperative period. Blood volume readjusts physiologically in the first 24 hours following surgery, which should be suspected in patients with positive 24-hour balance, absence of excessive thirst and hypotonic urine. Polyuria resolves spontaneously, and a close monitoring of sodium and urine osmolality every 4 to 6 hours is needed [43]. Patients undergoing surgery for acromegaly may have significant polyuria that can mimic DI due to the drop in blood GH and IGF1, that cause fluid retention when inappropriately high [27]. Urine specific gravity is usually > 1.005, patients are usually normonatremic, and do not show excessive thirst [4,43].

A suggested approach for patients with suspected DI is summarized in Fig. 3.

3.1.3.2. *Treatment of DI.*

We summarize the findings from 3 articles on the approach for patients with suspected DI [27,43,44]. Management of DI depends on the patient's status [43]. Patients with a preserved thirst mechanism can be maintained with oral or IV hydration [43].

Desmopressin replacement with oral, sublingual, subcutaneous or intravenous preparations is used only if polyuria is excessive and uncomfortable for the patient, particularly during the night, or if hypernatremia occurs [43]. A single dose is expected to control polyuria for 6 to 12 hours. While on treatment, fluid intake and urine output should be monitored. Serum sodium should be checked every 6 to 12 hours and urine osmolality every 12 hours until discharge [27]. Upon discharge, if polyuria is persistent, the patient should be prescribed desmopressin once daily in the form of a spray or sublingually, as needed [43]. In order to avoid the risk of hyponatremia, patients should be instructed to avoid excessive fluid intake. Similarly, patients should be instructed about the symptoms of hyponatremia such as nausea, vomiting, headache, lethargy and seizures [44]. Most cases of DI after pituitary surgery are transient. Therefore, if polyuria becomes less pronounced or ceases between days 4 and 7, desmopressin can be tapered and withdrawn [44].

Treatment of DI becomes more complicated in patients with adypsia/hypodypsia or intolerance to oral intake. The water deficit is calculated using the following equation: water deficit (L): $0.6 \times$ body weight (kg) $\times$ ([serum Na/140] − 1) [43]. In such cases, the physician should establish a weight goal at which the patient is euvolemic and normonatremic, by fixing a 24-hour urine output of 1.5 to 2 liters and determining a desmopressin dose for this purpose [43]. In general, there is a mandatory fluid intake of 1.5 to 2 L and daily fluid intake should be calculated as the sum of mandatory intake (liter) and the following difference (weight goal minus daily weight) (1 L = 1 kg). Serum sodium should be

Conscious patient, conserved thirst (General case)

Adequate fluid balance is usually maintained by free access to water according to thirst

Days 1- 3:

-Monitor vital signs and thirst, intake and output

-Measure plasma sodium every 12 hours

-Use desmopressin, starting with a low dose (oral, SL, IV or SC as available) 2 or 3 times a day:

- if polyuria is uncomfortable for the patient, particularly during the night
- in case of hypernatremia
- if polyuria lasts more than 48 hours

Day 3 to 7:

Periodically try to withhold desmopressin;

Measure plasma sodium on Day 7 to detect syndrome of inappropriate ADH secretion if present

Inadequate perception of thirst or altered consciousness

-Calculate water deficit: 0.6 × body weight (kg) × ([serum Na/140] − 1) and replace by intravenous or oral fluids

-Closely monitor plasma sodium, vital signs and daily weight

-Establish a weight goal at which the patient is euvolemic and normonatremic

-Use desmopressin, starting with a low dose (oral, SL, IV or SC as available) 2 or 3 times a day

-Fix a 24-hour urine output of 1.5-2 L and determine a desmopressin dose for this purpose

-Advise mandatory fluid intake of 1.5-2 L

-Daily weight

-Daily fluid intake = mandatory intake + (weight goal minus daily weight) (1 L = 1 kg)

Fig. 4. Suggested approach for management of diabetes insipidus after pituitary surgery. ADH: antidiuretic hormone; IV: intravenous; SC: subcutaneous; SL: sublingual.

measured depending on stability (weekly at the start, and less frequently thereafter), with thorough education of the patient's family. Monitoring serum sodium and patient education about symptoms of hyponatremia enable the detection of the Syndrome of inappropriate antidiuretic hormone secretion (SIADH) [27]. Similarly, the long-term management of DI requires thorough education of the patient and family members, with advice on increasing fluid intake in hot weather [43].

The treatment approach for patients with DI is summarized in Fig. 4.

3.1.4. *Evaluation of remission in patients with functional adenoma*

We identified 6 articles discussing the early postoperative hormonal evaluation in patients with functional adenoma [6,27,50–53].

In patients who underwent surgery for a prolactinoma, day 1 serum prolactin level < 10 ng/mL predicts early subsequent biochemical remission [6,50]. For patients with Cushing syndrome, the Endocrine Society considers morning serum cortisol values < 5 mcg/dL or urinary free cortisol < 10–20 mcg/d within 7 days of selective tumor resection as predictors of remission [51]. Some experts advise assessing morning serum cortisol on day 1 after surgery and, if it ranges between 2 and 5 mcg/dL, repeating the measurement at 3 weeks after surgery and then at 2–3-month intervals, as this category of patients are at a higher risk of developing subclinical Cushing [52]. Prete et al. advocates checking cortisol level every 6 hours post-ACTH-secreting adenoma resection, as the cortisol nadir typically occurs after 24 to 36 hours [27]. GC replacement regimens after pituitary surgery for Cushing disease are beyond the scope of this review.

In patients with acromegaly, day 1 GH < 2 ng/mL predicts biochemical remission in patients not treated with somatostatin analogues preoperatively [6,53].

3.2. *Late postoperative evaluation*

The late postoperative evaluation starts with a physical examination and a clinical follow-up 1 week after surgery, with an evaluation of serum sodium and cortisol levels; fT4 measurement is optional (Fig. 5). At 6 and 12 weeks post-surgery, follow-up includes evaluation of adrenal, thyroid, gonadal, GH axes, and prolactin level measurement, as clinically indicated. HPA axis assessment may include morning cortisol or ACTH stimulation test, or ITT if day 3 cortisol level is < 18 mcg/dL. Ophthalmological evaluation is advised at 6 weeks in case of preoperative visual field defect. MRI should be performed as a baseline assessment postoperatively at 12 weeks follow-up [6]. Long-term follow-up includes yearly hormonal evaluation or as dictated by the patient's clinical status, assessment of remission in hormonally active tumor, and assessment of tumor recurrence on sellar MRI annually for 3 to 5 years, then as clinically indicated [6]. More frequent pituitary MRI is needed in case of residual tumor or recurrence, as dictated by the type of tumor and extent of pituitary disease.

4. Knowledge gaps and future research

This review summarizes the available literature, most based on expert opinion and few observational studies on the postoperative management of patients after pituitary surgery, with emphasis on the HPA axis function and water/sodium balance in the early postoperative period. Further studies are needed to provide additional evidence on the most appropriate evaluation and management approach for patients after pituitary surgery and to assist clinicians in decision-making.

Human and animal rights

Not applicable.

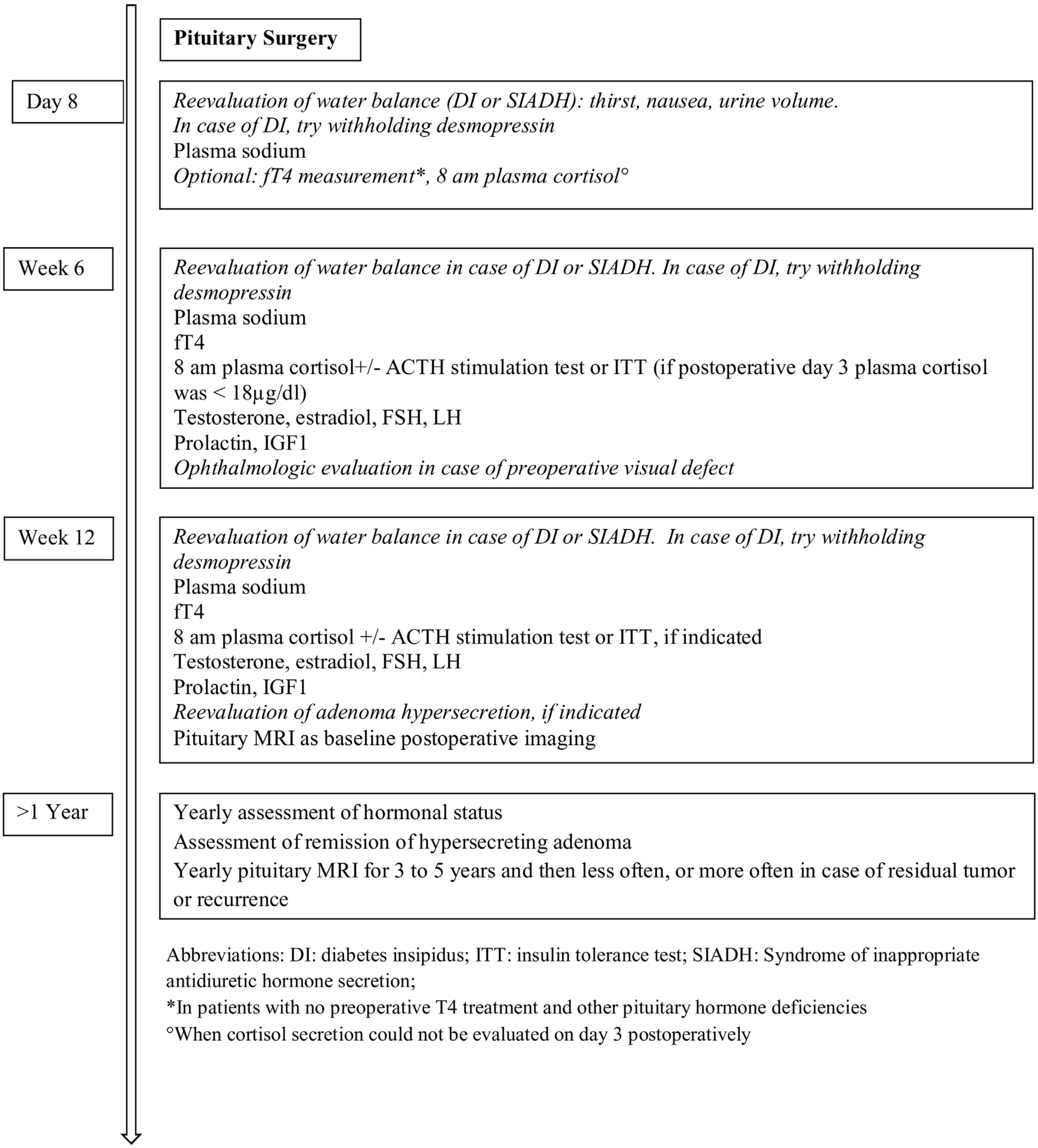

Fig. 5. Suggested approach for the late postoperative evaluation of patients undergoing pituitary surgery. DI: diabetes insipidus; ITT: insulin tolerance test; SIADH: syndrome of inappropriate antidiuretic hormone secretion; *: in patients with no preoperative T4 treatment and other pituitary hormone deficiencies;°: when cortisol secretion could not be evaluated on day 3 postoperatively.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

Disclosure of interest

The authors declare that they have no competing interest.

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Authors contribution

All authors attest that they meet the current *International Committee of Medical Journal Editors* (ICMJE) criteria for Authorship.

All authors contributed in the conceptualization, methodology, writing original draft, review and editing.

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Appendix 1. Summary of observational studies on patients undergoing pituitary surgery evaluating serum cortisol level in the early postoperative period, in correlation with definitive hypothalamic-pituitary-adrenal axis evaluation at follow-up

Author year	Sample size	HPA axis function before surgery	Timing of cortisol measurement	Serum cortisol level in the early postoperative period	Cortisol assay	Definitive evaluation, timing, test result	Authors' suggestions
Watts 1988 [1]	35	Normal function	Day 2 to 3 (24 hours after last dose of HC)	Group 1: $n = 27$ Cortisol > 9 mcg/dL Group 2: $n = 8$ Cortisol < 2.9 mcg/dL	Radio-immunoassay	IIH at 1 week CST at 1 month Group 1: both tests normal Group 2: 5 patients had transient AI (4 tested normal with IIH and CST at 1 to 3 months postoperatively and 1 patient stopped steroids alone and was doing fine) 3 were believed to have panhypopituitarism, 2 not tested, and one with subnormal CST	Cortisol > 9 mcg/dL: no evidence of AI > no further testing or treatment Cortisol < 2.9 mcg/dL: AI → discharge on HC and reevaluate at 1 month (CST) Patients with 8 a.m. morning cortisol level between 3 and 9 mcg/dL should be assumed to have AI and discharged on steroids until definitive testing done
Auchus 1997 [2]	17	Normal function	Day 3 (24 hours after last dose of HC)	Group 1: $n = 11$ Cortisol > 12.32 mcg/dL Group 2: $n = 2$ Cortisol < 12.32 mcg/dL (1 patient with cortisol < 2.17 mcg/dL; 1 patient with cortisol 2.17 mcg/dL) Group 3: $n = 4$ (did not complete the protocol) cortisol > 9.79 mcg/dL	Fluorometric analyzer and immunoassay	IIH 5 to 8 days after surgery Group 1: all passed the test Group 2: one passed the test and another failed (and failed CST at week 8 postop) Group 3: all remained clinically stable without steroids	Initial morning cortisol > 9.79 mcg/dL is 100% specific and 94% sensitive for preserved HPA integrity
Courtney 2000 [3]	42	NAV	Day 6 and 7 (24 hours after last dose of HC)	Group 1: $n = 8$ Cortisol < 4 mcg/dL Group 2: $n = 4$ Cortisol 4–9 mcg/dL Group 3: $n = 15$ Cortisol 9.1–16 mcg/dL Group 4: $n = 15$ Cortisol > 16 mcg/dL	Radio-immunoassay	IIH at weeks 4 to 6 postop Group 1: all patients failed IIH test Group 2: cannot predict which patient will pass IIH test → replace until definitive testing Group 3: 93% of patients pass IIH test Group 4: all patients passed IIH (> 19.93 mcg/dL)	Cortisol < 4 mcg/dL: replace, no need for definitive testing Cortisol between 4 to 9 mcg/dL: replace until definitive testing Cortisol between 9.1 to 16 mcg/dL: safe to withdraw steroids until definitive testing Cortisol > 16 mcg/dL: no evidence of AI → no need for additional testing
Marko 2010 [4]	100	Normal function	7 a.m. day 1	Group 1: $n = 93$ Cortisol level ≥ 15 mcg/dL Group 2: $n = 7$ Cortisol level < 15 mcg/dL	Chemiluminescence	CST at 4 to 6 weeks Group 1: all patients except 1 passed CST Group 2: all patients passed CST and remained asymptomatic for 6 to 36 months after surgery	Day of surgery cortisol level ≥ 15 mcg/dL predicts distant, normal and postoperative HPA axis function following transsphenoidal surgery

Author year	Sample size	HPA axis function before surgery	Timing of cortisol measurement	Serum cortisol level in the early postoperative period	Cortisol assay	Definitive evaluation, timing, test result	Authors' suggestions
Dupepe 2019 [5]	67	Patients without long-term steroids perioperatively	Early morning, day1, day 5	Group 1: $n = 21$ Day1 and 5 cortisol ≥ 18 mcg/dL Group 2: $n = 46$ Day 1 and 5 cortisol < 18 mcg/dL Group A: $n = 21$ Day 5 cortisol ≥ 15 mcg/dL Group B: $n = 22$ Day 5 cortisol < 15 mcg/dL Group C: $n = 23$ Day 1 cortisol ≥ 18 mcg/dL Group D: $n = 20$ Day 1 cortisol < 18 mcg/dL	NAV	Group 1: discharged without HC Group 2: continued on HC replacement with CST at week 4 postoperatively; 1 patient lost to follow-up; 2 patients with day1 cortisol < 18 but day 5 cortisol > 18 did not received HC and did not do definitive testing 40 out of 43 patients → passed CST (30 min cortisol ≥ 18 mcg/dL Group A: all pass the test Group B: 19 out of 22 passed CST Group C: 21 out of 23 passed CST Group D: 19 out of 20 passed CST	Day 5 values (both > 18 and > 15 mcg/dL) were better predictors of functional HPA with specificity and PPV of 100% (8.7%) of patients with day 1 cortisol ≥ 18 mcg/dL ultimately failed the CST → Day 1 measurements are less reliable indicators of an intact HPA than day 5 measurements
Mclaughlin 2013 [6]	139	Normal function	Day 1 and 2	Group 1: $n = 130$ Day 1 and 2 cortisol > 4 mcg/dL Group 2: $n = 9$ Day 1 or 2 cortisol level < 4 mcg/dL	Chemiluminescent immunoassay	Clinical and biochemical follow-up at week 3 to 6 postop, provocation testing was not routinely done Group 1: 3 were placed on steroids within 12 months postoperatively, 2 of them were weaned off steroids Group 2: 5 weaned off steroids within 3 to 28 weeks postoperatively	Day 1 and 2 cortisol levels above 4 mcg/dL predict normal HPA axis with 98% positive predictive value, 96% sensitivity and 57% specificity
Pofi 2019 [7]	109	Patients with evidence of AI and others without evidence of AI	9 a.m. day 8	Group 1: $n = 86$ Normal HPA axis before surgery Group 2: $n = 23$ Abnormal HPA axis before surgery	Immunoassay	Week 6 postoperative SST (post-SST cortisol level above 15.5 mcg/dL). In the whole cohort, 70.6% ($n = 77$) had normal HPA function 6 weeks after surgery and 29.4% ($n = 32$) still had adrenal insufficiency at 6-week assessment Group 2: $n = 8$ (34.8%) recovered at week 6, 13.3% and 20% recovered at 3 months and 9 to 12 months, respectively	A day 8, 9 a.m. cortisol level of 13.35 mg/dL had 100% specificity to predict normal HPA axis function at 6 weeks as tested by SST
Staby 2021 [8]	50	No evidence of AI	Day 1 Day 2	$n = 50$ Mean cortisol level on day 1 or 2 after surgery 17.6 mcg/dL	Elecsys cort2 assay	Synacthen stimulation test 6 months after surgery 3 had AI, all with basal day 1 or day 2 cortisol level < 10.9 mcg/dL	Using basal cortisol cut-off of 300 nmol/L (10.9 cg/dL) on day 1 or 2 predicts AI with sensitivity and NPV of 100% and specificity 81% and PPV 25%

Author year	Sample size	HPA axis function before surgery	Timing of cortisol measurement	Serum cortisol level in the early postoperative period	Cortisol assay	Definitive evaluation, timing, test result	Authors' suggestions
De Vries 2020 [9]	156	Patients with or without evidence of AI	6 to 8 a.m. 18 hours after HC withdrawal day 2 to 3	Group 1: $n = 140$: basal CRH test ≥ 5 days post-surgery: $n1 = 32$ peak cortisol level < 430 nmol/L (15.6 mcg/dL); $n2 = 108$: peak cortisol level > 430 nmol/L (15.6 mcg/dL) Group 2: $n = 156$: basal cortisol level; $n3 = 16$: basal cortisol < 80 nmol/L (2.9 mcg/dL); $n4 = 26$: basal cortisol between 80 (2.9 mcg/dL) and 220 nmol/L (8 mcg/dL); $n5 = 39$: basal cortisol between 220 (8 mcg/dL) and 325 nmol/L (11.78 mcg/dL); $n6 = 74$: basal cortisol > 325 nmol/L (11.78 mcg/dL)	Immunoassay	ITT, CRH or basal cortisol at least 6 weeks post-surgery Group 1: $n1 = 23$ confirmed AI out of 32; $n2$: 8 confirmed AI on follow-up Group 2: $n3$: all confirmed AI; $n4$: 16 confirmed AI on follow-up; $n5$: 4 confirmed AI on follow-up; $n6$: 2 confirmed AI on follow-up	CRH after at least 6 weeks after surgery: sensitivity 78% and specificity 90% Basal cortisol at least 6 weeks after the surgery: sensitivity 86% and specificity 92%, using an optimal cutoff of 220 nmol/L

HPA: hypothalamic-pituitary-adrenal; AI: adrenal insufficiency; IIH: insulin induced hypoglycemia; CST: cosyntropin stimulation test; NAV: not available; RCC: Rathke's cleft cyst.

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