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Corticosteroids and fetal maturation

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CORTICOSTEROIDS DURING LATE PREGNANCY
Corticosteroids are essential for fetal maturation in mammals. Cortisol stimulates structural and functional changes in many tissues to facilitate the transition from intra- to extrauterine life (Fowden et al. 1998); it also initiates the final endocrine cascade that leads to the onset of myometrial contractions and delivery in some species. Before birth, there is a gradual increase in fetal cortisol concentrations over the last few weeks, initiated by activation of the fetal hypothalamo-pituitary-adrenal axis, and a decrease in cortisol binding globulin concentrations. Animals not exposed to the prenatal cortisol rise have deficient enzyme activities in key bodily organs, particularly the lungs, leading to respiratory distress syndrome (RDS) and widespread organ dysfunction. Horses are different to other animals because fetal cortisol concentrations increase only during the final 24–48 h before delivery, and continue to increase after birth (Fowden et al. 1998). Foals that fail to complete this final maturational process display many features of immaturity. Premature foals typically have low body weights, adrenal insufficiency, hypoglycaemia associated with low body glycogen stores, hypothermia and low T3 concentrations, a poor suck reflex, inability to digest enteral feeds, lung and renal dysfunction, incomplete ossification and deficient muscular-skeletal development. Not surprisingly, premature foals have a worse prognosis for survival than full term neonatal foals suffering from other conditions (sepsis, PAS, HIE), even with high level intensive care. Moreover, post natal treatment with corticosteroids does little to induce adrenocortical activity and tissue maturation because of a deficiency in adrenal P450c17 enzyme activity.

TREATMENT WITH EXOGENOUS CORTICOSTEROIDS
Synthetic glucocorticoids (betamethasone 12 mg i.m. s.i.d. for 2 days, or dexamethasone 6 mg i.m. b.i.d. for 2 days) administered routinely to pregnant women delivering before 32 weeks are associated with a significant decline in the incidence of RDS, intraventricular haemorrhage and mortality in premature infants. Glucocorticoids are also used successfully in domestic animals both to stimulate precocious fetal maturation and induce delivery. However, attempts to induce delivery or promote precocious fetal maturation using corticosteroids in the mare have yielded conflicting results. Early work by Alm et al. (1975) demonstrated that high doses of dexamethasone (100 mg i.m.) given daily from 320–324 days of gestation significantly shortened gestation without compromising fetal health; others reported either no effect or adverse outcomes following similar treatment regimens (Burns 1973; Alm et al. 1975; Jeffcott and Rossdale 1977). Attempts to stimulate an endogenous cortisol rise by fetal ACTH injection (1 mg s.i.d. 300–302 days) significantly shortened gestation, but caused abortion in a third of mares because of damage to the amniotic membrane, while maternal ACTH administration (5 mg Depot. 300–302 days) reduced the risk of abortion but was not 100% effective (Ousey 2004). Recently, the author repeated the high dose dexamethasone protocol in pregnant Thoroughbred mares at 315–317 days and found that it induced precocious fetal maturation and early delivery, but also caused adrenocortical suppression in the resulting foals. Clinical results to date include favourable foal outcomes in 2 of 3 sick, pregnant mares treated with high doses of dexamethasone prior to euthanasia before full term.

EXPOSURE TO ENDOGENOUS CORTICOSTEROIDS
Maternal disease during pregnancy, for example colic, endotoxaemia or uterine torsion, may increase maternal cortisol concentrations. Although the fetus is protected from fluctuations in maternal cortisol by the placental enzyme, 11β-HSD Type 2, which coverts cortisol to inactive cortisone, in other species 10–20% cortisol still crosses the placental barrier. Moreover, problems such as fetal hypoxaemia, ascending infections via the cervix and placental pathology are likely to cause fetal stress and increase endogenous cortisol concentrations. Although these have not been measured directly, indirect evidence for fetal adrenocortical activity has been demonstrated by a rise in maternal progestagens, which are synthesised from pregnenolone from the fetal adrenals (Ousey 2004). Increased progestagen concentrations are observed in mares with chronic placental pathology and their foals also have increased adrenocortical activity after birth (Rossdale et al. 1991). Fetal ACTH injections also promote an increase in maternal progestagens. In practice, sustained rises in maternal progestagens before term are used as a clinical marker of fetal stress. Foals born from such mares have a greater chance of survival than those delivered from mares with no progestagen rise (LeBlanc et al. 2004). These results suggest that long-term exposure to either maternal or fetal endogenous cortisol may benefit the foal in terms of post natal survival.
However, animal studies have indicated that long-term or repeated exposure to corticosteroids may restrict fetal growth and have long-term effects on the health of the offspring (Fowden et al. 1998).

CONCLUSIONS

Prenatal exposure to corticosteroids is essential for equine fetal maturation and post natal survival. Maternal treatment with synthetic glucocorticoids is probably the best method for promoting precocious fetal maturation in mares that are expected to deliver before term. However, at present there is little information about the doses, drug choice, and timing of corticosteroids to be administered. Moreover, the effects of exogenous corticosteroids in sick, pregnant mares with fetal distress are unknown.

REFERENCES


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