Perioperative Evaluation and Management of Patients on Glucocorticoids

Dr.sara ghadimi

- Glucocorticoids (GCs) are one of the most commonly prescribed drugs with an estimated use prevalence of approximately 1% of the US population .
- They are very effective anti-inflammatory medications and considered first-line treatment for many autoimmune conditions.

- One important consequence of supraphysiological and/or long-term GC treatment is the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression leading to GC-induced adrenal insufficiency (AI), which is associated with increased morbidity and mortality.
- When associated with a stressor such as a surgical procedure, HPA axis suppression can result in adrenal crisis.

This outcome was recognized in early-20th-century studies when adrenalectomized dogs experienced circulatory shock after laparotomy that could be prevented by administering GCs . In the 1950s, multiple reports described patients on chronic GC therapy for rheumatoid arthritis who died shortly after orthopedic surgery. Postmortem examinations consistently revealed bilateral adrenal atrophy, leading to the conclusion that the adrenal glands' inability to respond to surgical stress was the cause of death.

The resultant concern about postoperative adrenal crisis in patients on GCs led to the routine use of high-dose perioperative GC replacement in clinical practice.

While underdosing perioperative GCs may place patients at risk for cardiovascular collapse, high doses carry a risk of hyperglycemia, hypertension, opportunistic infections, bone loss in a state of immobility, venous thromboembolism, and poor wound healing . This review outlines the key physiologic aspects of the stress response to surgery, the effect of different forms of GCs on the HPA axis, the evidence for perioperative GC administration, and our personalized approach to perioperative management in adults with GC-induced AI.

Regulation of the HPA Axis Perioperatively

The HPA axis is regulated by the classic negative feedback of cortisol as well as other neurohumoral inputs including vasopressin, the autonomic nervous system, inflammation, and opioids . This results in an estimated production of about 5.7 mg/m2 or 9.9 mg of cortisol per day in healthy adults which could increase to >100 mg during times of major stress .

Multiple factors determine the degree of HPA axis activation during a surgical procedure. Individual factors, including genetics, age, sex, comorbidities, and medications, as well as perioperative factors, such as type and duration of anesthesia and operative procedure and perioperative complications, contribute to the heterogeneity seen in studies evaluating the HPA axis response .

Different types of surgical procedures generate different degrees of HPA axis activation . Criteria to stratify the degree of surgical risk (Grade I-III), independent from the anesthetic risk, are summarized in Table 1 .

Corticosteroid coverage for surgery in patients taking exogenous corticosteroids

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For minor procedures or surgery under local anesthesia (eg, inguinal hernia repair), take usual morning steroid dose. No extra supplementation is necessary.
For moderate surgical stress (eg, lower extremity revascularization, total joint replacement), take usual morning steroid dose. Give 50 mg hydrocortisone intravenously just before the procedure and 25 mg of hydrocortisone every eight hours for 24 hours. Resume usual dose thereafter.
For major surgical stress (eg, esophagogastrectomy, total proctocolectomy, open heart surgery), take usual morning steroid dose. Give 100 mg of intravenous hydrocortisone before induction of anesthesia and 50 mg every eight hours for 24 hours. Taper dose by half per day to maintenance level.

However, in general, cortisol secretion is proportional to the degree of surgical stress:

The normal basal secretion of cortisol from the adrenal gland is approximately 8 to 10 mg/day.

During a minor surgery or illness, secretion of cortisol increases to approximately 50 mg/day. Small, transient cortisol responses are seen with minor stress (eg, inguinal hernia repair), returning to baseline within 24 hours after uncomplicated surgery.

Patients exposed to greater surgical stress (eg, subtotal colectomy) have greater cortisol responses (75 to 100 mg/day), normalizing by postoperative day 5.

The cortisol secretion rate can reach 200 to 500 mg/day with severe stress (such as major trauma), but secretion rates greater than 200 mg/day in the 24 hours after surgery are rare.

Table 1. Surgical stress associated with common surgical procedures, based on the modified Johns Hopkins surgical criteria [32]

Grade	General Characteristics	Characteristic Operations
Grade I (Minor)	Minimal to mild risk independent of anesthesia Minimal to moderately invasive procedure Potential blood loss of < 500 mL	Minor general surgical procedures (skin/subcutaneous tissue procedures, inguinal hernia repair, breast biopsy) Endoscopy (including cystoscopy, hysteroscopy, bronchoscopy, minor laparoscopy, arthroscopy) Minor gynecologic procedures (tubal ligation, dilation, and curettage) Minor otolaryngology procedures (myringotomy tubes, tonsillectomy/rhinoplasty)
Grade II (Moderate)	Moderate risk independent of anesthesia Moderately to significantly invasive procedures Potential blood loss of 500-1500 mL	Open or laparoscopic resection/reconstruction of the digestive tract; cholecystectomy Thyroidectomy Cystectomy, nephrectomy Hysterectomy or myomectomy Laminectomy Joint replacement
Grade III (Major)	Major to critical risk independent of anesthesia Highly invasive procedure Potential blood loss >1500 mL Usual postoperative intensive care unit stay with invasive monitoring	Any major orthopedic-spinal, oropharyngeal, or genitourinary repair or reconstruction Any intracranial, major vascular, or cardiothoracic procedure

- In Grade I procedures, no intraoperative cortisol peak is observed, whereas in Grade II procedures, peak cortisol occurs at the time of extubation and returns to baseline at 24 hours .
- With Grade III procedures, peak cortisol occurs 6 to 18 hours postoperatively, persists for 24 hours, and returns to baseline by postoperative day 5 to 7 .

Therefore, the maximum activation of the HPA axis occurs within the first 24 hour postoperatively, returning to baseline in <7 days even in patients undergoing Grade III operations.

In addition to an increase in cortisol secretion, immediately postoperatively there is an approximately 30% to 50% decrease in CBG, and this reduction persists at 24 hours after surgery, resulting in elevated free cortisol levels .

This increment in free cortisol could be associated with inflammation, given that interleukin-6 decreases CBG concentration by about half and the affinity of CBG for cortisol is reduced by neutrophil activation and fever, both common perioperatively .

The clinical team must be aware of GC withdrawal symptoms that may occur in patients on chronic GC on a fast perioperative taper; these patients who may experience AI-type symptoms despite being maintained on supraphysiological GC doses .

Pharmacological Properties of Glucocorticoids

Glucocorticoids have historically been classified as short, intermediate, and long-acting according to their biological half-life (Table 2). However, GCs have many other variable pharmacologic properties, including administration route, potency, and affinity for the GC receptor, resulting in a heterogeneous group of drugs with different potentials to suppress the HPA axis.

In general, the absorption rate after oral administration is rapid (30-45 minutes) and similar among different preparations with bioavailability ranging from 60% to almost 100% .

Intramuscular absorption is rapid, whereas the absorption after subcutaneous injections is slightly slower depending on the amount of adipose tissue present .

Systemic absorption from other formulations such as inhaled, topical, ophthalmic, buccal, or rectal administration is lower, but all can potentially suppress the HPA axis .

Topical and mucosal absorption of GCs depends on the integrity of the skin/epithelial barrier, which is modified by inflammation and influenced by the thickness of skin.

Certain GCs such as Triamcinolone after intra-articular and epidural injection are slowly absorbed resulting in sustained supraphysiological concentration.

Oral budesonide has a high first-pass effect in the liver where about 90% is inactivated.

Despite this, HPA axis suppression and cases of adrenal crises have been reported.

Table 2. Pharmacological properties of frequently used glucocorticoids [65–68]

Classification	Equivalent Glucocorticoid Dose (mg)	Glucocorticoid Activity	Mineralocorticoid Activity	Biological Half-Life (hours)	Plasma Half- Life (hours)	Bound in Plasma (%)
Short Acting						
Hydrocortisone	20	1	1	8-12	1.3-2.3	90
Cortisone acetate	25	0.8	0.8	8-12	0.5	—
Deflazacort	5	4	1	<12	1.3-1.9	40
Intermediate-Acting						
Prednisone	5	4	0.8	12-36	2-4	75
Prednisolone	5	4	0.8	12-36	2-4	95
Methylprednisolone	4	5	0.5	12-36	2-4	78
Triamcinolone	4	5	Negligible	12-36	0.5	68
Long-Acting						
Betamethasone	0.6	25-30	Negligible	36-72	5	64
Dexamethasone	0.375-0.75	30-40	Negligible	36-72	3.5-5	68

Incidence of Postoperative Adrenal Insufficiency

Postoperative AI in patients on chronic GCs is rare . However, establishing the true incidence is challenging.

In many cases, hypotension that resolves in response to GCs, in the absence of an alternative explanation, has been used as the criteria to establish the diagnosis of AI.

The risk for HPA axis suppression in relation to GC exposure depends on multiple factors including the type of GC, ability of the drug to reach the systemic circulation, dose, and duration of treatment.

In general, systemic treatments, long-acting GCs, higher doses, longer duration of therapy, higher potency, nighttime administration, multiple cycles of treatment, and multiple daily doses carry a higher risk for HPA axis suppression and AI .

The daily requirement of a patient with AI to maintain basal, nonstressed body functions is approximately 4 to 5 mg prednisone equivalent per day. To stratify the risk of HPA axis suppression, GC intake may be divided into low dose (<5 mg prednisone equivalent), medium dose (5-20 mg), and high dose (>20 mg) per day.

The duration of GC exposure can be considered as short-term (<1month), intermediate-duration (between 1-3 months), and long-term (>3 months).

Otherwise, most patients should receive a short course of GCs perioperatively based on the level of surgical stress and then return to their basal dose as they recover.

Low-dose GCs administered in the morning, for any duration of time, seem to have a low risk of causing clinically significant AI.

In a study of 50 patients on long-term prednisone (mean duration approximately 4 years), those receiving <5 mg/day showed a normal or near-normal response to the Cosyntropin stimulation test (CST) without AI-related events.

Accordingly, we do not recommend additional workup in patients taking <5 mg prednisone equivalent per day in the morning beyond the continuation of their glucocorticoids and monitoring them for any signs and symptoms of AI.

However, it is also important to consider the cumulative effect of previous glucocorticoids in patients in whom the dose of GCs has been tapered to less than 5 mg prednisone equivalent per day at the time of their surgical evaluation.

Such patients should receive a short course of parenteral GC therapy when unable to take their daily GC dose.

High-dose GCs taken for short-term frequently cause HPA axis suppression although rarely clinically significant AI.

Carella et al reported that a short course of high dose of prednisone (40 mg 3 times per day for 3 days followed by a taper during the subsequent 4 days) resulted in transient HPA axis suppression . HPA axis recovery based on a CRH and CST was seen 1 week after treatment.

t. Similarly, Spiegel et al showed that prednisone at doses of 40 mg/m2 to 100 mg/m2 daily for <1 month could result in HPA axis suppression with recovery in <1 week and no clinically significant AI events.

Therefore, the duration of therapy seems to have a greater impact than the dose on HPA axis suppression. Indeed, all historically reported adrenal crises have been in patients on chronic GC therapy. Therefore, we do not recommend any action outside of routine perioperative monitoring in patients who have been on GCs for <4 weeks prior to surgery.

Patients taking 5 mg or more of prednisone equivalent per day for >1 month may have variable degrees of HPA axis suppression . The risk of HPA axis suppression is higher in patients taking higher doses for a longer duration.

Such patients should not stop GCs prior to surgery without further evaluation of the HPA axis.

The majority of these patients can stay on their current dose of GC perioperatively and can be administered a short course of intravenous GC postoperatively until they resume their oral intake .

The time of the day of GC administration can influence the risk of HPA axis suppression.

In 8 healthy subjects who received 0.5 mg of dexamethasone at midnight for 2 consecutive nights, there was a more prolonged HPA axis suppression compared to those who received the same regimen at 8 AM or 4 PM.

The administration of multiple GC doses throughout the day carries a higher risk for HPA axis suppression than the same total daily dose taken once.

Myles et al in a crossover design compared cortisol levels after giving patients a single dose of prednisolone at 10 AM for 8 weeks vs the same total daily dose divided as half at 10 AM and the other half at 10 PM for 8 weeks, returning to a single daily dose after.

Cortisol levels were significantly lower in patients during the time the dose was split compared to when patients received a single daily dose of prednisolone.

Alternate-day (morning) GC regimens are associated with a lower incidence of iatrogenic Cushing syndrome and HPA axis suppression

The risk of AI with intraarticular GCs remains largely unrecognized and likely underestimated . Both the absorption and the ability to suppress the HPA axis are proportional to the GC dose, half-life, solubility, vascularization of the synovium (increased during inflammation), number of joints injected, and frequency of injections .

In a small randomized controlled study that used a single fixed dose of 80 mg of methylprednisolone knee injection vs placebo, 25% of the patients receiving GC developed HPA axis suppression between week 2 and 4 after injection, and then returned to baseline.

Epidural GC injections can also result in rapid and prolonged HPA axis suppression.

Until better quality data is available, we recommend evaluating the HPA axis in patients who have received 3 or more GC injections within 6 months before surgery.

Inhaled GCs are absorbed systemically by the pulmonary vasculature with a smaller fraction swallowed and absorbed by the gastrointestinal tract .

In a systematic review in patients with asthma using only inhaled GCs, higher risk of HPA axis suppression was seen with high doses of fluticasone equivalent (>1000 mcg/day), compared to medium (200-1000 mcg/day) and low doses (<200 mcg/day), resulting in AI in 18.5%, 5.4% and 1.5% of patients, respectively.

When analyzed by the duration of treatment, long-term use (>1 year) had a higher prevalence of AI compared to medium (1 month to 1 year) and short term (<1 month); duration of treatment was associated with abnormal HPA axis in 20.3%, 9.0%, and 1.3% of patients, respectively . Another meta-analysis showed that the risk of basal cortisol suppression was higher with fluticasone compared to other inhaled steroids at the same equivalent dose .

Topical GCs are classified based on potency into 7 classes and 3 subgroups: ultra-high (Class 1-3), moderate (Class 4-5), and low (Class 6-7) potency corticosteroids.

Topical GCs can be absorbed systemically through the skin depending on the surface area of application, location applied, and skin thickness and integrity of the skin (ie, ulcerated, injured, or inflamed skin results in greater absorption) .

Suppression of the HPA axis and AI can occur with the most potent topical GCs, clobetasol propionate 0.05% (Class 1), and betamethasone dipropionate 0.05% (Class 2).

Iatrogenic Cushing syndrome accompanied by HPA axis suppression has been reported in adults with doses of approximately 33 to 100 g/week of clobetasol propionate and 49 to 80 mg/week of beclomethasone dipropionate

Therefore, patients using potent topical GCs for prolonged periods of time or in combination with systemic GCs need to be cautious about the development of AI.

Uptodate recommend evaluation of adrenal function perioperatively in patients who have been on:

●≥750 mcg daily of fluticasone (1500 mcg daily for other IGCs) for more than three weeks prior to surgery

● ≥2 g/day of high potency or super high potency topical corticosteroids (class I-III) for more than three weeks prior to surgery

● In addition, patients who appear Cushingoid or exhibit signs or symptoms of adrenal insu"ciency should have their HPA axis evaluated

The ophthalmic and rectal routes of steroid application have been associated with HPA axis suppression in small studies or case reports. Ophthalmic solutions, when used excessively and for prolonged periods, can be systemically absorbed resulting in iatrogenic Cushing syndrome and HPA axis suppression .

Rectal GCs (enemas) have been associated with systemic absorption and HPA axis suppression particularly when the rectal mucosa is injured, inflamed, or ulcerated.

Many GCs are metabolized via cytochrome P450 3A4 (CYP3A4). Therefore, inhibition of this enzyme results in risk of higher GC levels and HPA axis suppression.

Multiple medications are known to inhibit CYP3A4; for example, ritonavir, a protease inhibitor, has a known interaction with inhaled fluticasone.

When taken concomitantly with ritonavir, fluticasone propionate at doses as low as 500 ug/day for 2 months can result in iatrogenic Cushing syndrome .

Table 3. Common drugs affecting the hypothalamic-pituitary adrenal axis [92, 97, 110, 111]

Drugs Affecting CRH and ACTH Synthesis or Secretion	
Opioids (morphine, oxycodone, fentanyl, tramadol, methadone, heroin)	
Benzodiazepines (midazolam, oxazepam, alprazolam, diazepam)	
Megestrol Acetate	
Medroxyprogesterone	
Drugs Affecting Cortisol Synthesis	
Azoles (Ketoconazole/Levoketoconazole, Posaconazole, fluconazole)	
Etomidate	
Metyrapone, Aminoglutethimide	
Trilostane	
Drugs Affecting Cortisol Action	
Mifepristone	
Drugs Affecting Cortisol Metabolism	
Cytochrome P450 3A4 Inhibitors (Decrease Cortisol Metabolism)	Cytochrome P450 3A4 Inducers (Increase Cortisol Metabolism)
Protease inhibitors (darunavir, indinavir, lopinavir, nelfinavir, telaprevir, ritonavir)	Antiepileptic drugs (phenytoin, fosphenytoin, phenobarbital, primidone)
Cobicistat, Azoles (itraconazole, voriconazole), clarithromycin, Grapefruit juice, mifepristone	Carbamazepine, rifampin, and mitotane
Calcium channel blockers (verapamil, diltiazem), amiodarone, cimetidine, conivaptan, erythromycin, and imatinib[b]	Nafcillin, rifabutin, bosentan, dorafenib, efavirenz, rifabutin, St John's wort[a]

[a]Less potent inducers.
[b]Less potent inhibitors.

Evaluation of Adrenal Function in Patients Using Glucocorticoids

Patients should undergo HPA testing if there is a plan to stop GC before surgery. Morning and random (during stress) serum cortisol levels and the CST are the most commonly used tests for the evaluation of the HPA axis.

Morning serum cortisol:

— The measurement of morning (prior to 8 AM) serum cortisol has been described as a good screening method for evaluation of secondary adrenal insufciency.

- In patients on chronic glucocorticoid therapy, an early morning cortisol <5 mcg/dL (138 nmol/L) 24-hour off glucocorticoid replacement dose is highly suggestive of an impaired HPA axis with the need for additional glucocorticoid intake perioperatively.
- Patients with an early morning cortisol level >10 mcg/dL (275 nmol/L) likely do not have a signifcant impairment of the HPA axis and may be continued on their current glucocorticoid replacement dose on the day of surgery . Such patients do not need additional perioperative glucocorticoid therapy.

- **In patients with an early morning cortisol level between 5 to 10 mcg/dL (138 to 275 nmol/L), we suggest further evaluation with a corticotropin (ACTH) stimulation test or empiric additional perioperative glucocorticoid therapy.**

ACTH stimulation tests

We suggest measurement of serum cortisol at 30 minutes after 250 mcg corticotropin (ACTH) stimulation for preoperative evaluation of the HPA axis. A cortisol level >18 mcg/dL (497 nmol/L) 30 minutes after 250 mcg ACTH stimulation predicts an adequate adrenal reserve during surgery with no need for glucocorticoid coverage perioperatively.

Patients with an inadequate response should receive additional glucocorticoid coverage.

Glucocorticoid “Coverage”

Awareness of the lack of evidence to support the use of high-dose perioperative GCs and the associated risks has resulted in a trend to recommend lower doses and shorter duration of these protocols—from >300 mg of hydrocortisone to about 100 to 200 mg/day and shorter tapers over <7 days—without increased mortality.

Table 6. Review articles that commented on perioperative glucocorticoid treatment regimen

Source	Year	Comments from the Authors	Conclusions on Treatment
Kehlet [151]	1975	"Glucocorticoid should only be given in a necessary and adequate dose" to avoid side effects	Most regimens are founded on empirical basis
Salem [8]	1994	The risk should be individualized based on the glucocorticoid preoperative dose, duration, and type of surgery	We are giving too much glucocorticoids
De Lange [157]	2008	There is no evidence to support excessive dosing (>200 mg hydrocortisone equivalent/day) or extensive duration in uncomplicated cases	We are giving too much glucocorticoids
Marik [158]	2008	"Stress doses are not routinely required as long as the patient continues their usual daily dose of glucocorticoids"	We are giving too much glucocorticoids
Fleager [155]	2010	"There are no evidence-based treatment guidelines that provide firm recommendations for the administration of perioperative steroids"	No evidence for current practice
Kelly [159]	2013	Based on the existing evidence, patients on long-term glucocorticoids do not require the once-standard high doses; just continue their maintenance doses perioperatively. Treat refractory hypotension with rescue doses of steroids	We are giving too much glucocorticoids
Hicks [160]	2015	"Current prescribing practices are highly variable, likely because of a lack of randomized controlled data and a wide range of preoperative treatment regimens"	"Recent data suggest that additional corticosteroid supplementation in the perioperative period may be unnecessary and may serve only to increase the risk of poor wound healing and infectious"
MacKenzie [161]	2016	"Despite little evidence for this practice (supraphysiological supplemental perioperative glucocorticoids), few have challenged this treatment paradigm"	"With few exceptions, the use of supraphysiologic glucocorticoid therapy for adults with presumed adrenal insufficiency due to exogenous glucocorticoid use should be regarded as unnecessary"
Liu [156]	2017	"Recommendations in major textbooks are confusing, inconsistent, and lacking in class A or B evidence"	There is no universal agreement regarding dose, duration, or regimen of supplemental glucocorticoid
Groleau [9]	2018	"It is not possible to conclude that perioperative administration of corticosteroids, compared to placebo, reduced the incidence of adrenal insufficiency"	Providing the daily maintenance dose without supplemental glucocorticoids may be sufficient
Khazen [162]	2018	"We found no evidence to support the use of supraphysiologic dose of glucocorticoid therapy provided the patient receive their usual dose of glucocorticoid preoperatively"	"A well-designed, large multicenter RCT is warranted"
Chilkoti [66]	2019	"There are no dogmatic guidelines regarding perioperative "stress dose" of steroids in patients on chronic steroid therapy; however, there is enough evidence that patients on long-term exogenous steroid therapy do not require the conventional high-dose perioperative corticosteroid, instead must be kept on their baseline maintenance dose"	We are giving too much glucocorticoids
Manou-Stathopoulou [163]	2019	"Clinical trials exploring glucocorticoid supplementation have provided conflicting data, reflecting the lack of understanding of the cortisol biology during the perioperative period"	More personalized targeted therapies are needed
Seo [11]	2021	Many clinical trials have low level of evidence, lack of power, without clear criteria for AI that results in high variation in the recommendations	No evidence for current practice
Laugesen [10]	2021	"Current evidence indicates substantial variation regarding risk and course of glucocorticoid-induced adrenal insufficiency … more research is needed to refine the diagnosis and to support evidence-based clinical decision-making"	No evidence for current practice

Many review articles discuss the topic and make recommendations without specific comments about the current practice.
AI, adrenal insufficiency; RCT, randomized controlled trial.

The current literature supports that in patients undergoing a surgical procedure, continuing the daily dose of GCs along with a short course of perioperative IV GCs based on the level of anticipated surgical stress is adequate.

In most perioperative scenarios, administration of ≤100 mg/day hydrocortisone with a rapid taper to preoperative GC dose is sufficient. Close monitoring for any evidence of hemodynamic instability is fundamental.

Uptodate suggest the following approach for perioperative glucocorticoid

Coverage:

Nonsuppressed HPA axis – For patients who have been taking exogenous glucocorticoids of any dose for less than three weeks, morning prednisone (<5 mg daily or its equivalent) for any duration, or less than 10 mg of prednisone or its equivalent every other day, we suggest continuing the same glucocorticoid regimen perioperatively . These patients are unlikely to have a suppressed HPA axis, and neither preoperative evaluation of the HPA axis nor supraphysiologic doses of glucocorticoids are needed.

Suppressed HPA axis – For patients who are currently taking prednisone >20 mg/day for three weeks or more and in patients with a Cushingoid appearance, we suggest additional perioperative glucocorticoid coverage, because HPA axis suppression should be assumed to be present . Our recommendations for specifc glucocorticoid regimens are based upon the type and anticipated duration of surgery.

Intermediate HPA suppression – For all other patients, the degree of HPA axis suppression is unknown, and biochemical evaluation of the HPA axis should be performed.

study suggests that patients with AI who are administered 20 mg of hydrocortisone 2 to 4 hours prior to intubation have a baseline cortisol level comparable to healthy individuals with an intact HPA axis.

Subsequently, providing 25 mg IV hydrocortisone every 6 hours for 24 hours, followed by 15 mg every 6 hours or 24 hours, resulted in no adverse events or symptoms suggestive of AI.

Considering this, 15 to 25 mg of hydrocortisone IV every 6 hours (60-100 mg/day) should provide enough perioperative coverage for even moderate to major operations in patients suspected to have GC-induced AI.

Table 5. Perioperative treatment regimens suggested for patient with glucocorticoid-induced AI

Regimen	Degree of Surgical Stress	Glucocorticoid Regimen
Patients currently on glucocorticoids	Garde I Minor	• Continue daily dose of glucocorticoid • 25 mg of IV hydrocortisone at induction if not able to tolerate PO • Resume oral daily preoperative glucocorticoid regimen
	Grade II Moderate	• Continue daily dose of glucocorticoid • 25-50 mg of hydrocortisone IV at induction • 15-25 mg hydrocortisone every 6 hours. until PO is tolerated and hemodynamically stable[a] • Resume oral daily preoperative glucocorticoid regimen
	Grade III Major	• Continue daily dose of glucocorticoid • 50 mg of hydrocortisone IV at induction • 25 mg of hydrocortisone IV every 6 hours on day 1 and until hemodynamically stable, then 15 mg IV every 6 hours until PO is tolerated[a] • Resume oral daily preoperative glucocorticoid regimen
Patients who stopped or plan to stop glucocorticoids before surgery		• Assess HPA axis in patients with intermediate to high risk (see Table 4) • The closer the date of discontinuing glucocorticoids before surgery, the higher the risk of AI • Treat based on the degree of surgical stress in those who have abnormal HPA axis
Adrenal crisis		• 100 mg of hydrocortisone IV (IM if no IV access) • 50 mg every 6 hours until hemodynamically stable and then taper[a] • Taper depending on clinical response-intravenous fluids (normal saline), dextrose 5% if hypoglycemia

These recommendations include the authors' personalized approach to perioperative management in patients with glucocorticoid-induced AI.
AI, adrenal insufficiency; HPA, hypothalamic-pituitary-adrenal; IM, intramuscular; IV, intravenous; PO, by mouth.
[a]Some experts favor continuous glucocorticoid infusion.

There is little data in perioperative management of pregnant patients on chronic GC. Cortisol levels increase throughout pregnancy secondary to increased CBG and to the HPA axis stimulation by placental CRH. The dose of GC replacement does not usually need to be increased during the first and second trimesters, but an increase in GC dosage of 20% to 40% from the 24th week forward is generally recommended

Accordingly, a 50% higher perioperative parenteral GC coverage, especially during the third trimester, and delivery seems reasonable. Careful perioperative monitoring of the hemodynamic status of pregnant women and their fetus is critical .


Thank you