Chapter

Corticosteroid Replacement Therapy

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Abstract

The advent of synthetic corticosteroids in the 20th century provided a vital breakthrough in the management of adrenal insufficiency. In this chapter we review the main indications and guidance for appropriate hormone replacement and also look into the management of therapy during special circumstances. For decades hydrocortisone has remained the cornerstone for glucocorticoid replacement but we explore the alternatives including recently introduced modified-release drug preparations and the future treatment considerations currently undergoing research and pre-clinical trials.

Keywords: Corticosteroids, Glucocorticoids, Hormone Replacement, Adrenal Crisis, Sick Day Rules, Novel Therapies

1. Introduction

Corticosteroid replacement therapy in adrenal insufficiency namely glucocorticoids such as hydrocortisone serve as life sustaining therapy therefore its appropriate administration when stable or unwell is of vital importance. In this chapter we explore the indications and guidance for corticosteroid replacement therapies including management during special circumstances such as emergencies, pregnancy and breastfeeding. We also look at current novel therapies and look towards future perspectives on treatment therapies under research.

2. Overview

Adrenal insufficiency was first postulated by the physician Thomas Addison of Guy's Hospital London in 1855. He characterized the condition of progressive anemia, bronze skin pigmentation and low blood pressure in disease of the 'suprarenal capsules' – now known as Addison's disease [1]. This is a condition epitomized by insufficient production of steroid hormones from the adrenal cortex: primarily glucocorticoids from the zona fasiculata but can also affect mineralocorticoid and adrenal androgen production (from the zona glomerulosa and zona reticularis respectively).

It has historically carried a high mortality rate until the advent of therapeutic corticosteroid preparations in the mid-20th century. Life expectancy is generally considered normal with the application of appropriate replacement therapy but there is a growing body of evidence of highlighting increased morbidity and reduced life expectancy likely related to increased cardiovascular risk with

hormonal over replacement and adrenal crises. Glucocorticoid administration is essentially life sustaining therapy; some patients will also require the co-administration of mineralocorticoids drugs and the adrenal androgen *dehydroepiandrosterone* (DHEA). The importance of replacement therapy is not only to starve off symptoms of hormone deficiency (including fatigue, muscle weakness, dizziness, weight loss, low mood, low libido) but also is imperative in maintaining key physiological processes (including gluconeogenesis, immune modulation, electrolyte balance, metabolism and haemodynamic modulation).

3. Conditions necessitating hormone replacement

Adrenal insufficiency requiring corticosteroid hormone replacement therapy is triggered by conditions or factors interrupting the normal function of the hypothalamic–pituitary–adrenal axis (HPA axis). Most causes are acquired in nature rather than congenital and can be divided into *primary adrenal insufficiency* (direct adrenal hormone synthesis dysfunction) and *secondary adrenal insufficiency* (inadequate ACTH production).

Hormone deficiency is a deficit deemed unable to meet the physiological demands of the body, most notably in response to stress. In deficiency states glucocorticoid replacement therapy is always required. However because mineralocorticoid and adrenal androgen production is only partially mediated by ACTH; replacement therapy of these hormones is not usually required in secondary adrenal insufficiency.

The most common cause of primary adrenal insufficiency in the developed world is autoimmune in nature – approximately 70% of cases [2] with antibodies present against the 21-hydroxylase enzyme.

Other notable causes of primary adrenal insufficiency include:

- Infection (e.g. tuberculosis)
- Malignancy (e.g. adrenal metastases)
- Iatrogenic (e.g. post-adrenalectomy, ketoconazole)
- Inherited (e.g. congenital adrenal hyperplasia).

Notable causes of secondary adrenal insufficiency include:

- Pituitary tumors
- Hypothalamic/pituitary infections or inflammation (e.g. tuberculosis, lymphocytic hypophysititis)
- Iatrogenic (e.g. post transpenoidal surgery, radiotherapy)
- Isolated ACTH deficiency
- Long term exogenous glucocorticoid therapy (causing suppression of HPA axis).

Corticosteroid replacement therapy is often required lifelong but, depending on the cause, therapy may be able to be safely withdrawn in future if adrenal function recovers.

4. Historical perspective

Early animal studies in 1930 proved bovine adrenal extracts could transiently treat symptoms of adrenal insufficiency. The later production of synthetic desoxycorticosterone acetate in 1938 was the major step in providing a therapeutic agent to successfully treat adrenal insufficiency. In 1950 commercial therapeutic use of hydrocortisone was established after recognition of cortisol as the key end product of adrenal cortex hormone synthesis [3]. To current day hydrocortisone therapy still remains the mainstay replacement therapeutic drug.

5. Assessing for glucocorticoid deficiency

Suspicion of glucocorticoid deficiency can be initially indicated by typical symptomology, hypotension and skin hyperpigmentation (in cases of primary adrenal insufficiency associated with excess ACTH production). Baseline biochemistry can often reveal a combination of hyponatraemia, hyperkalaemia or hypoglycaemia. Morning cortisol and ACTH levels are useful markers in preliminary testing with cortisol levels <140 nmol/L being indicative of deficiency. Elevated or low ACTH levels assist in defining primary vs. secondary adrenal insufficiency respectively (an ACTH level two-fold the upper reference range is consistent with primary adrenal insufficiency). There is no evidence to support the role of random cortisol levels to diagnose adrenal insufficiency [4].

A corticotropin (ACTH) stimulation test is considered the gold standard confirmatory test in primary adrenal insufficiency. Typically baseline cortisol and ACTH levels are taken followed by the administration of a 250 μg IV corticotropin bolus and further monitoring of cortisol levels at 30 minutes and/or 60 minutes. Acceptable cortisol levels indicating sufficient adrenal response remain controversial. Newer monoclonal antibody cortisol immunoassays (including Roche II Elecsys) display increased sensitivities and specificity, allowing for a diagnostic peak cortisol threshold of >400 nmol/L [5].

In cases of secondary adrenal insufficiency an insulin tolerance test – ITT (or insulin stress test) has proved to be more successful in detecting cortisol deficiency in comparison to corticotropin stimulation testing in studies [6]. In testing the aim is to induce extreme hypoglycaemia (<2.2 mmol/L) with the administration of (0.15 units/kg soluble insulin). In normal circumstances hypoglycaemia leads to hypersecretion of the insulin antagonizing hormones ACTH and growth hormone (GH) from the anterior pituitary gland; with a subsequent cortisol rise of <500 nmol/L is considered an inadequate response. It is a potentially harmful test and therefore should be undertaken with care. It is contraindicated in ischaemic heart disease, epilepsy and severe panhypopituitarism; in these circumstances glucagon is often used instead of insulin as the stress provocation agent. Notable scenarios for effective ITT utility include following borderline corticotropin stimulation testing and following recent pituitary surgery [7].

6. Glucocorticoid replacement

Human endogenous glucocorticoid release follows a circadian rhythm i.e. an internal process following a 24 hour cycle. There are also 60–90 minute ultradian oscillations during the day to consider. These processes are ultimately under the control of the hypothalamic suprachiasmatic nuclei (SCN) and subsequent corticotropin-releasing hormone (CRH) secretion that stimulates pituitary ACTH

synthesis variably [8]. The circadian rhythm may be altered by changes to activity, aging, sleep and mood.

Typically in a 24 hour profile we see an early morning ACTH/cortisol peak with declining levels during the daytime until quiescence at midnight. There is then a brisk elevation during late sleep leading on to the early morning peak we see at the beginning of the cycle. It is this pattern that administered glucocorticoid therapy ideally attempts to recreate.

Hydrocortisone is the most commonly administered glucocorticoid therapeutic agent for adrenal insufficiency. Clinic data from the UK revealed 72% of patients were managed with hydrocortisone, 26% with prednisolone and 2% with modified release hydrocortisone [9]. Data from the European Adrenal Insufficiency Registry. (EU-AIR) study additionally showed that over 80% of patients were on conventional hydrocortisone replacement therapy on enrolment [10].

In clinical practice the use of hydrocortisone or prednisolone are often preferable due to their more predictable pharmacokinetics compared to their precursor hormones cortisone and prednisone [9]. The normal functioning adrenal glands are thought to produce 5-10 mg cortisol per m^2 body surface area/per day; this equates to an oral hydrocortisone dose of 15-25 mg/per day for an adult [11]. Due to its short half-life hydrocortisone is usually given in 2–3 divided doses with the largest dose in the morning and the last dose at least 4–6 hours prior to bedtime to avoid sleep disturbances. Prednisolone is a glucocorticoid analogue with a greater avidity for the glucocorticoid (GC) receptor. Studies have shown once daily prednisolone administration to be superior to thrice-daily hydrocortisone in imitating the physiological cortisol profile and reducing over replacement at a recommended dose of 3-5 mg daily [12]. Other potential benefits of prednisolone include cost-effectiveness and increased medication compliance although the comparative long-term metabolic side effect risk between hydrocortisone and once daily prednisolone remain controversial [13–15].

6.1 Novel glucocorticoid replacement therapies

Plenadren® is a novel modified-release form of hydrocortisone given European marketing authorization in November 2011. This once daily preparation contains both immediate-release and extended-release components with an aim to more closely mimic the body's physiological circadian rhythm. It can be considered an alternative for patients who continue to feel unwell on conventional therapy, given typically at a dose of 15-25 mg daily. Evidence from 2 randomized-controlled trials (RCTs) has shown a reduction in CV disease risk parameters with modified release hydrocortisone compared to conventional therapy [9]. Though Plenadren® carries a significantly higher cost basis to the other traditional therapeutic glucocorticoid medications and carries a higher vulnerability to malabsorption during intercurrent gastrointestinal illness [16].

Chronocort® is another novel modified-release form of hydrocortisone with delayed absorption, taken at night with an aim to replicate the physiological early morning cortisol rise and circadian rhythm more closely. It has completed phase III trials for the use in adrenal insufficiency and congenital adrenal hyperplasia; currently awaiting licensing authorization in Europe.

Continuous subcutaneous hydrocortisone infusions (CSHI) were first used from 2007. These offer variable hydrocortisone delivery often through traditional 'insulin pumps' helping to replicate the circadian rhythm most accurately compared to oral therapies. This requires a high degree of patient education and autonomy. Those that can benefit include those patients poorly tolerant or responsive to tablets especially in light of gastric absorption issues. Studies using continuous infusions

have shown better normalization of morning ACTH levels [3]. From minimal comparative studies there has been no consistent evidence of improvement in subjective health outcomes. One RCT showed a mild increase in weight and fasting glucose levels in patients on hydrocortisone infusions but it was felt likely attributable to supra-physiological hydrocortisone dosing (based on elevated urinary and salivary cortisol levels in comparison to the oral hydrocortisone group recipients).

The therapy remains uncommon in healthcare systems, potentially cumbersome and is best commenced by experienced endocrine units. The Endocrine Society 2016 guidance on management of primary adrenal insufficiency suggests reserving such treatment for patients encountering major difficulties on conventional therapy [4].

6.2 Mineralocorticoid replacement

Most patients with primary adrenal insufficiency will exhibit mineralocorticoid deficiency. As release is also under the control of the renin-angiotensin system (RAS) deficiencies can also be caused by reduced renin levels (*hyporeninemic hypoaldosteronism*) due to conditions including diabetic nephropathy, sickle cell anemia, myeloma and medications (e.g. NSAID, beta blockers, Ciclosporin).

Mineralocorticoids are important in circulatory homeostasis and salt balance. Deficiencies can lead to salt craving, postural hypotension, dizziness, hyponatraemia, hyperkalaemia and reduced cognition. To alleviate symptoms replacement therapy is typically met through the use of fludrocortisone and as well advice to increase dietary salt. The Endocrine Society 2016 guidance on management of primary adrenal insufficiency suggests a starting dose of fludrocortisone 50-100mcg in those with confirmed deficiency (assessed by way of plasma renin and aldosterone levels) [4]. Typically higher doses of replacement therapy are required for the more physically active and less sedentary patient cohorts [11].

6.3 Androgen replacement

Primary adrenal insufficiency can also affect adrenal androgen reserve. In women adrenal androgen precursors DHEA and androstenedione are major contributors to the physiological production of potent androgens and oestogen in the zona reticularis. Clinically deficiencies can lead to notable axillary and pubic hair loss.

The benefits of replacement therapy are not very clear. There is some evidence to suggest that health related quality of life markers can be improved with synthetic DHEA in patients with primary adrenal insufficiency [3]. The Endocrine Society notes that there is insufficient evidence to advocate routine androgen replacement therapy but suggests a 6 month trial of DHEA for women with ongoing symptoms of low libido, low mood and/or low energy levels despite optimized glucocorticoid and mineralocorticoid replacement. A single DHEA dose of 25-50 mg in the morning can be considered in the first instance [4].

7. Glucocorticoids *(dose titration and monitoring)*

Signs of glucocorticoid under replacement may include development of lethargy, nausea, headaches, muscle aches, weight loss, increased skin pigmentation and hypotension. Biochemistry may reveal elevated potassium levels and reduced sodium levels. On the contrary signs of over replacement may include weight gain, facial puffiness, insomnia, and glucose intolerance. Longer term over replacement

can lead to established hypertension, type 2 diabetes mellitus, osteoporosis and increased overall CV risk. Stability of replacement therapy is therefore of importance to achieve and optimal dosing will vary between individuals with differences including body composition, absorption, metabolism and protein binding.

The Endocrine Society recommends measuring the adequacy of replacement primarily with clinical assessment including weight, postural blood pressure, energy levels and signs of frank glucocorticoid excess. It is advised against routine hormonal monitoring, instead for titration of treatment based on clinical response. In cases where malabsorption is suspected further analysis with serum or salivary cortisol day curves are recommended as a guide for dosing [4] but there is a lack of reliable biomarkers for treatment monitoring and notably measured concentrations of ACTH are not a useful parameter [11, 17].

7.1 Mineralocorticoids *(dose titration and monitoring)*

Fludrocortisone under replacement is common and can be often seen compensated by supra-physiological glucocorticoid doses which puts patients at high risk for developing the subsequent metabolic sequelae associated with hypercortisolaemia. Signs of over replacement with fludrocortisone include hypertension and oedema. The Endocrine Society recommends reviewing replacement dosing clinically by assessing for salt craving, postural hypotension, oedema and blood electrolytes (aiming for normokalaemia). It is also advised the hypertension is initially managed by dose reduction following the addition of antihypertensive agents if necessary [4].

It is common to use plasma renin activity as a guide for appropriate Fludrocortisone replacement although the data to support its usefulness is limited. The ideal renin target levels lie in the upper reference range. Caution must be taken with interpretation as levels can be affected by variables such as body position, time of day and medications. Additionally liquorice and grapefruit potentiate the mineralocorticoid effects of hydrocortisone and should thus be avoided [4, 11].

7.2 Androgens *(dose titration and monitoring)*

Adequate replacement with DHEA may be noted by improved libido, mood and energy levels on assessment. The Endocrine Society recommends taking morning (pre-dose) DHEAS levels to guide treatment, aiming for levels in the mid-normal range [4]. Levels may be taken by saliva, serum or urine. There are however potential side effects of DHEA therapy related to androgen excess including hirsutism, acne, deepened voice and hair loss. Studies have shown some benefits to bone density, lean mass and psychological wellbeing scores [18].

8. Sick day rules, emergency advice and adrenal crises management

During periods of acute illness and physiological stress there are increased demands of cortisol production placed on the body. Glucocorticoid doses must be increased accordingly to match demands and prevent the onset of an adrenal crisis (commonly evidenced by hypotension, nausea, abdominal pain, reduced consciousness and electrolytes disturbances). Therefore in the presence of illness such as infection with fever, diarrhea/vomiting, significant trauma or significant psychological stress/bereavement; there is general consensus that glucocorticoid doses should be doubled for the duration of illness/antibiotic course (patients taking Plenadren® are best placed switching to hydrocortisone during these periods for

better physiological cortisol profiling). Management of therapy is also of important consideration in the perioperative setting with general advice of giving hydrocortisone 100 mg IV or IM just prior to surgery or at anesthetic induction and weaning doses back to baseline during the recovery period as applicable. Fludrocortisone doses do not need to be routinely increased as hydrocortisone/prednisolone also convey mineralocorticoid receptor activity which is potentiated at higher doses due to saturation of 11β-hydroxysteroid dehydrogenase enzyme (this is not the case for dexamethasone which does not exert mineralocorticoid activity).

At diagnosis patients should be well educated in the sick day management of steroid therapy often provided through endocrine specialist nurses and reinforced

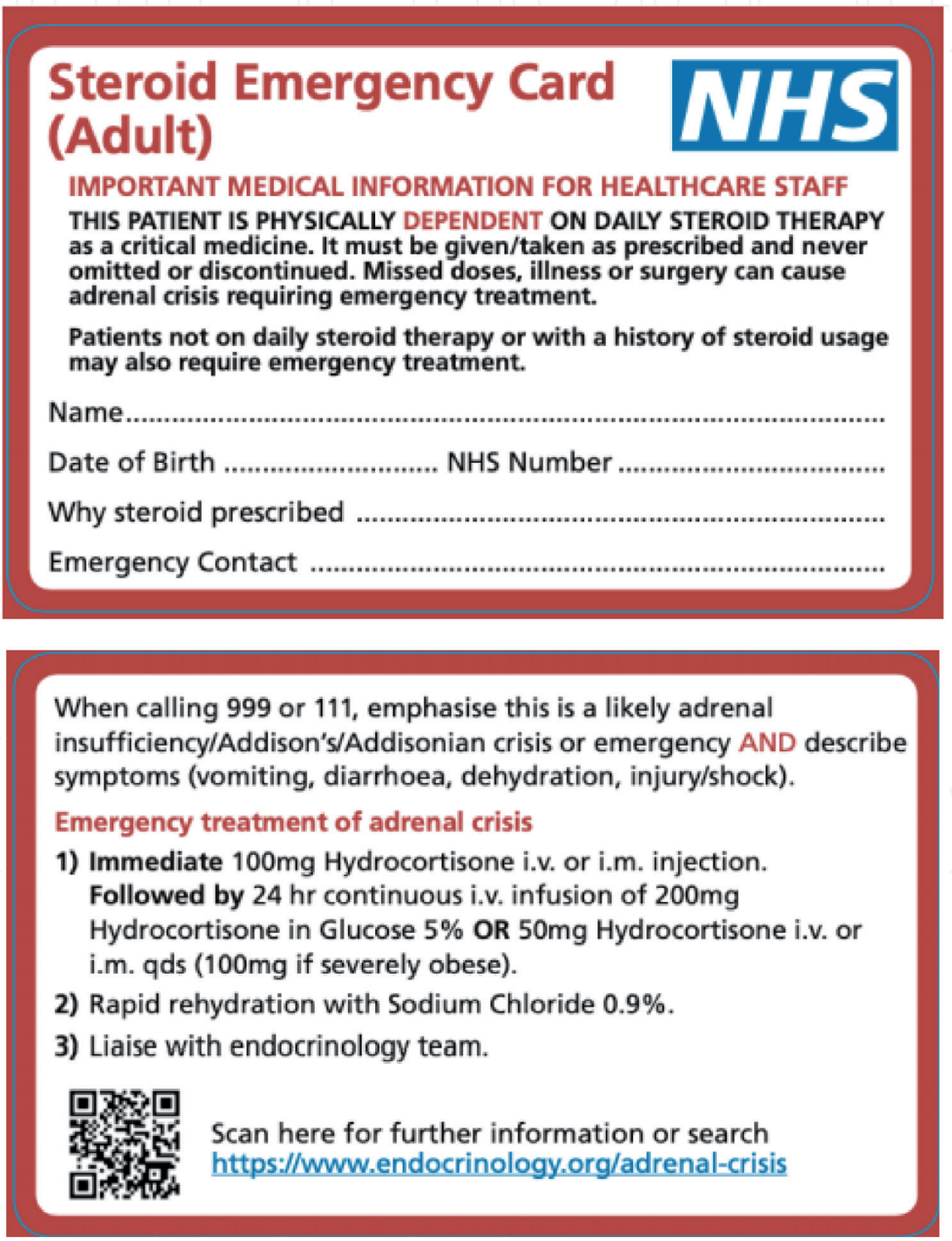

Figure 1.
Example of a European (UK) steroid emergency card (https://www.endocrinology.org/media/3873/steroid-card.pdf).

through patient specific literature and leaflets. Patients should be provided with a supply of IM 100 mg hydrocortisone with counseling provided to patients and carers on its emergency use. In the event of severe illness and/or inability to tolerate oral glucocorticoids; stat IM 100 mg hydrocortisone should be given alongside contact to emergency medical services as these patients may require admission for parenteral hydrocortisone, fluids and stabilization. Further advice and support can be provided by specialist endocrine team and national support organizations such as *The Pituitary Foundation* and *Addison's Self-Help Group* in the UK. Steroids emergency cards (**Figure 1**), bracelets and necklaces are increasingly commonplace in Europe. *The Endocrine Society* suggests that all patients with adrenal insufficiency carry medical alert identification so that medical personnel can be prompted to increase steroids doses to avert adrenal crises and to administer parenteral hydrocortisone immediately in emergency circumstances [4].

An adrenal crisis if a life threating scenario that requires prompt intervention. Data from the *European Adrenal Insufficiency Registry* has shown an incidence rate 7.94 adrenal crises per 100 patient years [19] which is consistent with rates seen in other studies [20]. There are no systematic dose–response studies for the appropriate dosing of hydrocortisone during a crisis therefore management is mostly undertaken on an empirical basis. Underdoing of therapy can be harmful therefore general guidance is to give 100 mg of parenteral hydrocortisone followed by a 200 mg/day infusion or 6 hourly 50 mg boluses alongside appropriate intravenous fluid resuscitation and treatment of the intercurrent illness. To prevent future crises it is important the preceding medical and behavioral factors are explored including medicine concordance and knowledge of sick day rules. It is also recommended that patients with adrenal insufficiency receive an annual influenza vaccine and pneumococcal vaccination above the age of 60, as well as continuing to alert healthcare staff of their steroid dependent status prior to procedures or in light of acute illness [4, 11].

9. Pregnancy and breast feeding

The diagnosis of primary adrenal insufficiency in pregnancy is a rare entity and is a challenge to diagnose due to a degree in overlap in symptomology. The corticotropin stimulation test remains the most appropriate and safe diagnostic tool. A higher minimum post stimulation cortisol is expected during pregnancy and from a small cohort study of healthy pregnant woman levels of 700 nmol/L, 800 nmol/L and 900 nmol/L have been suggested as diagnostic thresholds for the first, second and third trimesters respectively [4]. Timely diagnosis and management of this condition are imperative for reducing maternal/foetal morbidity and mortality.

There is a gradual increase of free cortisol levels during pregnancy with a significant influence of CRH secretion from the placenta peaking in the third trimester (up to 2–3 fold). There is also a notable increase in estrogen driven cortisol binding globulin levels. Therefore an increase in glucocorticoid dosing is expected during pregnancy; with a 20–40% dose increase often necessitated after the 24th week of gestation reflecting the physiological increased cortisol demand in pregnancy [21].

During pregnancy hydrocortisone is the preferable glucocorticoid replacement agent and dexamethasone is best avoided due to its lack of inactivation by 11β-hydroxysteroid dehydrogenase type 2 when traversing the placenta. Reviewing hormone replacement challenging but is best placed by assessing for signs/symptoms of over or under replacement including weight gain/distribution, fatigue, blood pressure and glycaemic control; with recommendation of at least

one endocrine clinical review per trimester from *The Endocrine Society* [4]. Patient education and glucocorticoid self-adjustment in relation to sick days rules remain important in the gestational period and advice should be readily available from endocrine specialist teams.

Plasma renin activity is not a reliable measure in judging suitability of Fludrocortisone dosing due to physiological increments in plasma levels during pregnancy. Therefore assessment should include review for signs/symptoms of over or under replacement including weight gain, salt craving, blood pressure and excessive fluid retention. Progesterone has anti-mineralocorticoid effects therefore fludrocortisone doses often need to be increased in the third trimester [11]. However as hydrocortisone exhibits mineralocorticoid activity, an increased dose of hydrocortisone in the second/third trimesters may negate the need to increase the fludrocortisone dose [21].

A delivery care plan should be made in advance from the endocrinologists for the obstetricians. This should involve the administration of a 100 mg parenteral hydrocortisone bolus prior to the active stage of labour followed by 6 hourly 50 mg boluses or a continuous infusion. Cortisol requirements rapidly reduce post-delivery. Patients can be given doubled dosing of gestational hydrocortisone doses in the initial 24-48 hours post-delivery; with prompt down titration back to pre-pregnancy doses if clinically stable [11, 21].

Studies exploring medicines excretion into breastmilk and subsequent effects on infants are rare. Glucocorticoids are expressed in breast milk in minimal amounts and are unlikely to pose any significant harm to breast feeding infants. Therefore in most cases the benefits of replacement therapy will outweigh any potential risk. Greater caution should be employed in those taking high dose steroid therapy i.e. >160 mg daily hydrocortisone or > 40 mg daily prednisolone. In such cases infants should be monitored more closely for potential signs of adrenal suppression and consideration of delaying breast feeding until a few hours post dose administration to minimize exposure.

10. Dosing in special circumstances

There has been minimal clinical research into the effect of exercise or prolonged traveling on patients with adrenal insufficiency. A small randomized-control cross over trial with pre-exercise hydrocortisone revealed no discernable benefits (in metabolic, hormonal or QoL parameters) in short strenuous exercise compared to placebo [22]. Generally dose increments of hydrocortisone or fludrocortisone is not required in exercise regimens and patients should keep to the principles of warming-up, staying well hydrated and warming-down. However with very intense or prolonged exercise (e.g. marathons) or challenging environmental conditions (e.g. hot weather) increased doses may be warranted at 1.5 to 2 times usual dosing during duration of exercise [23, 24]. Patients are encouraged to take extra hydrocortisone with them (or their alternative glucocorticoid medications) when traveling abroad. On long haul flights greater than 12 hours a doubled dose of hydrocortisone is recommended on the day of the flight. Patients should also carry a letter from their endocrinologist with them to enable them to bring their emergency kit along with them. Severe psychological shock such as bereavement or a road traffic accident may also warrant short term doubling of hydrocortisone dosing.

Studies have confirmed changes in the diurnal cortisol pattern in shift workers [25]. Therefore with night shift workers medications should be taken in line with their current sleep–wake cycle with the first dose taken upon waking irrespective if this is in the evening time.

11. Drug interactions

Drugs such as carbamazepine, phenytoin, topiramate and rifampicin induce the hepatic CYP3A4 enzyme which increases cortisol metabolism; grapefruit juice also has a similar effect. Drugs such as ketoconazole, etomidate, abiraterone acetate and tyrosine kinase inhibitors are known to reduce steroidogenesis and lower cortisol levels. Liquorice ingestion can inhibit the 11β-hydroxysteroid dehydrogenase type 2 enzyme leading to cortisol led over-activation of renal mineralocorticoid receptors causing fluid retention, hypertension, hypokalaemia and metabolic alkalosis [11].

On the contrary antiretroviral drugs such as ritonavir are potent enzyme inhibitors and can commonly cause cushingoid features and adrenal suppression. Patients on any interfering medications may need titration of hormone replacement therapy and closer monitoring under endocrinologist review. Additionally it is important to note that those with combined adrenal insufficiency and hypothyroidism should receive glucocorticoid replacement therapy first as proceeding with thyroxine initially can increase cortisol metabolism and precipitate an adrenal crisis.

12. Future perspectives

Although hydrocortisone generally remains the cornerstone of adrenal insufficiency hormone replacement. There have been advancements in delivery modalities including modified released preparations (Plenadren®, Chronocort®) and continuous subcutaneous hydrocortisone infusions (CSHI) for which further comparative RCTs would be beneficial to further explore any benefits in metabolic and QoL parameters. Subcutaneous 100 mg hydrocortisone has also been shown to have similar pharmacokinetics and increased satisfaction rates in comparison to intramuscular delivery in a randomized crossover study [26] and therefore could be considered for increased adoption in emergencies circumstances.

Previously it was common place to manage Cushing's disease with bilateral adrenalectomy with occasional deployment of adrenocortical tissue autotransplantation. This has shown variability in long term graft survival and degree of cortisol production [27, 28]. This is now no longer common practice with advancements in techniques in localizing and resecting autonomous corticotroph pituitary lesions. Successful allotransplantation has also been described to the level of individual case reports including simultaneous kidney-adrenal and kidney-adrenal-pancreas transplantation [29, 30] and a young girl with a successfully functioning intramuscular adrenal allograft at 3 years follow up [31]. Xenotransplantation has been explored in more recent research with good results in pre-clinical studies with transplanted adrenocortical cells displaying the ability to survive, become vascularized and to supersede the hosts' organ in secreting sufficient cortisol levels [32].

There has been growing interest and understanding in the realms of the extraction and reprogramming of pluripotent stem cells (from human embryonic or somatic origins) towards obtaining adrenocortical resembling cells with steroidogenic properties as observed in several pre-clinical studies. Reprogramming can be achieved through the forced expression of steroidogenic factor 1 (SF1) allowing cells the maintained ability to secrete steroid hormones in response to physiological and pharmacological stimuli once transplanted into murine specimens [3]. Encapsulation devices with biocompatible semi-permeable membranes have shown efficacy in type 1 diabetic undergoing islet cell transplantation in sparing the need for immunosuppression [33] which should pave the way for preventing rejection (without need for immunosuppression) from transplantation of adrenocortical tissue regardless of original source. Further research and collaboration is required to translate these therapies into relevant clinical studies.

There are reports that 15–30% of patients can retain some corticosteroid production even years after diagnosis [11]. Individual studies have reviewed the ability to regenerate adrenal function with B-cell depleting therapy and tetracosactide therapy both in isolation and combined. There is some evidence of partial or full response and is an area which may warrant further research [34–36].

Gene therapy is another area of interest in regards to management of 21-hydroxylase deficiency. With the intravenous injection of an adenoviral-Cyp21a1 vector in murine studies have displayed a return to functioning enzyme production and steroidogenesis but the effects appear to be transient [37–40]. It is yet to be seen whether these pre-clinical findings will translate into sustained and effective treatments in humans but is another area with potential for future considerations.

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Conflict of interest

The authors declare no conflict of interest.

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