Glucocorticoids in pregnancy.

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Abstract
The physiological changes that occur during pregnancy include altered regulation of the Hypothalamo-Pituitary-Adrenal (HPA) axis. The fetoplacental unit plays a major role in this context, together with alteration of circulating Cortisol Binding Globulin (CBG) levels, with a net effect to increase both total and free cortisol levels. Importantly, there are several pathological conditions that require steroid treatment or replacement during pregnancy and optimizing therapy is clearly crucial. The potential for acute and chronic adverse effects that can impact upon both the mother and the fetus makes the decision of how and when to instigate steroid therapy particularly challenging. In this review we describe the physio-pathological changes to the HPA axis that occur during pregnancy, tools to assess endogenous glucocorticoid reserve as well as discuss treatment strategies and the potential for the development of adverse events.

Introduction

Glucocorticoids (GCs) are steroid hormones derived from cholesterol. They are produced by the adrenal cortex in response to stress or illness under the control of the Hypothalamo-Pituitary-Adrenal axis (HPA) and coordinate many functions including inflammatory and immune responses, metabolic homeostasis, cognitive function, reproduction, and development [1].

Cortisol is the principal circulating glucocorticoid secreted in humans. It is produced in relatively high amounts, estimated to be approximately 15 mg/day, and in the circulation, the majority (approximately 90%) is bound to cortisol-binding globulin (CBG). It is only the free, unbound fraction that has bioavailability to enter tissues and cells and modulate their function[2]. The circulating half-life of cortisol varies between 70 and 120 minutes.

GCs play a crucial role during pregnancy and fetal development[3]. They enable implantation, in early pregnancy (between weeks 7 and 14), they are responsible for fetal adrenal development and repression of adrenal androgen synthesis to enable female genital development and having adequate endogenous glucocorticoids reserve is essential during labour.

Fetal GC production is primarily regulated by differential expression of the enzymes required for hormone synthesis rather than the dynamic function of the HPA axis. Expression of these enzymes increases significantly before birth, increasing GC exposure in order to ensure appropriate development of the lungs and other organs[3]. Maternal GCs have the potential to cross the placenta and fetal exposure to excessive levels of GC can impact upon fetal growth[4] as well as potentially program the fetus for life-long diseases such as glucose intolerance, diabetes, hypertension and strokes[5,6]. The physiological mechanisms[2] that prevents fetal exposure to excess maternally derived GCs are reliant upon the expression of the isozymes of enzyme 11β-hydroxysteroid dehydrogenase type (11β-HSD) within the placenta. 11β-HSD enzymes are key molecules involved in the control of the traffic of GCs through the placenta catalysing the inter-conversion of the active GC, cortisol and the inactive GC, cortisone. There are 2 distinct isoforms, 11β-HSD1 and 2 which are different in terms of enzymatic activity, co-factor specificity and tissue expression[7,8]. Both are expressed in the human decidua and placenta and both have been associated with a number of pregnancy-related complications. 11β-HSD1 is widely expressed in key glucocorticoid target organs including adipose tissue, skeletal muscle, liver and brain[6]. It predominantly converts inactive cortisone to active cortisol through its NADPH-dependent reductase activity[9] and thus amplifies local GC concentrations. Dysregulation of 11β-HSD1 activity has been implicated in the pathogenesis of the metabolic syndrome, preeclampsia and hypertensive disorders of pregnancy[1].

11β-HSD2 has only NAD+ dependent dehydrogenase activity[10] and converts active cortisol to inactive cortisone. The main role for 11β-HSD2 is to protect the mineralocorticoid receptor (MR) from activation by GCs; Aldosterone and cortisol have a simialr affinity for, and capability of activating the MR [11]. It has a role in the placenta to protect the fetus from GC excess through inactivation of maternally derived cortisol to inactive cortisone[6] and therefore acts as a major

"barrier" to materno-fetal cortisol transfer[4]. Reduced placental 11β-HSD2 activity has been related to preeclampsia and adverse pregnancy outcome[6].

HPA axis physiology during pregnancy

Pregnancy has a profound physiological impact upon HPA function. By the latter stages of the first trimester, oestrogen drives an increase in CBG. This, together with decreased hepatic clearance of the bound hormone, results in a two- to three-fold increase in total cortisol concentrations which peak during the second and third trimester[11]. In addition, plasma free cortisol and urinary free cortisol (UFC) begin to rise significantly during the final few weeks of the second trimester. At around this time, the placenta functions as a true endocrine organ secreting large amounts of corticotropin-releasing hormone (CRH) into the maternal bloodstream increasing levels such that they are 1000- to 10000-times those seen in non-pregnant women. The progressive rise in CRH during pregnancy stimulates fetal cortisol production promoting fetal organ maturation which is then coupled with the timing of labour[1]. In parallel, it stimulates maternal ACTH release from the pituitary gland, leading to adrenal gland hypertrophy[12] which underpins the increased responsiveness to ACTH that is observed during pregnancy[13]. While GCs inhibit hypothalamic CRH synthesis and secretion, they paradoxically stimulate placental CRH synthesis. Cortisol itself also stimulates placental CRH release resulting in a positive feedback loop which persists until the time of delivery[14]. The net result is a 'resetting' of the HPA axis to a higher level during pregnancy[13] causing a physiological hypercortisolaemic state without features of circulating GC excess. Physiologically, the rise in free cortisol towards the end of the pregnancy is necessary in order to prepare the mother for the metabolic demands of labour and maturation of the foetus. After delivery, the HPA axis 'recovers' from this hyperactivity. Levels of total plasma cortisol and CBG remain elevated for 2-3 months postpartum while UFC and plasma free cortisol return to baseline shortly after labour[11].

The most commonly used test to determine the adequacy of endogenous cortisol reserve is the short synacthen test (SST) that involves measuring a basal cortisol level and a further cortisol measurement 30 minutes after injection (im or iv) of synthetic ACTH. These tests are often avoided in pregnancy, but when they are performed out of clinical necessity, the alteration in HPA axis functionality as well as changes in CBG can make their interpretation challenging. In comparison with non-pregnant individuals, different 30-minute cortisol cut-offs to designate a 'pass' or a 'fail' should be used reflecting the increased total cortisol production across the trimesters of pregnancy. 30-minute total cortisol levels reflecting a pass and indicative of adequate adrenal reserve have been suggested as 700nmol/L (25 μg/dL) for the first trimester, 800nmol/L (29 μg/dL) for the second trimester, and 900nmol/L (32 μg/dL) for the third trimester[15]. Moreover, in the setting of recent-onset HPA axis failure (eg. immediately after trans-sphenoidal surgery for pituitary adenoma, lymphocytic hypophysitis or Sheehan's syndrome) (10.1186/s12902-016-0117-7) SST

may be misleadingly normal with the adrenal glands that are still responding to supraphysiologic amount of ACTH as those used for the test.

Breastfeeding and steroids

There are very few studies that have tried to evaluate the potential impact of steroid treatment and replacement during lactation. *Bae et al.* reported negligible excretion of prednisolone in breast milk and concluded that, even with doses as large as 30mg of prednisolone, the exposure of the suckling infant to prednisolone in the breast milk would be extremely small[16]. *Ost et al.* showed similar results in lactating women receiving variable daily prednisolone doses (10 to 80 mg). Even at the highest doses, it was estimated that the infant would ingest less than 0.1% of the prescribed maternal dose. Accepting that the literature is sparse, it seems reasonable to state that at the physiological replacement doses of GCs that are prescribed in most cases of adrenal insufficiency (AI), there is unlikely be sufficient transfer of GCs to cause significant harm in breast-fed children. However, expert opinion has recommended avoiding breastfeeding within 4h of drug administration when the dose is greater than Prednisolone 20 mg/day[17].

Adrenal Insufficiency during pregnancy

Adrenal insufficiency (AI) is a life-threatening disease resulting from deficient production or action of GCs, with or without concomitant deficiency in mineralocorticoids and adrenal androgens. The commonest symptoms include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, and salt craving. AI is classified as primary, secondary, or tertiary. Primary AI results from adrenal cortex intrinsic disease. In the majority of cases (80–90%) this is caused by autoimmune adrenalitis, and defines classical Addison's disease. Secondary and tertiary types of AI are often collectively named "Central AI" and are caused by impaired production or action of ACTH. Secondary AI is most frequently associated with pituitary disease (most commonly non-functioning pituitary adenomas) that interfere with the synthesis and release of ACTH. Finally, tertiary AI is the term usually used to describe AI associated long-term administration of exogenous GCs. and consequent HPA axis suppression[18].

All patients with AI are at higher risk of morbidity and mortality, some of which is attributable to potentially life-threatening adrenal crises (ACs). These acute events are characterised by hypotension, electrolyte abnormalities, hypoglycaemia, vomiting, abdominal pain and a reduced level of consciousness. They typically occur during periods of physiological stress, such as an

infection, when the physiological needs for cortisol are greater than the amount that is available within the circulation[19].

AI is relatively rare during pregnancy and its prevalence is not well known. Analysing AI from a series of 15,700 deliveries, some authors reported an estimated incidence of 1:3,000 births over a 12-year period (10.3109/00016348909009909). In the literature, the underlying causes for AI during pregnancy are almost equally distributed between primary (44%) and secondary (45%) causes(10.1530/EJE-17-0975). Among the latter, prolonged exogenous glucocorticoid treatment for pre-existing various conditions (such as asthma, rheumatoid arthritis and inflammatory bowel disease or post-transplant) is the most common cause. Aside of oral and parenteral formulations, topical cream can also contain high percentages of potent steroids which, in turn, can cause HPA suppression, maternal cushingoid features and fetal adverse outcomes (10.4314/ahs.v15i4.4). In this context it is extremely important to bear in mind that these woman should be advised of possible adrenal crises if not aware of the GC dosage adjustment in case of stressful situations (a double dose for the period of illness and the requirement of parenteral glucocorticoid in case of vomiting or emergency situations). Patient and partner education regarding self-administration of parenteral hydrocortisone, and the wearing of an alert bracelet or equivalent it is essential in these cases. Other pregnancy-related causes of secondary AI are Sheehan's syndrome (due to postpartum pituitary necrosis) and lymphocytic hypophysitis occurring usually in postpartum setting or in the last trimester(10.1530/EJE-17-0975).

Women with known AI that is appropriately treated can expect to have uneventful pregnancies of normal length without fetal compromise. However, if unrecognized or inadequately treated, AI can lead to maternal and / or fetal morbidity and mortality during gestation, labour or in the immediate post-partum period. The diagnosis of AI during pregnancy is particularly challenging due to its extreme rarity and overlapping with common symptoms (nausea and vomiting, fatigue, hyponatremia) that might be related to pregnancy itself. It is this diagnostic difficulty that potentially contributes to a lack of clinical recognition of AI [20]. Once the diagnosis is suspected, the SST remains the gold standard test to assess the integrity of HPA axis. As described above, different 30-minute cortisol cut-offs indicative of a pass or fail need to be considered depending upon the trimester of pregnancy [15].

With respect to the choice of specific GC for replacement, different steroid formulations can be used in pregnancy including hydrocortisone, cortisone acetate, prednisolone, and prednisone. It should be noted that prednisone and cortisone both require activation by maternal 11β-HSD1 (to form prednisolone and cortisol respectively) in order to generate adequate active circulating GC levels. Dexamethasone is not inactivated by placental 11β-HSD2 and therefore can cross the placenta to gain access to the developing fetus [20] and as a result, its use is not advocated. Adrenal crises can occur during pregnancy if GC replacement is withheld or not adjusted appropriately [21].

There are very few studies that have tried to address the question as to the optimal dosing strategy for pregnant women with AI. In most cases, during the first and second trimester, there is no need to adjust GC replacement dose unless there is evidence of intercurrent illness[22]. In the third trimester, there is variability in the approach between individual clinicians. However, in most situations, GC replacement dose should be increased by approximately 20–40% during the third trimester, consistent with the physiological increase in free cortisol[21]. Emergency steroid cover during the active phase of labor is crucially important for all women with AI. 100mg hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 hour, or both), followed by hydrocortisone 200mg every 24 hours either via continuous intravenous infusion or 50mg every 6 hours is recommended. After delivery, for the first 2 to 4 days a double oral dose should be maintained, provided there are no complications and pre-pregnancy dose can be restored thereafter[23].

Cushing syndrome during Pregnancy

Cushing's syndrome (CS) includes various causes of endogenous overproduction of GCs (ACTH-secreting pituitary adenoma (Cushing's disease), adrenal or neuroendocrine tumor) and is often diagnosed in women of childbearing age. Pregnancy in CS is rare as hypercortisolism and hyperandrogenism suppress gonadotropin secretion leading to irregular menses, amenorrhea and anovulation in many patients with CS. However, although rare, pregnancy in women with CS can occur and the consequences of maternal and fetal exposure to hypercortisolism can be life-threatening[24]. Moreover, management of CS during pregnancy is highly challenging both in terms of diagnosis and therapy.

To date, less than 200 cases of CS during pregnancy have been reported in the literature with adrenal adenoma reported to be the most frequent aetiology in 40–60% of cases[25] (10.1111/1471-0528.14918). Pituitary adenomas represent 15–40% of cases while adrenal carcinomas (ACC) represented less than 10% of cases (10.1530/EJE-17-1058). This contrasts with non-pregnant women where Cushing's disease (due to ACTH-secreting pituitary adenoma) is the predominant cause.

Establishing the diagnosis of CS during pregnancy is difficult because, as with AI, many of the classical features of CS overlap with common features of pregnancy (fatigue, weight gain, hirsutism, acne and emotional instability). Hypertension, hyperglycemia and hypokalemia are also commonly associated with both CS and pregnancy. Although the classic think, purple striae of CS are usually different from the thin white striae that often occur in pregnancy[26], a categorical distinction to facilitate the diagnosis can be difficult. However, symptoms and signs that arise in the first 20 weeks, should raise clinical suspicion: it has been suggested that CS should be excluded in all pregnant women presenting with hypertension, hyperglycaemia, ecchymosis, striae purple and muscle weakness[27]. However, It is important to exclude ACC because of its poor prognosis. ACC

usually presents with advanced disease and several symptoms such as resistant hypertension and proteinuria, without a classical Cushingoid phenotype, could be confused with pre-eclampsia.

Securing a biochemical diagnosis of CS during pregnancy is equalling challenging as the majority of the biochemical characteristics used to diagnose hypercortisolism will be altered during pregnancy. However, during a normal pregnancy, the circadian rhythm of cortisol secretion is usually maintained, but it can be blunted during the third trimester. Moreover, high levels of total cortisol make dexamethasone suppression testing less reliable during pregnancy. One study reported that less than 40% of women without CS during pregnancy had a normal suppression after dexamethasone administration [28]. It can take up 5 weeks to normalize the response to dexamethasone post-delivery.

Urinary free cortisol (UFC) increases about 1.4- to 1.6-fold during the second and third trimester, respectively. Thus, unless levels are more than 3-times higher than the upper limit of normal values, this cannot be considered a reliable marker of CS after the first trimester [29]. However, salivary cortisol may be more helpful, especially during the first and the second trimesters[30].

The placental secretion of ACTH and CRH can lead to a failure of suppression of pituitary ACTH levels in 50% of women with adrenal CS[28]. The utility of other diagnostic tools that are commonly used to establish the diagnosis of CS (CRH, desmopressin and high-dose dexamethasone suppression test) cannot be assessed as they have not been performed in a sufficient number of patients during pregnancy.

Maternal complication of CS during pregnancy include hypertension (68%), diabetes or glucose intolerance (25%), preeclampsia (14%), osteoporosis and fractures (5%), cardiac failure (3%), psychiatric disorders (4%), wound infections (2%) and maternal death (2%). Whilst upregulation of placental 11β-HSD2 can afford a degree of fetal protection, increased fetal morbidities including prematurity (43%), intrauterine growth retardation (21%), stillbirths (6%), spontaneous abortion or intrauterine death (5%) and hypoadrenalism (2%) have all been reported[20].

The management of patients with CS during pregnancy should be based on the treatment of comorbidities, and balancing the risks and benefits of surgery. Medical treatments should be reserved for particular cases or where surgery could be life-threatening. Most patients can be managed conservatively controlling comorbidities without necessarily using specific drugs[20], (especially if CS is discovered late in pregnancy), in some cases, the use of inhibitors of steroidogenesis or centrally acting drugs may be needed[31]. Metyrapone can be used to control hypercortisolism but has the potential for significant adverse effects. It can increase the frequency of preeclampsia due to deoxycorticosterone accumulation [32] and in the foetus can impair adrenal steroid synthesis as it passes through the placental barrier. Ketoconazole has also been used and can control hypercortisolism during pregnancy. It is well tolerated by both the mother and the fetus[25] but has been associated with intrauterine fetal growth retardation and impaired androgen action, although one case report describes the use of ketoconazole in pregnancy resulting in the

birth of a normal male infant without genital abnormalities[33]. Cabergoline is safe and can be useful in the treatment of Cushing's disease[25]. Mitotane is contraindicated due to a risk of teratogenicity[32]. Surgical treatment, either of the pituitary or adrenal, should ideally be performed during the second trimester. Surgeries performed later in pregnancy are characterised by increased risk of preterm birth and intrauterine growth restriction [25,32]. It is fundamentally important to recognise that patients treated surgically are likely to have AI for the rest of the pregnancy, so appropriate GC replacement therapy should be instigated.

Congenital Adrenal Hyperplasia during pregnancy

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive diseases caused by mutations in genes involved in the cortisol biosynthetic pathways. Different hormonal imbalances can occur and CAH can manifest through a range of clinical and biochemical phenotypes with differing degrees of GC, mineralocorticoid and/or sex steroid production defecit[34]. 21-Hydroxylase deficiency is responsible for more than 95% of CAH cases[35] and is characterised by impaired cortisol and aldosterone production together with androgen excess. It is the magnitude of the enzymatic deficit that distinguishes between Classic-CAH (CCAH, less than 2% of activity) and Non-Classic-CAH (NCCAH, more than 50% of activity). The latter is estimated to be one of the most common autosomal recessive disorders. Women with CCAH who are planning to conceive are usually treated with prednisone, prednisolone, or hydrocortisone, all of which are inactivated by placental 11β-HSD2[35]. Women with CAH on GC replacement will require modification of their treatment dose as with other causes of AI and crucially also require stress dose hydrocortisone cover during the active phase of labour and increased oral replacement in the immediate post-partum period (see section above on AI). Women with NCCAH who are infertile or have history of prior miscarriage, a GC treatment with a steroid that does not traverse the placenta is also recommended (10.1210/jc.2018-01865)

In patients with CAH, pre-conception counselling and genetic testing in both the patient and partner are important to help inform about the risk of the possibility of CAH within the developing fetus. Increased exposure of a female fetus to androgen excess drives virilisation resulting in the development of a broad spectrum of genital abnormalities including common urogenital sinus (instead of a separate urethra and vagina), clitoromegaly and fusion of the labioscrotal folds. In this context, prenatal treatment with Dexamethasone that crosses the placenta (and is not inactivated by 11β-HSD2) to access the fetal circulation has been advocated to suppress fetal adrenal androgen excess with the aim of limiting virilisation. Data from 325 pregnancies has suggested that prenatal treatment results in a weighted mean difference of -2.33 on the Prader scale[36]. Unfortunately, the doses of Dexamethasone usually used for this protocol are about 60-times higher than physiological GC requirements for the fetus[37] and 6-times higher than for the mother[38]. The use of prenatal dexamethasone continues to be contentious and should still be regarded only

as experimental[35]. The risk-benefit analysis must consider the need to treat multiple unaffected fetuses[34]. Dexamethasone must be initiated by the 7th week of gestation (ideally at 6th, the presumed date of genital sensitivity to androgens) or 9th week of amenorrhea and continued until birth to ensure its efficacy[39]. Time of initiation is crucial in its efficacy to alter genital morphology. When instigated at an appropriate time, 80–85% cases have normal female genitalia [40]. As a genetic diagnosis of CAH by chorionic villous biopsy cannot be performed until 10 to 12 weeks of gestation, all pregnancies at risk for CAH would need to be treated, and although female foetuses can be identified through analysis of circulating fetal DNA, normal pregnancies will still be treated with pharmacological dose of Dexamethasone [35].

Although no harmful effects have been documented that can clearly be attributed to this treatment, rare adverse events have been reported in children of mothers treated with dexamethasone [41]. A study on 600 CAH-affected pregnancies that were treated with dexamethasone, reported no significant difference in birth weight or length or head circumference when compared to untreated, but affected siblings[42]. However, in a further study, prenatal treatment was associated with modest, but manageable maternal 'cushingoid' features (weight gain, striae, edema, gastro-intestinal disturbance, mood swings, minimal hypertension and gestational diabetes)[36] without major risk to the mother. However, many women reported that they would not repeat prenatal treatment in a future pregnancy[43]. More recently, there is accumulating data suggesting that there may be long-terms risks associated with prenatal treatment with dexamethasone. In particular, there are concerns over potential teratogenicity (e.g. cleft palate(PMID. 11091360, 10.1016/j.rdc.2017.04.013), birth weight, brain development and behaviour and potential long-term impacts on cognitive function. New-borns treated prenatally with dexamethasone weighed, on average 400g less than controls and the association of reduced birth weight with increased risk of chronic disease (including hypertension, type 2 diabetes and cardiovascular disease) in adult life is well-described[35]. Although data are inconclusive, adverse effects upon brain development impacting upon memory, anxiety and gender-role behaviour have been reported[35]. Similarly, some studies have reported an adverse impact upon mental health, quality of life and cognitive function. Finally, a retrospective epidemiological study found that antenatal dexamethasone used to induce late-gestation pulmonary maturation was an in dependent risk factor for development of asthma at 3 to 6 years of age [39].

Taking all the risks and benefits into account, the most recent Endocrine Society guidance has placed a higher priority on preventing unnecessary prenatal exposure of the fetus and mother to dexamethasone and avoiding potential harms associated with this exposure rather than minimizing the emotional toll of atypical external genital development on parents and patients[35].

Antenatal treatment with GCs

Currently, the antenatal administration of GCs to promote fetal survival and lung maturation in

pregnant women at risk of preterm labour is common practice. Whilst the validity and therapeutic benefit of the use of GCs in this context is not in doubt, it does offer an opportunity to evaluate the potential longer-term adverse effects associated with pre-natal GC exposure.

Betamethasone and dexamethasone are frequently used due to their glucocorticoid activity with no mineralocorticoid activity [10.1016/0002-9378(95)90208-2 - 10.1007/s12098-014-1376-9]. There are two main intramuscular recommended regimens of therapy: either four 6mg doses of dexamethasone given 12 apart, or, given the faster impact on lung maturation, two 12mg doses of betamethasone 24h apart [10.1007/s12098-014-1376-9]. The effects of betamethasone can become evident after 24h of treatment, although sometimes maybe delayed until 7 days after the adminstration. Since 1994, the NIH Consensus Conference [3 – PMID 7823388] strongly recommended the antenatal administration of GC between 24 and 34 completed weeks of gestation. This specific timeframe was chosen because the efficacy of antenatal steroid treatment depends upon the expression of steroid receptors within the lung and this is directly related to gestational age. However, more recently, in view of the benefits of steroid administration on cerebral and gastrointestinal systems as well as reducing the incidence of RDS and transient tachypnea of the newborn during Cesarean delivery, steroids use has been extended to below 24 weeks of gestation and prior to an elective delivery between 34 and 36 week, [10.1136/bmj.d1696 - 10.1097/AOG.0b013e31824ea4b2]. There is no literature supporting the use of antenatal steroids for term pregnancies.

A meta-analysis demonstrated an overall reduction of 50% in the incidence and severity of respiratory distress syndrome (RDS) in children antenatally treated with GCs for lung maturation[44,45]. Treatment with antenatal corticosteroids (betamethasone, dexamethasone, or hydrocortisone) was found to be associated with a reduction in the most serious adverse outcomes related to prematurity, including perinatal death, neonatal death, moderate/severe, intraventricular haemorrhage, necrotising enterocolitis, need for mechanical ventilation and systemic infections in the first 48-hours of life, with no increased risk in maternal death[46]. Similarly, aiming to assess the effectiveness and safety of repeated dose of prenatal corticosteroids, *Crowther et al.* demonstrated that repeated doses of GCs reduced the risk of RDS and serious infant outcome[47].

Whilst the clinical benefits of pre-natal GC treatment for this indication are clear, there is the potential to cause some adverse effects. There is evidence to suggest a modest decrease in birth weight[46] and recent studies have highlighted that individuals who had received antenatal betamethasone 30-years earlier, had increased insulin resistance and 7% had elevated basal cortisol levels [48]. Other studies have suggested that infants treated prenatally with GCs, are at an increased risk of severe neurodevelopmental outcomes, altered female offspring body fat composition at 5 years and subfertility in adulthood [6]. Finally, betamethasone therapy with the aim of fetal lung maturation may result in maternal HPA axis suppression for 4-7 days post-dose. (10.1177/1933719108324140, PMID 1244745). This should be addressed when cortisol is

measured because of severe hyponatraemia (frequently as a consequence of preeclampsia) and found to be undetectable. Moreover, there are very few studies in the literature assessing the recovery of HPA axis function in a systematic manner. In the context of suppressive doses of glucocorticoids, the results of the SST can guide clinicians to predict recovery of AI and may guide the frequency of repeat testing and inform as to the likelihood of restoration of HPA axis function (10.1210/jc.2018-00529) .

Conclusions

GCs are essential for the mother and for fetal organ development and growth. Both GC excess and deficiency are associated with adverse outcomes. During pregnancy, the maternal HPA axis undergoes dramatic endocrine changes and activation resulting in increased cortisol levels which are crucial in sustaining fetal development and assisting the mother during delivery. Conditions with inadequate endogenous GC reserve have the potential to put both the mother and baby at significant health risk. Adequate and appropriate replacement therapy is fundamentally important including adjustment across pregnancy, in particular providing adequate GC covering during the active labour and in the immediate post-partum period.

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Table 1. Suggested management of glucocorticoid (GC) treatment in pregnancy.

Disease	Pre-conception	1st trimester	2nd and 3rd trimester	Delivery	Post-partum
Adrenal insufficiency	1. Hydrocortisone 10–12 mg/m^2/day (usually 15–20mg) in 2 or 3 divided oral doses; 2. Cortisone acetate (once daily 25-37.5 mg/day), prednisone or prednisolone (3-5mg/day) can also be used. 3. Avoid dexamethasone as it is not inactivated by 11β-HSD2. * prednisone and cortisone both require activation by maternal 11β-HSD1 (to form active prednisolone and cortisol respectively); * women on other GCs should be switched to hydrocortisone.	Maintain preconception doses. No need to adjust GC replacement dose unless there is evidence of intercurrent illness. Consider parenteral GCs for intractable vomiting.	Adjust according to clinical course, usually a 20–40% increase in the third trimester is needed.	100mg hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 hour, or both), followed by hydrocortisone 200mg every 24h either via continuous intravenous infusion or 50mg every 6h is recommended.	Adjust according to clinical condition or intercurrent illness. For the first 2 to 4 days a double oral dose should be maintained, provided there are no complications and pre-conception dose can be restored thereafter.
Congenital Adrenal Hyperplasia	1. Use prednisone, prednisolone or hydrocortisone, all of which are inactivated by placental 11β-HSD2; 2. Consider steroid treatment in women with NCCAH who are infertile or have history of miscarriage; 3. Pre-conception counselling and genetic testing in both the patients and partners; 4. Avoid dexamethasone treatment.	Maintain preconception doses. No need to adjust GC replacement dose unless there is evidence of intercurrent illness. Consider parenteral GCs for intractable vomiting	Adjust according to clinical course, usually a 20–40% increase in the third trimester is needed.	100mg hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 hour, or both), followed by hydrocortisone 200mg every 24h either via continuous intravenous infusion or 50mg every 6h is recommended.	Adjust according to clinical condition or intercurrent illness. For the first 2 to 4 days a double oral dose should be maintained, provided there are no complications and pre-conception dose can be restored thereafter.
Antenatal treatment for lung maturation			4 x 6 mg doses of dexamethasone given 12 h apart **or** 2 x 12 mg doses of betamethasone 24 h apart. * Consider the possibility of tertiary adrenal insufficiency.	If Adrenal insufficiency has been diagnosed, follow treatment above.	If Adrenal insufficiency has been diagnosed, follow treatment above.
All above	Patient should be advised of possible adrenal crises; GC dose adjustment in case of stressful situations (a double dose for the period of illness and parenteral glucocorticoid in case of vomiting or emergency situations); Patient and partner education regarding self-administration of parenteral hydrocortisone, and the wearing of an alert bracelet or equivalent it is essential in these cases.				