Review Article

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Glucocorticoids in pregnancy

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Abstract

The physiological changes that occur during pregnancy include altered regulation of the hypothalamo-pituitary-adrenal axis. The fetoplacental unit plays a major role in this, together with alteration of circulating cortisol-binding globulin 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 hypothalamo-pituitary-adrenal 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.

Keywords

Glucocorticoids, pregnancy, congenital adrenal hyperplasia, Addison's disease, Cushing's disease, lung maturation, steroids

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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 GC 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 min.

GCs play a crucial role during pregnancy and fetal development.[3] They enable implantation and 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. Adequate endogenous GC reserve is also 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 cerebrovascular disease.[5,6] The physiological mechanisms[2] that prevent fetal exposure to excess maternally-derived GCs are reliant upon the expression of the isozymes of 11β-hydroxysteroid dehydrogenase (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 two 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 GC 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 similar 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]

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Table 1. Suggested management of GC treatment in pregnancy.

Disease	Pre-conception	First trimester	Second and third trimesters	Delivery	Post-partum
Adrenal insufficiency	1. Hydrocortisone 10–12 mg/m^2/day (usually 15–20 mg) in two or three divided oral doses; 2. Cortisone acetate (once daily 25–37.5 mg/day), prednisone or prednisolone (3–5 mg/day) can also be used. 3. Avoid dexamethasone as it is not inactivated by 11β-HSD2. Note: (a) Prednisone and cortisone both require activation by maternal 11β-HSD1 (to form active prednisolone and cortisol respectively); (b) 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. Parenteral GCs if intractable vomiting.	Adjust according to clinical course, often a 20–40% increase in the third trimester is needed.	100 mg of hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 h, or both), followed by hydrocortisone 200 mg every 24 h either via continuous intravenous infusion or 50 mg every 6 h is recommended.	Adjust according to clinical condition or intercurrent illness. For the first two to four days a double oral dose should be maintained, provided there are no complications and preconception 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 women and partners; 4. Dexamethasone treatment should still be regarded as experimental and not routine.	Maintain preconception doses. No need to adjust GC replacement dose unless there is evidence of intercurrent illness. Parenteral GCs if intractable vomiting	Adjust according to clinical course, often a 20–40% increase in the third trimester is needed.	100 mg hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 h, or both), followed by hydrocortisone 200 mg every 24 h either via continuous intravenous infusion or 50 mg every 6 h is recommended.	Adjust according to clinical condition or intercurrent illness. For the first two to four days a double oral dose should be maintained, provided there are no complications and preconception dose can be restored thereafter.
Antenatal treatment for lung maturation			4 × 6 mg IM doses of dexamethasone given 12 h apart or 2 × 12 mg IM doses of betamethasone 24 h apart. Note: IV administration can be considered in anticoagulated women, 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	Women 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); Education for the woman and the partner regarding self-administration of parenteral hydrocortisone, and the wearing of an alert bracelet or equivalent is essential.				

GC: glucocorticoid; 11β-HSD: 11β-hydroxysteroid dehydrogenase; NCCAH: non-classic congenital adrenal hyperplasia.

HPA axis physiology during pregnancy

Pregnancy has a profound physiological impact upon HPA function. By the latter stages of the first trimester, increased oestrogen drives an increase in CBG. Together with decreased hepatic clearance of the bound hormone, this results in a two- to three-fold increase in total cortisol concentrations which peak during the second and third trimesters.[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 10,000 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 adrenocorticotropic hormone (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 fetus. After delivery, the HPA axis 'recovers' from this hyperactivity. Levels of total plasma cortisol and CBG remain elevated for two to three 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 min after intramuscular or intravenous injection 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-min cortisol cut-offs to designate a 'pass' or a 'fail' should be used reflecting the increased total cortisol production across the trimesters of pregnancy. Total cortisol levels at 30 min, reflecting a pass and indicative of adequate adrenal reserve have been suggested as 700 nmol/L (25 μg/dL) for the first trimester, 800 nmol/L (29 μg/dL) for the second trimester and 900 nmol/L (32 μg/dL) for the third trimester.[15] Moreover, in the setting of recent-onset HPA axis failure (e.g. immediately after trans-sphenoidal surgery for pituitary adenoma, lymphocytic hypophysitis or Sheehan's syndrome),[16] 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 evaluated 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 30 mg of prednisolone, the exposure of the suckling infant to prednisolone in the breast milk would be extremely small.[17] 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. Whilst historical advice had been to avoid breast feeding within 4h of high dose steroid administration (18), there is currently little evidence to support this and current guidance dose not recommend any change in breast feeding behaviour in those women taking glucocorticoid therapy.[18,19]

Adrenal insufficiency during pregnancy

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 interferes 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.[20]

All women 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.[21]

AI is relatively rare during pregnancy and its prevalence is not well known. Analysing AI from a series of 15,700 deliveries over a 12-year period, an estimated incidence of 1:3000 births has been estimated.[22] In the literature, the underlying causes for AI during pregnancy are almost equally distributed between primary (44%) and secondary (45%) causes.[23] Among the latter, prolonged exogenous GC 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, high dose inhaled and parenteral formulations, topical cream (e.g. those used for the skin-lightening particularly in African women[24,25]) can also contain high percentages of potent steroids which, in turn, can cause HPA suppression, maternal 'Cushingoid' features and fetal adverse outcomes.[26] In this context, it is extremely important to bear in mind that these women should be advised of possible ACs 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 GC in case of vomiting or emergency situations). Education for the woman and the partner regarding self-administration of parenteral hydrocortisone, and the wearing of an alert bracelet or equivalent is essential in these cases. Other pregnancy-related causes of secondary AI are Sheehan's syndrome (due to post-partum pituitary necrosis) and lymphocytic hypophysitis occurring usually in postpartum setting or in the last trimester.[23]

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.[27] Once the diagnosis is suspected, the SST remains the gold standard test to assess the integrity of HPA axis. As described above, different 30-min 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. A summary of the current approach to the management of pregnant women taking glucocorticoid therapy is provided in Table 1. 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,[27] and as a result, its use is not advocated. ACs can occur during pregnancy if GC replacement is withheld or not adjusted appropriately.[28]

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.[29] 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.[28] Emergency steroid cover during the active phase of labour is crucially important for all women with AI. One-hundred milligrams of hydrocortisone intramuscularly (or intravenously) at the onset of active labour (cervix dilation >4 cm or contractions every 5 min for 1 h, or both), followed by hydrocortisone 200 mg every 24 h either via continuous intravenous infusion or 50 mg every 6 h is recommended. After delivery, for the first two to four days, a double oral dose should be maintained, provided there are no complications and pre-pregnancy dose can be restored thereafter.[30] A specific note should be made about betamethasone therapy for fetal lung maturation (see below) which may result in maternal HPA axis suppression for four to seven days post-dose.[31,32] 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 GCs, 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.[33]

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 tumour) 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 women 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.[34] 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[35,36] followed by pituitary adenomas, which represent 15–40% of cases. Although some series describe adrenal carcinomas (ACC) as responsible for CS in less than 10% of cases during pregnancy,[35] new evidence suggested a higher percentage (13%) of prevalence.[37] This contrasts with non-pregnant women where Cushing's disease (due to ACTH-secreting pituitary adenoma) is the predominant cause and ACC is involved only in 8% of cases.

Finally, although described only in few case reports, CS during pregnancy can be also caused by primary bilateral macronodular adrenal hyperplasia, in which luteinizing hormone/human choriogonadotropin (hCG) receptors have been shown to be aberrantly expressed in the adrenal cortex and to induce adrenal steroid synthesis, cellular proliferation and/or adrenal hyperplasia under hCG stimulation.[38]

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, hyperglycaemia and hypokalemia are also commonly associated with both CS and pregnancy. Although the classic thin, purple striae of CS are usually different from the thin white striae that often occur in pregnancy,[39] 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, purple striae and muscle weakness.[40] 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 and thus may mimic pre-eclampsia.

Securing a biochemical diagnosis of CS during pregnancy is equally 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 healthy women during pregnancy had normal suppression after dexamethasone administration.[41] It can take up five weeks to normalize the response to dexamethasone post-delivery.

UFC increases about 1.4- to 1.6-fold during the second and third trimester, respectively. Thus, unless levels are more than three times higher than the upper limit of normal values, this cannot be considered a reliable marker of CS after the first trimester.[42] However, late night salivary cortisol may be more helpful, especially during the first and the second trimesters.[43]

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.[41] 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 women during pregnancy.

Maternal complication of CS during pregnancy include hypertension (68%), gestational diabetes mellitus (25%), preeclampsia (14%), osteoporosis and fractures (5%), cardiac failure (3%), psychiatric disorders (4%), wound infections (2%) and maternal death (2%). While upregulation of placental 11β-HSD2 can afford a degree of fetal protection, increased fetal morbidities including prematurity (43%), intrauterine growth restriction (21%), stillbirths (6%), miscarriage or intrauterine death (5%) and hypoadrenalism (2%) have all been reported.[27]

The management of women 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. In most cases, CS during pregnancy can be managed conservatively controlling comorbidities without necessarily using specific drugs[27] (especially if CS is discovered late in pregnancy), but in some cases, the use of inhibitors of steroidogenesis or centrally–acting drugs may be needed.[44] 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[45] and in the fetus 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[35] but has been associated with intrauterine fetal growth restriction 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.[46] Cabergoline is safe and can be useful in the treatment of Cushing's disease.[35] Mitotane is contraindicated due to a risk of teratogenicity.[45] 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.[35,45] It is fundamentally important to recognise that women 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 deficit.[47] 21-Hydroxylase deficiency is responsible for more than 95% of CAH cases[48] 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.[48] 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). In women with NCCAH who are infertile or have history of prior miscarriage, GC treatment with a steroid that does not cross the placenta is recommended (see Table 1).[48]

In women with CAH, pre-conception counselling and genetic testing of both the woman and the 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 have suggested that prenatal treatment results in a weighted mean difference of –2.33 on the Prader scale.[49] Unfortunately, the doses of dexamethasone usually used for this protocol are about 60 times higher than physiological GC requirements for the fetus[50] and 6 times higher than for the mother.[51] The use of prenatal dexamethasone continues to be contentious and should still be regarded only as experimental.[48] The risk-benefit analysis must consider the need to treat multiple unaffected fetuses.[47] Dexamethasone must be initiated by the seventh week of gestation (ideally at sixth, the presumed date of genital sensitivity to androgens) or nine weeks after the last menstrual period and continued until birth to ensure its efficacy.[52] 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.[53] 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 fetuses can be identified through analysis of circulating fetal DNA, normal pregnancies will still be treated with pharmacological dose of dexamethasone.[48]

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.[54] 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.[55] However, in a further study, prenatal treatment was associated with modest, but manageable maternal 'cushingoid' features (weight gain, striae, oedema, gastro-intestinal disturbance, mood swings, minimal hypertension and gestational diabetes)[49] without major risk to the mother. However, many women reported that they would not repeat prenatal treatment in a future pregnancy.[56] More recently, there is accumulating data suggesting that there may be long-term risks associated with prenatal treatment with dexamethasone. In particular, there are concerns over potential teratogenicity (with some weak evidence showing increased prevalence of cleft palate[57–60] although not confirmed in all the study series[61]), birth weight, brain development and behaviour and potential long-term impacts on cognitive function. Newborns treated prenatally with dexamethasone weighed, on average 400 g 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.[48] Although data are inconclusive, adverse effects upon brain development impacting upon memory, anxiety and gender-role behaviour have been reported.[48] 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 independent risk factor for development of asthma at three to six years of age.[52]

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 (on parents but also in the future for the women) caused by the development of atypical external genital in the foetus.[48]

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. While the validity and therapeutic benefit of the use of GCs in this context are not in doubt, this therapy 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 GC activity with no mineralocorticoid activity and for the greater affinity of these fluorinated steroids in crossing the placenta compared to the non-fluorinated.[62,63] There are two main intramuscular

recommended regimens of therapy (see Table 1): either four 6 mg doses of dexamethasone given 12 h apart, or, given the faster impact on lung maturation, two 12 mg doses of betamethasone 24 h apart.[63] The effects of betamethasone can become evident after 24 h of treatment, although sometimes may be delayed until seven days after the administration. The gestational age range at which antenatal corticosteroids should be considered has been a reason for debate for long time. Previous reviews showed unclear benefit at gestations less than 26 weeks and beyond 36 weeks.[64] Since 1994, the NIH Consensus Conference[62] 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. Recently, Gyamfi-Bannerman et al. demonstrated a clinical benefit in terms of a primary outcome of neonatal requirement for respiratory support in the first 72 h of life in 2831 women from 34 weeks until 36 weeks + 5 days. However, this was associated with increased neonatal hypoglycaemia for which the long-term effects still remain unknown.[65] Thus, the use of antenatal corticosteroids must consider the balance of risks and benefits in late preterm pregnant women (from 35 weeks + 0 days).[66] 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.[63,67] 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 h of life, with no increased risk in maternal death.[66] 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.[68]

While the clinical benefits of prenatal 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,[66] 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.[69] Finally, 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 five years and subfertility in adulthood.[6]

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 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 the baby at significant health risk. Adequate and appropriate replacement therapy is fundamentally important including adjustment across pregnancy, in particular providing adequate GC cover during active labour and the immediate post-partum period.

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Informed consent

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Guarantor

JWT is the guarantor of the present work.

Contributorship

Both RP and JWT contributed to the literature review, construction, writing and editing of the article.

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