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Review

Maternal, fetal, and neonatal outcomes associated with long-term use of corticosteroids during pregnancy

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Key content

- Antenatal corticosteroid use is strongly associated with reduced neonatal mortality and morbidity arising from preterm delivery.
- Betamethasone and dexamethasone are the corticosteroids of choice to enhance fetal lung maturation in this situation.
- Maternal medical conditions such as autoimmune diseases, asthma and allergies may necessitate long-term use of corticosteroids during pregnancy.
- The maternal, fetal and neonatal effects in pregnant women using chronic corticosteroids are reviewed. The question as to whether the standard course of antenatal corticosteroids is necessary if preterm delivery is anticipated is discussed.

Learning objectives

- To review the production of endogenous corticosteroids in pregnancy.
- To be aware of the effect of chronic corticosteroid use on fetal lung maturity during pregnancy.
- To appreciate the maternal, fetal and neonatal effects of exogenous corticosteroid use in pregnancy.

Ethical issues

- Is the fluorinated antenatal corticosteroids course given for preterm delivery indicated in women using corticosteroids on a chronic basis?
- What are the fetal and neonatal outcomes of chronic corticosteroid use by the pregnant woman?
- How should women taking chronic corticosteroids be managed?

Keywords: corticosteroids / fetal lung maturity / pregnancy

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Introduction

Corticosteroids are potent anti-inflammatory and immunosuppressive medications that are frequently used during pregnancy for a variety of fetal and maternal indications. Pregnant women who are at risk of preterm delivery routinely receive corticosteroids at a late stage of gestation to stimulate fetal lung maturation and reduce neonatal complications associated with preterm delivery. Furthermore, maternal medical conditions including autoimmune diseases, allergies, asthma and dermatological conditions may necessitate the use of corticosteroids throughout pregnancy.[1–4]

It is unclear whether chronic maternal use of corticosteroids substitutes the need for antenatal corticosteroids when the pregnant woman is at risk of preterm delivery. Additionally, the effect of chronic maternal use of corticosteroids on the course of pregnancy and fetal and neonatal outcomes is not well evaluated. This work aims to review the impact of chronic maternal corticosteroid use on the pregnant woman, the fetus and the neonate. The production of endogenous corticosteroids, the pharmacological properties of exogenous corticosteroids in relation to fetal exposure and the clinical aspects of managing the pregnancy for women using corticosteroids on a chronic basis will be discussed.

Endogenous corticosteroid production in pregnancy

Glucocorticoids are hormones involved in successful implantation of the embryo and appropriate growth and development of the fetus and placenta.

During periods of stress, the hypothalamic–pituitary–adrenal (HPA) axis acts as a mediator of the glucocorticoid response. Stress also causes release of corticotrophin-releasing hormone (CRH), which in turn increases the levels of adrenocorticotrophin hormone (ACTH) in the body.[5] ACTH then stimulates the adrenal cortex to release cortisol into the blood. There is a negative feedback relationship between cortisol and glucocorticoid and mineralocorticoid receptors, which are present in the pituitary gland and hypothalamus.[6]

The maternal HPA undergoes phenomenal regulatory changes during pregnancy. One such change is a three-fold rise in cortisol levels compared with non-pregnant periods.[6] This is important in the development and maturation of fetal organs. Cortisol levels are at their highest during the third trimester, when CRH is downregulated, corresponding to maximal fetal organ maturation.[7]

The mechanisms that cause this increase in cortisol levels are:

1. estrogen stimulation of corticosteroid binding globulin
2. placental secretion of large amounts of CRH, which, in turn, stimulates the maternal pituitary gland, thus elevating levels of ACTH and cortisol.

In response to the above mechanisms, maternal cortisol increases the placental synthesis of CRH, and a positive feed-forward drive is initiated.[6,7] This further increases cortisol levels.

Despite these changes, the diurnal secretion of cortisol remains unchanged throughout pregnancy. However, as pregnancy progresses into the later trimesters, the response of the HPA axis to physical and mental stress is increased.[7,8]

The fetus is protected by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 enzyme (11β-HSD2), which is able to metabolise substantial amounts of cortisol. This placental barrier is functional throughout pregnancy, but factors such as maternal anxiety, infection and inflammation may compromise this protective mechanism.[8]

When maternal plasma cortisol levels fall during the postpartum period, the function of HPA slowly returns to its non-pregnant state.[9] After delivery of the placenta in the third stage of labour, levels of CRH fall sharply, returning to normal by 12 weeks postpartum.[9,10] ACTH levels also temporarily fall after delivery, rising at 3–4 days postpartum. On the other hand, the levels of cortisol remain normal in the postnatal period owing to an increase in corticosteroid-binding globulin levels and the adrenal gland hypertrophy that occurs in pregnancy.[10]

Exogenous corticosteroids

There are certain structural differences that exist between exogenous corticosteroids and their endogenous equivalents. Introduction of a double bond at the first and second carbon position of endogenous corticosteroids such as cortisone and hydrocortisone has produced prednisone and prednisolone. Similarly, structural modifications among exogenous corticosteroids, particularly prednisolone, have led to the production of more potent corticosteroids such as dexamethasone and betamethasone, which increase glucocorticoid activity and reduce mineralocorticoid activity. In obstetric practice, prednisolone, dexamethasone and betamethasone are the most commonly reviewed synthetic corticosteroids.[1,2]

Fetal exposure to exogenous corticosteroids

Exogenous corticosteroids have different pharmacokinetic and pharmacodynamic properties (Table 1). These differences are of clinical significance to determine their fetal exposure and placental transfer. In the mother, the drug properties of absorption, distribution, metabolism and elimination, and the protein binding control fetal exposure, whereas in the fetoplacental unit, these properties affect the

Table 1. Pharmacological properties of exogenous corticosteroids[11–16]

	Plasma half-life (minutes)	Biological half-life (hours)	Glucocorticoid (anti-inflammatory) potency	Mineralocorticoid potency	Placental transfer (%)	Maternal: fetal ratio
Cortisol (hydrocortisone)	90	Short-acting (8–12)	1	1	15	6.7:1
Cortisone	30	Short-acting (8–12)	0.8	0.8	-	-
Prednisone	60	Intermediate-acting (12–36)	4 ضعيف	0.8	100	1:1
Prednisolone	200	Intermediate-acting (12–36)	4	0.8	10–12.5	8–10:1
Methylprednisolone	180	Intermediate-acting (12–36)	5	0.5	44	2.24:1
Dexamethasone	200–300	Long-acting (36–54)	20–30	0	50	2:1
Betamethasone	300+	Long-acting (36–54)	20–30	0	33	3:1

amount of drug that can cross the placenta, as well as metabolism, distribution and elimination of the drug in the fetoplacental unit.[1]

Pharmacological properties of exogenous corticosteroids

The plasma half-life refers to the time required for the initial concentration of a drug in the body to be reduced by half. Plasma half-life varies with the formulation used; the plasma half-life of betamethasone, for example, ranges between 6.5 and 9 hours. Dexamethasone has an average plasma half-life of 4 hours following oral administration and 4.6 hours following parenteral administration of dexamethasone sodium phosphate, while the half-life of prednisolone is approximately 3 hours following oral or intravenous administration.

Biological half-life represents the duration of influence on the target tissue, which is longer than the plasma half-life. Betamethasone and dexamethasone are long-acting corticosteroids with biological half-lives ranging between 36 and 54 hours, while prednisolone is a medium-acting corticosteroid with a biological half-life of 12–36 hours.[1,11–16]

The degree and selectivity of protein binding by corticosteroids affect its biological activity. Only the non-protein-bound fraction is biologically active. Plasma binding of synthetic betamethasone and dexamethasone is 60% and 75%, respectively, which is constant across a wide concentration range. Whether protein binding varies between different preparations of synthetic corticosteroids is unknown.[1,11]

Other properties of exogenous corticosteroids that can affect fetal exposure are the potency and the pro-drug formulation. Potency refers to the degree of drug activity in the biological system, which is determined by its affinity to its receptor, as well as its efficacy. On the other hand, exogenous corticosteroid pro-drug formulation affects its pharmacokinetic characteristics. For example, betamethasone is available in two formulations: a slow-release, dual-acting suspension containing both phosphate and acetate ester, and a fast-releasing phosphate ester. The dual betamethasone suspension has a longer half-life compared with the fast-releasing betamethasone phosphate, which has higher peak concentrations.[1,11–16]

Pharmacokinetic properties during pregnancy

Absorption, distribution, metabolism and elimination of drugs may be altered during pregnancy because of the physiological changes that occur during this period. Most previous studies have assessed the pharmacokinetic properties of exogenous corticosteroids in non-pregnant women, therefore their findings may not be transferable to pregnant women.[1,17,18]

The clearance and volume of distribution of betamethasone were found to be higher in pregnant women than non-pregnant women, while the half-life remained unchanged. The increased clearance of betamethasone can be caused by increased metabolism by the placental enzymes.[19] On the other hand, it has been shown that betamethasone has a shorter half-life in women carrying twins compared with women with singleton pregnancies.[20]

Maternal plasma volume expansion leads to decreased albumin serum concentrations with gestation. Consequently, protein-binding capacity reduces, despite elevated maternal albumin synthesis. For synthetic corticosteroids such as betamethasone and dexamethasone, which bind to albumin specifically, the unbound, biologically active proportion subsequently increases. As only the unbound fractions pass through the placenta, greater amounts reach the fetus as the pregnancy proceeds. In contrast, the fetal concentration of albumin increases to be equal to or even higher than concentrations of maternal albumin at term. Accordingly, the amount of corticosteroid bound to fetal albumin increases, making it less biologically active.[1,17,21–24]

There is a scarcity of high-quality data regarding the pharmacokinetic properties of antenatal corticosteroids in women with plural pregnancies or pregnant women who are obese. It has been suggested that the maternal and umbilical cord blood serum concentrations of betamethasone are similar in obese women and in those with twin gestations.[25,26]

The pharmacokinetics of exogenous corticosteroids in pregnancy remains largely unknown and the implications of these pharmacokinetic properties on the mother and fetus are yet to be established.

Fetoplacental transfer

The properties of the drug, placental characteristics and other maternal and fetal-related factors affect the permeability of drugs through the fetoplacental unit.[27,28]

Placental 11β-HSD2 is a potent barrier that controls the passage of maternal glucocorticoids. It catalyses the rapid conversion of bioactive glucocorticoids to their inactive metabolites (cortisol and corticosterone to cortisone and 11-dehydrocorticosterone, respectively). However, this barrier is incomplete, and some maternal corticosteroids are able to cross the placenta to the fetus intact.[29,30] The metabolism profile of 11β-HSD2 and its transplacental passage differ considerably between endogenous and synthetic glucocorticoids. These also differ between the different pharmaceutical preparations of synthetic glucocorticoids based on their chemical structures, so they have different fetal/maternal serum concentrations.[1,31]

Earlier work has assessed the in vitro 11β-HSD2 metabolism profile for corticosteroids. Around 67% of cortisol and 51% of prednisolone were converted to

inactive 11-keto metabolites in the placental tissue, whereas this was true for only 1.8% of dexamethasone and 7.1% of betamethasone.[10]

As poor substrates for 11β-HSD2, dexamethasone and betamethasone readily pass the placenta, while prednisolone is rapidly converted to inert prednisone by 11β-HSD2. The fetal plasma concentration of betamethasone is three-fold lower than the maternal plasma concentration,[32,33] while the fetal plasma concentration of dexamethasone is 0.3–0.5 times that found in maternal plasma.[34–37] Prednisolone concentration in the fetus is 8–10 times lower than maternal concentrations,[38] whereas 44% of methylprednisolone received by the mother is transferred to the fetus.[39] Around 15% of hydrocortisone crosses the placenta unmetabolised (Table 1).[40]

Placental saturation

Placental enzyme saturation has been suggested, where the conversion capacity of 11β-HSD2 decreases with increasing corticosteroid concentrations.[41,42] Maternal use of high doses of corticosteroids, or corticosteroid use for a prolonged period of time, may result in greater amounts of corticosteroids crossing the placental barrier, thus increasing fetal exposure;[37,43] however, further details are needed to describe placental saturation and its precise implications.

Use of corticosteroids for fetal lung maturity

The United Nations Commission has identified antenatal corticosteroids as one of the top 13 life-saving commodities used across the reproductive, maternal, newborn and child health continuum.[44] Antenatal corticosteroids enhance fetal lung maturation and prevent respiratory distress syndrome (RDS) in preterm deliveries, which is a major cause of neonatal morbidity and mortality.[45]

Preterm fetal exposure to antenatal corticosteroids enhances tissue and alveolar surfactant production, increases lung compliance and its fluid clearance, improves parenchymal structure maturation and reduces vascular permeability. Consequently, antenatal corticosteroids reduce complications of immature lung structure and function associated with preterm delivery.[45]

A systematic review of 21 studies representing 4269 infants assessed the effect of antenatal corticosteroids on fetal and neonatal morbidity and mortality in women at risk of preterm delivery. Antenatal corticosteroids were associated with a reduction in respiratory distress syndrome (risk ratio [RR] 0.66; 95% confidence interval [CI] 0.59–0.73). Other complications associated with preterm delivery, such as neonatal death, cerebroventricular haemorrhage, respiratory support, necrotising enterocolitis and intensive care admissions, were also reduced in association with administration of antenatal corticosteroids.[46]

Extensive evidence of the improved neonatal outcomes associated with administration of antenatal corticosteroids led the Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) to recommend a single course of betamethasone, given intramuscularly in two 12-mg doses, 24 hours apart, or four intramuscular, 6-mg doses of dexamethasone every 12 hours for women at risk of preterm delivery.[47,48]

Other dosing regimens have been evaluated. For example, the RCOG guideline advocates the reasonable use of any dosing regimen of betamethasone and dexamethasone, as long as 24 mg of either drug is given within a 24–48 hour period, while the recent ACOG guideline suggests there are no additional benefits for courses with shorter dosage intervals, even when delivery appears imminent.[47,48]

The fluorinated synthetic corticosteroids betamethasone and dexamethasone have more potent glucocorticoid activity than cortisol by 20–30 fold. They are poor substrates for placental metabolism by 11β-HSD2 and have insignificant mineralocorticoid action, which make them perfect candidates for the management of women at risk of preterm delivery compared with other corticosteroids.[31] Limited information is available about alternatives to enhancing fetal lung maturity in women at risk of preterm labor. Hydrocortisone can be an alternative when betamethasone and dexamethasone are not available.[49]

The effectiveness of antenatal corticosteroids appears to diminish over time. Repeat doses provide the short-term benefits of less respiratory distress and fewer health problems. Uncertainties about the safety of this practice have been raised because of concerns about the risk of decreased neonate length, weight and head circumference at birth associated with repeated doses. Accordingly, the use of a single repeat course of antenatal corticosteroids has been suggested for selective patients, while regularly scheduled repeat courses or serial courses (more than two courses) are not currently recommended for routine practice.[45,48,50,51]

Impact of maternal chronic use of corticosteroids on fetal lung maturity

The use of fluorinated corticosteroids before preterm birth to prevent neonatal morbidity is an established part of obstetric practice. However, debate arises when the pregnant woman receiving long-term corticosteroids for her comorbidities becomes at risk for preterm delivery: shall additional fluorinated corticosteroids be given, or is the long-term use of corticosteroids sufficient to induce fetal lung maturity?

All corticosteroids cross the placenta to the fetal circulation to some degree (Table 1). According to Uptodate®, "in women incidentally receiving high-dose hydrocortisone for treatment of a medical disorder, a standard course of betamethasone or dexamethasone, when indicated for fetal lung maturation, is recommended."[52]

An alternative opinion, based on observations, is that the fetuses of mothers receiving high doses of corticosteroids may undergo adrenal suppression associated with transplacental passage. Additional doses of fluorinated corticosteroids could theoretically potentiate adrenal suppression. Moreover, concerns have been raised about long-term neurological sequelae with repeated doses of fluorinated corticosteroids.[53]

It is unlikely that any fetal benefit from chronic maternal use of corticosteroids is comparable to that from a targeted course of antenatal fluorinated corticosteroid therapy in pregnancies complicated by imminent delivery at 24–34 weeks of gestation. Withholding antenatal fluorinated corticosteroid therapy, however, leaves the fetus at increased risk for neonatal morbidity and mortality. Thus, it would seem reasonable to give a course of antenatal fluorinated corticosteroid therapy in this circumstance, regardless of the mother's chronic non-fluorinated corticosteroid therapy history.

Maternal exposure to exogenous corticosteroids

Teratogenesis

Human studies: conflicting

Animal studies have indicated an increased prevalence of cleft palate in rats, mice and rabbits exposed to corticosteroids. However, human data are more difficult to interpret because the index maternal condition being treated and other medications are confounding factors, as is the patient's ethnic origin.

A meta-analysis of four case–control studies demonstrated an increased risk of oral clefts with first-trimester corticosteroids (odds ratio [OR] 3.35; 95% CI 1.97–5.69). Similarly, a meta-analysis of five cohort studies showed an increase in major abnormalities in corticosteroid-exposed pregnancies, (OR 3.03; 95% CI 1.08–8.54); however, the pooled OR was 1.45 (95% CI 0.80–2.60) when the analysis included one more study in which major and minor malformations were not separated.[54] On the other hand, analysis of data from the Danish Birth Registry, which included 51 973 first-trimester corticosteroid-exposed pregnancies, did not find an increased risk of orofacial clefts.[55]

As the birth prevalence of isolated cleft lip with or without cleft palate is in the order of 0.77 per 1000 births, the increase attributable to administration of corticosteroids (if this is confirmed) takes the prevalence to approximately 1 in 400–500 births.[56]

A review of seven studies on topical corticosteroids found no significant associations between congenital abnormality and corticosteroid use.[57] Similarly, inhaled and intranasal corticosteroids were not found to be associated with congenital abnormalities.[58]

Preterm delivery

Causative effect not proven yet

The use of inhaled corticosteroids during pregnancy does not appear to affect the rate of preterm deliveries.[58] The use of systemic corticosteroids during pregnancy has been linked with increased preterm births; however, it is difficult to confirm whether this is related to the corticosteroids per se, or the original maternal condition that the corticosteroids were prescribed for. On reviewing this subject, the UK Teratology Information Service concluded that there may be an association between chronic corticosteroid use and preterm birth, but a causative effect is not proven.[59]

Fetal growth restriction

The UK Teratology Information Service review concludes that there is no robust evidence to suggest that corticosteroid use during pregnancy is associated with impaired fetal growth; nevertheless, an association cannot be ruled out.[59]

A dose-dependent relationship has been suggested between cumulative antenatal corticosteroid exposure and reduced fetal growth. A lower total treatment burden (i.e. one or two courses) results in fewer cases of fetal growth restriction than greater cumulative exposure (i.e. four or more courses).[50,60–62] Reduced fetal size that is associated with multiple courses of corticosteroids does not result in reduced size in infancy.[62] Furthermore, there is no evidence of associated paediatric cardiometabolic disease, such as diabetes or cardiovascular disease,[63] as might be expected from conditions with fetal growth reduction.

On the other hand, Vesce et al. prospectively studied 160 women who received 0.5 mg of betamethasone daily throughout pregnancy and a control group of 160 women who did not receive this treatment. In the betamethasone group, the drug was given for treatment of recurrent abortion. After excluding pregnancies with maternal diseases that could affect fetal growth, no difference was found in the birth weights of babies born to women between the two groups.[64]

Gestational diabetes

In many settings, all pregnant women are screened for gestational diabetes; however, in the UK, the National Health Service operates a risk factor assessment. The guidelines for indication of a screening glucose tolerance test (GTT) do not list chronic maternal treatment with corticosteroids as a risk factor for the development of gestational diabetes.[65] Chronic corticosteroid use in pregnancy has been associated with an increased risk of gestational diabetes of 5–10 fold.[66,67] Thus, it would seem prudent to offer GTT for corticosteroid-treated pregnant women if universal screening is not adopted.

Peripartum management for women using corticosteroids on a chronic basis

For women with adrenocortical failure, such as those with Addison's disease, a peripartum 'stress dose' of corticosteroids

is essential to prevent vascular collapse. This applies to both labour and caesarean section.[68] The situation for women who are chronically treated with corticosteroids is less clear; there may be associated adrenocortical suppression with an inability to generate endogenous stress responses. Authorities are divided on whether or not a stress dose is required. It has been suggested that the daily doses of corticosteroids these women receive is sufficient to cover the perioperative period,[69] but others suggest that the need for perioperative glucocorticoids should be determined based on the preoperative dose and duration of glucocorticoid, as well as the nature and duration of surgery.[70]

Postpartum relapse of maternal disease may occur because of a rapid decrease in endogenous corticosteroids levels after placental delivery, and this can take up to 3 months to compensate. If disease relapse is thought likely, it is suggested to increase exogenous corticosteroids around the time of delivery, with a subsequent slow withdrawal of the additional dose. The slow withdrawal period has been described in non-pregnant patients as a method of reducing disease reactivation.[71]

Box 1. Learning points regarding systemic chronic corticosteroid use during pregnancy

- All corticosteroids cross the placenta; notably, fluorinated corticosteroids such as betamethasone and dexamethasone cross more readily
- There is conflicting evidence of teratogenesis; however, concerns exist regarding an increased prevalence of orofacial clefts
- Fetal growth restriction might be associated with high doses
- Concomitant use of mifepristone should be avoided
- Screening for gestational diabetes should be offered
- Hydrocortisone stress doses for peripartum management should be individualised
- There are no adverse effects reported in breastfed infants
- There is no evidence to withhold additional antenatal corticosteroids because of a mother's chronic use of corticosteroids
- Given concerns for alterations in the hypothalamic–pituitary–adrenal axis, routine neonatal and/or paediatric evaluation is advised

The safety of corticosteroids when breastfeeding

No adverse effects of maternal corticosteroid use during lactation have been reported in breastfed infants; however, it is sensible to reduce infant exposure as much as possible. With this in mind, the use of prednisolone instead of prednisone and avoiding breastfeeding for 4 hours after a dose – theoretically – should decrease the dose received by the infant. Additionally, it is recommended to avoid breastfeeding for 2–4 hours after a 1-g infusion of methylprednisolone. Since betamethasone is not well studied, it is best to avoid it in favour of a shorter-acting and better-studied alternative because of its potency and low protein-binding ability, which would favour its passage into breastmilk. Other corticosteroids such as hydrocortisone, cortisone and dexamethasone are not well studied.[72]

Interaction between corticosteroids and obstetric medications

There are few drug interactions between corticosteroids and medications used in obstetrics. The combined use of mifepristone and corticosteroids is considered contraindicated when corticosteroid treatment is required for long-term management of serious conditions and illnesses, such as immunosuppression following transplantation. Estrogen derivatives may increase the serum concentration of systemic corticosteroids. Monitoring for increased therapeutic or toxic effects of systemic corticosteroids is suggested if an estrogen derivative, such as the combined oral contraceptive pill, is initiated or the dose is increased. Likewise, monitoring for decreased effects is suggested if an estrogen derivative is discontinued or the dose is decreased; however, this interaction is moderate in severity.[73]

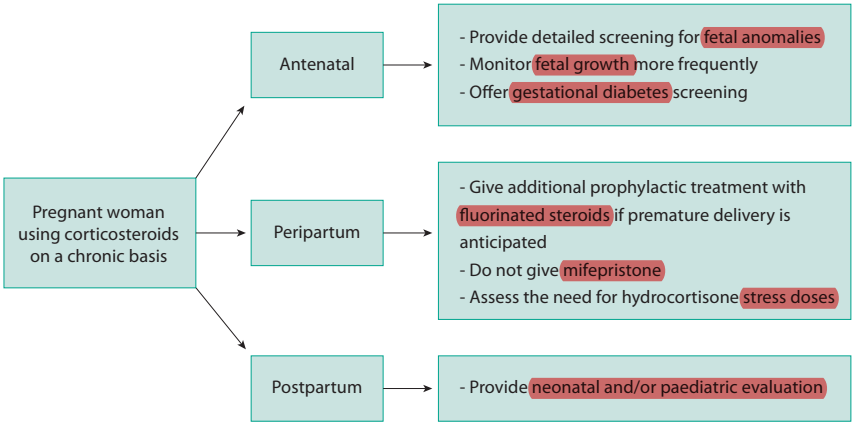

Figure 1. Management recommendations for pregnant women using corticosteroids on a chronic basis.

Neonatal exposure to exogenous corticosteroids

There is a lack of knowledge about the impact of maternal chronic use of corticosteroids on fetal lung maturity and neonatal outcomes; most available data result from repeated doses of antenatal corticosteroids that were given to enhance fetal lung maturity. There is an association between multiple courses of antenatal corticosteroids and decreased fetal weight, height and head circumference.[60,74,75] Also noteworthy are the trends towards an increased risk of neonatal sepsis and pituitary-adrenal axis suppression associated with multiple courses of antenatal corticosteroids.[51] Two case reports found an association between chronic maternal use of corticosteroids and neonatal adrenal suppression.[37,43]

Animal and human studies have raised concerns about adverse neurodevelopmental effects from multiple exposures to corticosteroids.[76,77] Although no definitive association has been found, one large randomised trial found an association between multiple courses of antenatal corticosteroids and adverse long-term neonatal outcomes,[78] increased risk of cerebral palsy and assessments for attention deficit disorder.[53,79,80] Of note, within the specific subgroup of infants with multiple antenatal corticosteroid exposures who were delivered at term, an association was found between increasing neurodevelopmental impairment and decreasing gestational age at initiation of exposure.[81]

Therefore, neonatal assessments of fetuses with chronic corticosteroid exposure should pay particular attention to cardiovascular haemodynamics, serum electrolytes and steroid hormone levels. However, such assessments are ubiquitously included in routine assessments of premature neonates admitted to the neonatal intensive care unit, including 17-alpha hydroxyprogesterone from newborn bloodspot screening tests.

Our recommendations

Learning points based on the current review are presented in Box 1. Figure 1 provides recommendations for the management of pregnant women using corticosteroids on a chronic basis.

Conclusion

The widespread use of corticosteroids means that it is common to encounter pregnant women who use corticosteroids on a chronic basis. There is conflicting evidence of a three-fold increased incidence of orofacial cleft in pregnancies exposed to systemic corticosteroids. A small reduction in fetal growth is suggested, but long-term growth deficiencies have not been confirmed. Screening for gestational diabetes is advocated. The overall safety profile during pregnancy is fair; therefore, corticosteroids should not be withheld when needed for maternal indications. Neonatal complications are uncommon; however, neonatology assessment is advised.

Additional doses of antenatal corticosteroids are required if preterm delivery is suspected. The literature lacks long-term follow-up of fetuses exposed to chronic maternal corticosteroids.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

DA and SL conceived the idea. All authors wrote the first draft, revised and approved the final version of the manuscript.

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