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Lina Göransson

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Hypotalamus-hypofys-binjurebarksaxeln och perinatal behandling av prematurföl

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Handledare:
Elisabeth Persson, SLU, Institutionen för anatomi, fysiologi och biokemi
Sara Wernersson, SLU, Institutionen för anatomi, fysiologi och biokemi

Examinator:
Eva Tydén, SLU, Institutionen för biomedicin och veterinär folkhälsovetenskap

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SUMMARY

The danger and vulnerability associated with a preterm birth seem to be closely correlated with a dysfunction of the fetal hypothalamic-pituitary-adrenal (HPA) axis, whose maturation in the foal is without a doubt as delicate as it is important. Not only is this endocrine cascade vital for the foal in order to cope with neonatal stress, it also appears to be fundamental for the final fetal intrauterine maturation, as well as for the onset of foaling.

Equine gestation exhibits some rather unique features, indicating a somewhat different significance of the endocrine changes associated with HPA maturation, compared to many other species. This hormonal cascade is rapid and confined to a narrow time during late gestation in the horse, and the risk of the foal completely missing it therefore becomes prominent.

Induced parturition in the mare may be operated through uterotonic agents, which occasionally bring about premature foals. Desirable seems the ability to initiate equine labour while simultaneously enhancing fetal HPA maturation, as in humans and ruminants through perinatal glucocorticoid administration. However, similar treatment in the horse has resulted in various, sometimes fatal, outcomes.

In the light of the distinctive features of equine gestation, difficulties are encountered following such administration of glucocorticoids and ACTH. Favourable results have however also been displayed in the horse, motivating attempts to overcome the associated obstacles. To ensure a successful therapy, increased knowledge about the endocrinology of equine gestation will be necessary.

SAMMANFATTNING

En för tidig födsel innebär en väldig fara för den nyfödda individen. En bidragande orsak är ofta en bristfällig hypotalamus-hypofys-binjurebarksaxel, vars utveckling ter sig lika känslig som betydelsefull för ett föl. Utöver förmågan att hantera neonatal stress, förefaller denna endokrina kaskad vara av yttersta vikt för den slutliga intrauterina fetala utvecklingen, liksom för initieringen av fölning.

Hästens dräktighet skiljer sig något från många andra djurslags, och betydelsen av de endokrina förändringarna associerade med HPA-axelns mognad förefaller något annorlunda. Den hormonella kaskaden är hastig och begränsad till en kort tidsperiod sent under hästens dräktighet, vilket ökar risken för att fölet helt missar denna.

Fölning kan sättas igång artificiellt med hjälp av uterotona preparat, vilka dock kan associeras med födseln av underutvecklade individer. Fördelaktigt vore således att parallellt kunna initiera fölning och stimulera den fetala HPA-utvecklingen, vilket hos idisslare och människa kan åstadkommas med hjälp av perinatal administrering av glukokortikoider. Liknande behandling av häst har undersökts men med varierande, ibland fatala, resultat.

Då hästens dräktighet innefattar dessa specifika karaktärsdrag, uppstår svårigheter vid administrering av glukokortikoider och ACTH. Vissa studier har dock uppvisat lyckade resultat hos häst, vilket motiverar eventuella försök till att lösa dessa problem. Nödvändig är således utökad kunskap om endokrinologin bakom ekvin dräktighet, innan dylik behandling kan bli aktuell.

INTRODUCTION

The fetal development before and to a certain extent after birth, is all about preparing the new individual for what is waiting outside the safe environment that the uterus means (Fowden et al., 2012). Numerous and extensive physiological changes are needed in order to ensure neonatal survival (Fowden & Forhead, 1998). Amazing is the fact that these changes repeatedly take place without complications, resulting in the birth of a fully mature foal ready for the world in which it suddenly finds itself. Sometimes however, immature foetuses are born incapable of coping with the challenges of neonatal life.

Maturation of the fetal hypothalamic-pituitary-adrenal (HPA) axis during late pregnancy seems to be the key to several of these changes in many species (Fowden & Forhead, 1998; Fowden et al., 2012). Premature individuals commonly display a dysfunctional HPA axis, making them more vulnerable and likely to suffer from disease and death. Some rather distinctive features of equine gestation indicate a somewhat different importance of these endocrine changes in the horse, compared to many other species. Due to this, some authors suggest that the fetal foal is more likely to miss out on the late maturational changes, and thus that a larger number of premature foals are born compared to other precocial species (Fowden et al., 2012).

In human medicine, synthetic glucocorticoids are used successfully to aid maturation of the fetal HPA axis and induce its endocrine effects on organogenesis (Fowden & Forhead, 1998). Maternal administration before delivery when preterm labour is expected, along with treatment of the infant postpartum, is applied frequently. Similar administration has also been used effectively in ruminants (Ousey, 2006), but has displayed various outcomes when scarcely investigated in the horse. Despite the differences distinguishing equine gestation from that of other species, could such perinatal therapy be applied in order to successfully enhance fetal maturation in the horse as well, giving Mother Nature a helping hand?

MATERIAL AND METHODS

When searching for articles, the databases of PubMed and Web of Knowledge were used predominantly, along with Scopus to a certain extent. Search words did always comprise "equine OR horse OR mare" and "foal OR fetus OR neonatal OR prenatal OR premature." Initially, additional words included combinations of "HPA-axis OR hypothalamic-pituitary-adrenal axis" together with "glucocorticoids OR cortisol" as well as "fetal development OR gestation OR parturition OR delivery OR organogenesis." As the work proceeded, searching came to include more specific words such as "betamethasone OR dexamethasone" and "induced parturition" as well as "treatment OR administration." After the primary sift of relevant findings, further articles were found through references of these as well as through related articles as suggested by the databases.

LITERARY REVIEW

An overview of the fetal HPA axis

In many species, irrespective of how or when it happens, the importance of a mature fetal HPA axis enabling the fetus to cope with postnatal life, is evident (Silver et al., 1984; Hart et al., 2009a). Although the details of the developmental changes this endocrine system undergoes during pregnancy appears somewhat different between species (Silver & Fowden, 1994), there is a great resemblance regarding the fundamental functions of a mature HPA axis.

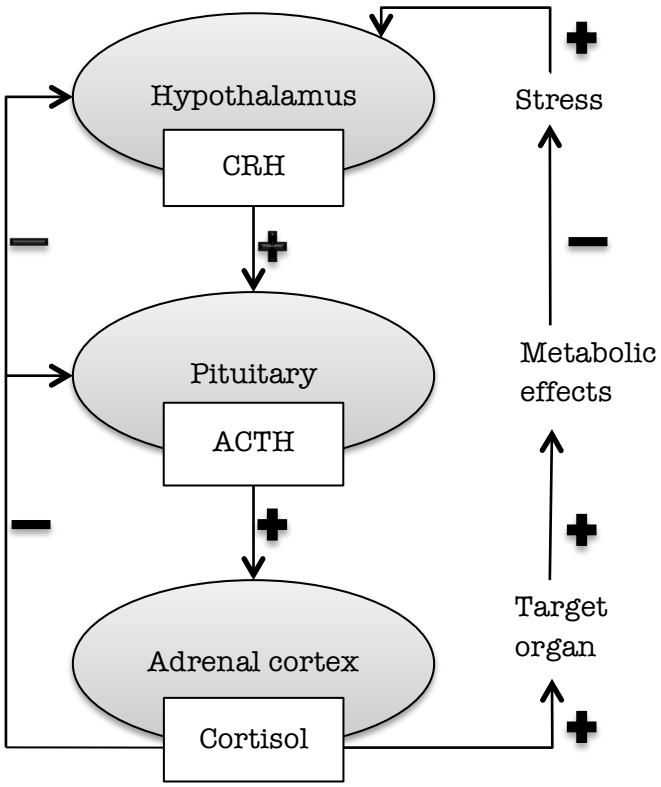

Figure 1: The hypothalamic-pituitary-adrenal (HPA) axis (based on Hart and Baron [2011]).

Numerous types of environmental and physiological stress factors can activate the HPA axis through stimulation of the nervous system (Hart & Barton, 2011). This initiates the hypothalamic secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These hormones stimulate the pituitary gland, resulting in the release of adrenocorticotropic hormone (ACTH). In turn, ACTH stimulates the adrenal cortex to synthesise and secrete corticosteroid hormones, including glucocorticoids such as cortisol. The adrenal cortex comprises three zones: the innermost *zona reticularis*, the middle *zona fasciculata* and the outer *zona glomerulosa*. Cortisol is produced predominantly in the *zona fasciculata.* This hormone exerts its effect on cells and tissues throughout the body, in order to ease the initial reason for HPA stimulation. The synthesis of cortisol is regulated through negative feedback, as increased cortisol concentrations lessen the activity of the HPA axis on all levels.

In addition to the ability to cope with stress, this fetal endocrine cascade appears to be of even further importance during gestation. Studies show that stimulation of the HPA axis and a resulting fetal cortisol surge towards term, evident in all species, is of great importance for many aspects of final fetal maturation as well as parturition (Cudd et al., 1995; Ousey et al., 2011).

Equine gestational length

The gestational period in the mare normally ranges from 320 and 360 days in Thoroughbred mares (Rossdale & Silver, 1982). Equine gestation thus encompasses an exceptionally wide 95% confidence interval regarding full term period. Gestational length can often be used to define full term and prematurity in other species, but does not constitute a safe measure in the horse, since even full term foals might display signs of immaturity (Rossdale et al., 1984).

Rossdale and Silver (1982) emphasize the importance of a spontaneous delivery, as each fetus possess an individual maturational pace and optimal gestational length, which might not always be according to what is expected for that species. Consequently, foals born spontaneously at a younger gestational age might be just as or even more mature than foals born later. Likewise, foals born before full term gestational length may be viable, whereas those delivered through induction usually exhibit some signs of prematurity, irrespective of gestational age at delivery (Rossdale & Silver, 1982).

The premature foal

Precocial animals such as the horse must by the time of birth be able to quickly stand and move, regulate body temperature as well as possess excellent hearing and vision (Rossdale & Silver, 1982). Premature foals often lack these qualities to an extent that becomes dangerous, and are therefore less likely to survive neonatal life.

These individuals often display numerous organ systems not fully developed, largely due to an immature HPA axis it seems (Ousey et al., 1998). Pulmonary insufficiency as well as failure of the cardiovascular system presented as cool extremities and low pulse is typical (Rossdale & Silver, 1982; Fowden & Forhead, 1998). So are gastrointestinal dysfunction and an inability to properly stand and suck. This, often associated with a reduced transfer of maternal antibodies and insufficient amounts of IgG in colostrum, has severe adverse effects on the immune system. Additionally, hypoglycaemia is common, along with hypothermia due to difficulties regulating body temperature.

Many of these features have been used to distinguish the premature foal from the fully mature (Rossdale et al., 1984). Not only do actual fetal plasma cortisol and ACTH values postpartum function as important criteria, but for instance also size, haematological parameters, carbohydrate metabolism and the renin-angiotensin-aldosterone system (RAAS). This further emphasise the importance of the HPA axis and cortisol during fetal foal development, considering its significance for the above mentioned physiological processes.

Premature labour does occur during equine gestation for various reasons, sometimes unknown. At times though, parturition must be induced artificially before term due to for instance medical reasons (Ousey, 2006). In the mare, uterotonic agents such as oxytocin and prostaglandins are regularly used. These inducers are however often associated with obvious signs of prematurity (Rossdale & Silver, 1982).

Important to acknowledge is that factors causing intrauterine stress might also lead to an early onset of parturition (Hart et al., 2009b). Such foals display a different endocrine profile compared to the premature individuals described above, and will not be included in this review.

The effects of fetal cortisol during gestation

The marked differences between premature and full term individuals illustrate the vital importance of fetal cortisol, as the former often exhibit several adverse developmental characteristics (Rossdale et al., 1982; Silver et al., 1984). That cortisol is in addition an important mediator during parturition in many species, including the horse, is also evident (Cudd et al., 1995; Fowden & Silver, 1995). The particulars behind the effects of cortisol remain not fully understood, in the equine especially, and will thus not be thoroughly discussed in this paper.

Organogenesis

Fetal intrauterine life does not demand nearly as much from the individual as life outside this safe environment does. For precocial animals especially, there is really not much time for adaption after birth (Rossdale & Silver, 1982). Many of the organ systems and physiological processes that have not been important earlier, must be structurally and functionally ready for new challenges immediately postpartum (Fowden et al., 2012).

Table 1. Maturational effects of fetal cortisol on various tissues (based on Fowden [1995]; Fowden & Forhead [1998]; Ousey [2006])

Tissue	**Maturational change**
Liver	Deposition of glycogen Induction of enzymes for gluconeogenesis and fatty acid oxidation Induction of β-adrenergic receptors
Lung	Surfactant production Structural maturation of alveoli Induction of β-adrenergic receptors Lung liquid re-absorption
Gut	Structural maturation of gastrointestinal tract Induction of digestive enzymes Acid and gastrin secretion
Pituitary	Maturation of corticotrophs Decrease in propiomelanocortin mRNA levels
Adrenal	Induction of phenylethanolamine *N*-methyl transferase enzyme Cytoarchitechtural maturation of *zona fasciculata* Induction of receptors for adrenocorticotrophic hormone Induction of 11β-hydroxylase and P450 cytochromes
Bone marrow	Switch from fetal to adult haemoglobin synthesis Increase in blood neutrophil:lymphocyte ratio
Placenta	Induction of 17α-hydroxylase Separation of fetal and maternal tissue
Kidney	Increased glomerular filtration rate Induction of ion-exchange pumps

Extensive studies of human and ovine pregnancy illustrate the importance of HPA maturation and the associated cortisol surge for the critical final fetal maturation of several organ systems. The extent of this maturation at birth has a considerable importance for what might distinguish a survivor from a non-survivor (Hart et al., 2009b). The table above gives a brief but good view over the extensive final developmental processes, to which that late-gestational fetal cortisol surge seems to be the key.

Onset of parturition

That the endocrine cascade of a stimulated fetal HPA axis contributes to the onset of labour is clear. This is supported by numerous studies, in which administration of such hormones has significantly reduced gestational length in ruminants and primates, as well as in the horse (Rossdale et al., 1992; Ousey et al., 2011). However, to what extent and exactly how glucocorticoids may initiate parturition is not fully understood, certainly not in the equine, which seem to display rather unique endocrine details associated with this process.

Uterine quiescence until the very end of pregnancy is necessary to prevent early onset of labour. This silence is maintained through high progestagen concentrations inhibiting myometral activity, followed by a rapid hormonal decline prior to parturition (Fowden et al., 2012). An important source of maternal progestagens in many species is the *corpus luteum*, which however appears to be of less significance in the mare.

The fetal adrenals and the placenta seem to comprise a rather unique fetoplacental steroidogenic unit during equine gestation, compared to for instance that of the ovine (Fowden & Silver, 1995). Maturation of the fetal foal HPA axis results in an escalating fetal adrenal production of pregnenolone (P_5), probably due to the induced expression of necessary enzymes (Fowden et al., 2012). In turn, the placenta then synthesises various progestagens using P_5. These progestagens are most likely released into the maternal circulation, contributing to the raised plasma concentrations seen in the mare towards term (Rossdale et al., 1992; Ousey et al., 1998). These studies display a progesterone peak a few days prior to parturition, followed by a decline during the last day or hours, the latter thus allowing myometral activity. Such declining levels of progesterone are associated with the fetal cortisol surge preceding labour. This phenomenon is thus likely to reflect a further alteration of the enzyme expression in the fetal adrenals, replacing the synthesis of P_5 with that of cortisol (Fowden et al., 2012).

Plasma cortisol levels in the fetal foal

A cortisol surge following maturation of the fetal HPA axis can be seen close to gestational term in all species (Fowden & Silver, 1995). Yet again, the horse is to be distinguished from for instance the sheep, in which these fetal endocrine and developmental changes are confined to the last 15-20% of total gestational length. In the mare, the very same maturational events are instead limited to 1-2% of equine gestation (Cudd et al. 1995; Fowden & Silver, 1995). Maturation of the fetal HPA axis is thus extremely rapid and constricted to a very narrow period of time in the equine (Fowden & Silver, 1995). So is the sequential cortisol surge, which cannot be detected until the very last days or hours before parturition (Silver &

Fowden, 1994; Cudd et al. 1995). Comparative studies between fetal lambs and foals have also shown that the actual cortisol production rate towards term is higher in the latter (Nathanielsz, 1975).

Accordingly, in the fetal foal the adrenal weight is doubled during the last 5% of gestation only, primarily due to development of the *zona fasciculata*, responsible for synthesis of cortisol (Fowden et al., 2012). Corresponding changes can be noticed during ovine and porcine gestation, however at a much slower rate and initiated proportionally earlier in relation to the cortisol surge and parturition.

The time during which fetal cortisol may exert its effect on the final fetal maturation is thus extremely short during equine gestation. Hence, the probability of the foal not experiencing this vital endocrine cascade at all increases drastically (Fowden et al. 2012). Prematurity in the horse consequently appears to be an even greater threat towards sufficient fetal development and postnatal survival, compared to many other species.

The expression of necessary enzymes

Cortisol synthesis in the adrenal seems to be dependent on three steroidogenic enzymes: cholesterol side chain cleavage ($P450_{SCC}$), 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17α-hydroxylase ($P450_{C17}$) (Han et al., 1995). The expression of these appears to increase in the fetal adrenal as gestation progresses, exactly how is however still largely unknown.

All three enzymes seem to be expressed in the fetal adrenal cortex in most species. However, based on a limited number of studies, the ontogenetic changes seem to be yet another aspect distinguishing equine gestation from that of many other animals (Cudd et al., 1995; Fowden & Silver, 1995). Concurrent with the delayed fetal cortisol surge, these key enzymes do not increase quantitatively in the *zona fasciculata* of the fetal adrenal until late equine gestation. Whereas this enzymatic expression is significant in the fetal lamb adrenal at 90% of gestation, extremely small amounts of each enzyme are displayed at the corresponding time during equine gestation (Fowden & Silver, 1995).

Cytochrome $P450_{SCC}$ catalyses the conversion of cholesterol to pregnenolone (P_5), whereas 3β-HSD further catalyses the switch from P_5 to progesterone (Fowden et al., 2012). Both enzymes increase quantitatively in the equine fetal *zona fasciculata* from around gestational day 150 and 280, respectively. This is proportionally later than during for instance ovine gestation (Han et al., 1995). Cytochrome $P450_{C17}$ is responsible for the synthesis of cortisol from progesterone. The authors performing the study of the original article, Han et al. (1995), asserts that this enzyme is not detectable during equine gestation, but that at birth however, all three enzymes are present in abundance throughout the *zona fasciculata*. The authors emphasize that it is unknown if this neonatal abundance of $P450_{C17}$ is due to a rapid quantitative increase just before or after parturition. Other authors however, suggest that the enzyme is present in low concentrations up until just prior to parturition, when its expression rapidly escalates (Fowden et al., 2012). Perhaps this is a plausible assumption based on the

fact that fetal cortisol concentrations increase quickly before delivery, which would thus mirror a rapid upregulation of the responsible enzyme at the same time.

Regardless of when this delayed expression of $P450_{C17}$ begins, it is likely that the onset of an early parturition might lead to a lack of sufficient amounts of this enzyme. Such individuals may thus exhibit an adrenal production of P_5 and, to a lesser extent, progesterone whereas the production of cortisol has seldom yet begun. This reflects the low cortisol concentrations and the reduced or lacking adrenocortical response often seen in premature foals at the time of birth, following induced delivery (Nathanielsz, 1975; Ousey et al., 1998). Consequently, progesterone levels usually remain high in premature foals as a likely result of the absent adrenocortical switch prior to delivery, normally increasing cortisol synthesis on behalf of P_5.

Corticosteroid binding capacity

The fetal cortisol surge preceding parturition in the horse is not only due to increased cortisol production and greater adrenocortical responsiveness, unlike most other species. During equine gestation, the effect of cortisol is further enhanced by a declining corticosteroid binding capacity (CBC) (Cudd et al., 1995). Again, this seems to further distinguish the pregnant mare from the sheep as well as human, in which CBC on the contrary increases towards term (Fowden & Silver, 1995).

Most circulating glucocorticoids are bound to various plasma proteins, such as corticosteroid binding globulin (CBG), due to the lipophilic nature of the hormone (Hart & Barton, 2011). This fraction functions as a circulating reservoir, since cortisol cannot be stored in the adrenals. As glucocorticoid receptors are found in the cellular cytoplasm, only free cortisol can reach these and exert its effects after diffusion across the plasma membrane. In the horse, expression of CBG appears to decrease as gestation progresses, resulting in a greater amount unbound fetal cortisol towards term (Cudd et al., 1995). CBC seems to decline significantly ten days prior to parturition, although most markedly over the last three days. Thus, the concurrent fetal cortisol surge in the foal will be amplified, which seems to perhaps compensate for the extremely short time during which cortisol concentrations normally increase.

Some authors argue that the reduction of fetal plasma CBC is initiated somewhat earlier than the actual elevation of fetal cortisol concentrations during equine gestation (Cudd et al., 1995; Fowden et al., 2012). The amplified cortisol concentrations might thus in fact occur during a longer period of time, than suggested merely by measurements of fetal plasma cortisol levels.

Plasma cortisol and ACTH levels in the neonatal foal

Equine fetal cortisol concentrations do not only increase rapidly and shortly just before parturition, but continue to rise to a maximum during the immediate hour postpartum (Nathanielsz, 1975; Rossdale et al., 1982). After a few hours only however, cortisol levels rapidly decrease to reach a lower basal level (Rossdale et al., 1982; Ousey et al., 1998). Within 24 hours it might be as low as 30% of the maximum concentration, as shown by Nathanielsz (1975). Similarly, accompanying levels of fetal ACTH appear to be greatest at

birth, only to thereafter decline parallel to the neonatal cortisol concentrations (Silver et al., 1984).

On the contrary, premature foals delivered following induced parturition, generally display extremely low cortisol concentrations at birth (Nathanielsz, 1975; Rossdale et al., 1982). These levels fail to increase during the nearest hour postpartum, and do not decline to a normal basal level closely thereafter (Rossdale et al., 1982; Silver et al., 1984). Thus, final cortisol levels a few days later actually end up higher in the premature than in the full term foal (Ousey et al., 1998).

Whereas plasma cortisol concentrations at birth appear unusually low in premature foals, concurrent levels of ACTH tend to be very high instead (Silver et al., 1984). Also, the latter appears not to decline postpartum as in full term foals. The authors suggest that the reason might be the low cortisol concentrations failing to inhibit ACTH secretion, exerting no negative feedback on the pituitary gland in the foal.

Perinatal adrenocortical responsiveness

As presented, maturation of the fetal HPA axis and the adrenal gland as well as the subsequent fetal cortisol surge, appear not to happen until during late pregnancy in the mare. In accordance, fetal foal adrenocortical responsiveness to endogenous as well as exogenous stimulation shows no enhancement until the very end of equine gestation, compared to that of other species (Silver et al., 1984). This attribute appears to be yet another one making foals in particular especially vulnerable to a premature birth.

Several studies where fetal injections of exogenous ACTH have been applied in order to evaluate fetal adrenocortical responsiveness throughout equine gestation, display no significant effects until around day 290 (Fowden et al., 2012). One such investigation performed by Silver and Fowden (1994), allowed fetal foal examination through chronic catheterization of pregnant mares. A bolus dose of $ACTH_{1-24}$ was administered to groups of foetuses at different gestational ages. The sequential alterations of fetal plasma cortisol were the means to assess fetal adrenocortical responsiveness. The results clearly displayed no such hormonal changes in fetal foals younger than 295 days. Thereafter however, the plasma cortisol concentrations progressively increased in magnitude following exogenous stimulation, to exhibit a fourfold rise of basal cortisol levels three days prior to parturition.

Equivalent tests postpartum reveal that fetal adrenocortical responsiveness normally seems to be greatest at birth, only to decrease shortly and within the first week thereafter (Silver et al., 1984; Hart et al., 2009a). On the contrary, such adrenocortical responsiveness seem to be small or even completely absent at birth in premature foals, resembling that of late gestation (Rossdale et al., 1982; Silver et al., 1984).
The reason for low plasma cortisol levels and the lack of adrenocortical responsiveness in the premature foal, despite unusually high concentrations of ACTH, has been a query among researchers. The considerable amounts of ACTH simply appear unable to increase the fetal plasma cortisol levels (Silver et al., 1984; Silver & Fowden, 1994). One suggestion is that the

physiological stress of the actual parturition imposes the high levels of ACTH, but that the premature fetal adrenals are unable to respond to this stimulation. Since adrenocortical responsiveness does not become significant until during late gestation, it is likely that such developmental changes will be lacking due to prematurity, thus comprising the problem postpartum.

DISCUSSION

Although current inducers, such as oxytocin and prostaglandins, commonly used in the mare are very effective as in the rapid onset of parturition, the use of synthetic glucocorticoids and exogenous ACTH should really be further investigated as a possible alternative. The latter treatment seems to come with advantages regarding fetal maturation, certainly not associated with such uterotonic agents (Ousey, 2006). Besides the onset of parturition, synthetic glucocorticoids may generate the same enhancement on fetal maturation as endogenous cortisol, while depot ACTH appears to be able to induce adrenocortical stimulation.

Administration of glucocorticoids is used regularly in human medicine, as well as to ruminants, and its ability to initiate labour while simultaneously enhancing fetal HPA maturation and function is evident. Studies on similar treatment in the equine have previously been made, although sparse and sometimes with adverse results. In the light of the rather unique features of equine gestation, difficulties are encountered following such administration of glucocorticoids and ACTH. These obstacles must be overcome in order to create a successful therapy also in the horse.

How to know exactly when administration will be effective is a prominent problem. The variability of equine gestational length, in combination with the short period of time to which that final fetal cortisol increase is confined, creates such a dilemma. As Ousey et al. (2006) suggest, a high bolus dose of synthetic glucocorticoids is needed to mimic this endogenous cortisol surge. Accordingly, Ousey et al. (2011) successfully reduced gestational length through high doses of maternally administered glucocorticoids during late gestation, while concurrently enhancing fetal maturation. Nevertheless, identical dosage regimens used at the exact same gestational age might display a wide range of outcomes, reflecting an individual variation in fetal maturation as suggested by the authors. If fetal cortisol concentrations have already significantly risen at the time of administration, there is a substantial risk of adrenocortical suppression instead of HPA-activation.

Opposing to such difficulties imposed by the extremely short fetal cortisol increase, the nature of this hormonal surge could be advantageous one might think. The exceptionally rapid elevation of fetal cortisol, further amplified by increased cortisol binding capacity, suggests that the foal should be able to respond quickly to treatment. That is, when administration occurs at the appropriate time however.

Concurrent with this delayed cortisol surge, the fetal adrenal seems unable to respond to stimuli until late gestation. Accordingly, Ousey et al. (1998) show that fetal injection of

ACTH at day 300 of equine gestation does increase fetal plasma cortisol concentrations. The same cannot be seen following equivalent administration during earlier gestation, as shown by Silver and Fowden (1994). Such treatment thus requires that adrenal maturation has already begun in the individual fetal foal, otherwise the gland will be insensitive to exogenous ACTH.

Assessment of fetal foal maturation at the time of administration is thus of immense importance, and constitutes yet another problem to be solved. Ruminants for instance, in which glucocorticoid treatment has been successful, display a gestational length less variable, and the timing of birth as well as the degree of fetal maturation is easier to predict. Measuring actual fetal cortisol concentrations is a possible means of estimating fetal foal maturation. So is gauging of cortisol levels following ACTH challenges while examining fetal adrenocortical responsiveness. Although suitable for the purpose, such invasive procedures might in themselves be a danger to the sensitive fetus (Ousey, 2006).

Ousey et al. (2011) present the issue regarding maternal administration over fetal injections, as the effectiveness of the latter might be shadowed by its invasiveness. Fetal injections of ACTH have displayed an unacceptably high abortion rate (Ousey et al., 1998), whereas the corresponding maternal treatment appeared safer (Ousey et al., 2000). The mares however, in which induction of parturition might be necessary due to medical reasons, are often diseased or physiologically stressed. High endogenous cortisol and progesterone levels might already be present, and thus administration of additional glucocorticoids or ACTH could very well cause endocrine disruptions. Similarly, a commonly used synthetic glucocorticoid is dexamethasone, exerting anti-inflammatory effects through decreased production of prostaglandins (Ousey, 2006). Dexamethasone might thus endanger the endocrine pathways of equine gestation. As long as these normal endocrine changes are not fully understood, it is impossible to completely estimate the disruption possibly caused by such administration.

An alternative to prenatal treatment to increase fetal viability is the administration of ACTH postpartum. Studies by Rossdale et al. (1982) and Silver et al. (1984) indicate that treatment with long-acting depot ACTH soon after birth rapidly increases plasma cortisol concentrations, even in premature foals initially displaying low cortisol levels and no adrenocortical responsiveness. Additionally, the former study implies that as a result of prolonged stimulation exerted by depot ACTH, adrenocortical responsiveness increases towards short-acting ACTH, even in premature foals. The authors compare this to the prenatal gradual stimulation of the adrenal gland by endogenous ACTH, leading to a progressive increase of adrenocortical responsiveness. Silver et al. (1984) could not detect the same improvement following administration of depot ACTH, but suggest that dosage and method might have contributed to varying results. These studies, now performed quite some time ago, suggest a reasonable method and favourable results. However, more recent studies further investigating a similar type of administration have not been found for this literary review.

Although distinctive features of equine gestation hamper mere extrapolation from other species, studies indicate that administration of exogenous glucocorticoids and ACTH could become beneficial in the horse as well. In the latter, the effectiveness of such treatment has

been debated, but findings suggest that it could initiate parturition along with fundamental improvements of fetal maturation also in the equine. Lacking is though the comprehensive knowledge about the endocrinology of equine gestation and parturition, to enable both safe and effective administration of synthetic glucocorticoids and ACTH. With that knowledge though, such perinatal treatment could also in the equine become a possible means of giving Mother Nature that sometimes well needed helping hand.

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