New Perspectives on the Late-Term Mare and Newborn Foal

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1. Introduction

A successful perinatal program requires the collaborative efforts of those trained in reproduction and neonatology. In ambulatory situations, one person must often specialize in both areas; additionally, that person must have the equipment and expertise available to manage obstetrical complications and to provide neonatal resuscitation and nursing care. Periparturient complications during late pregnancy may include severe maternal illness or colic, reproductive tract disease, or fetal anomalies. The most serious threats to uteroplacental health and foal survival are perinatal sepsis, hypoxia/ischemia, and maturation disorders. The challenge is to improve our ability to recognize mares with jeopardized pregnancies at an earlier stage in gestation or in the disease process. This goal can be accomplished in two ways: (1) more proactive antepartum monitoring and reporting of clinical cases in the field and (2) the use of controlled experimental disease models designed to improve our understanding of the evolution of uteroplacental dysfunction.

Many clinical trials designed to examine hormone changes in the at-risk mare or evaluate the efficacy of various treatment modalities on pregnancy outcome are underpowered statistically. Only anecdotal observations and conclusions can be inferred, because there is not a large enough number of clinical cases with similar problems from which to draw significant conclusions. Until larger, multicentric collaborative trials validate the usefulness of monitoring specific hormones or the efficacy of various therapies designed to manage and maintain complicated pregnancies, it is the author’s recommendation that no one therapy or monitoring aid should be relied on exclusively. Any mare receiving therapy to prolong an abnormal pregnancy should receive frequent assessment. That way, the clinician can promptly determine if silent or undetected fetal demise occurs without ensuing abortion or if parturition occurs without the customary warning signs.

This paper will focus on new or controversial management strategies and monitoring techniques for the late-term mare with periparturient complications. The current understanding of pregnant-mare physiology will be reviewed when applicable to help practitioners decide if and how they might incorporate some of these interventional therapies into their daily practice. Newborn foal evaluation will conclude this section with an emphasis on normal behavior guidelines and a brief review of neonatal immunity.
2. Controversies Regarding Hormone Therapy in the Late-Term Mare

Hormonal Profiles

The search continues in equine perinatology for hormones that reflect fetal and placental wellbeing. Progestagens and estrogens remain the most likely candidates, but the specific endocrine mediators responsible for maintenance of pregnancy during late gestation and stimulation of the final stages of fetal maturation and initiation of parturition remain the focus of considerable research and controversy. In many compromised equine pregnancies, the pre-partum changes of these hormones and their metabolites may be too acute to provide advanced warning of impending fetal demise. Non-lethal forms of fetal compromise associated with infection, hypoxia, or disrupted patterns of fetal development may be even harder to detect using the hormonal assays currently available.

Progestagens

The pre-partum hormonal changes in the mare are different from those of other large-animal species. In most other species, progesterone (P4) is the dominant progesteragen during pregnancy, and concentrations of P4 decline before spontaneous labor, which suggests that P4 withdrawal is conducive to active labor. In the mare, P4 is produced by the ovaries until days 120–150 of gestation; at that time, the fetoplacental tissues begin to synthesize P4 from the pregnenolone (P5) supplied by the fetal adrenal glands. After days 180–240 of pregnancy, P4 concentrations are negligible in both maternal and fetal circulations. Instead, P4 is metabolized into a number of other progestagens that include saturated pregnanes and unsaturated pregnenes.1,2 In the mare, progestagens other than P4 remain relatively constant until 3 wk pre-partum. After that time, progestagen levels rise gradually before parturition.1,3,4 In particular, the concentration of 5α-pregnane,3,20-dione (5α-DHP), a direct metabolite of P4, increases gradually during the last few weeks of gestation and then declines precipitously within days or hours of delivery.5,6 Interestingly, in human females, 5α-DHP, rather than P4, undergoes a pre-partum decline.7

Commercial radioimmunoassays (RIAs) and enzyme-linked immunosorbent assays (ELISAs) used to measure “progesterone” concentrations in pregnant mares can be used to measure some of these other progesterone metabolites that predominate during late pregnancy. This is possible, because the antibodies used in these assays cross-react with many of the other progestagens, particularly the α-pregnanes. Values may vary between labs because of the different levels of cross-reactivity between the different assay technologies.8,9 Using a validated ELISA, progestagen values reported for mares between 180 and 310 days of gestation range from 2 to 6 ng/ml.10

In healthy, late-term mares, progestagens are produced by the uteroplacental tissues from the precursor, P5, supplied by the fetal adrenals.2,11 Fetal-derived P5 is then converted to P4 by uteroplacental metabolism and secreted into the umbilical circulation or metabolized further to 5α-DHP in the endometrium or other progestagens within the fetus or uteroplacental tissues. At least 10 progestagens have been identified and measured in the late-term mare.1 Seven of these metabolites increase with advancing gestational age, but levels of P4 remain virtually undetectable. Little is known about the biological activity of most of these compounds, although 5α-DHP is known to inhibit myometrial contractility in women.12 It also binds more strongly than P4 to the uterine progesterone receptor in mares.13

During the last week of gestation, an unknown stimulus results in an increase in fetal adrenocorticotropic hormone (ACTH) and the appearance of the enzyme 17α-hydroxylase. This enzyme is responsible for the conversion of progesterone to cortisol.14 This pre-partum surge in fetal cortisol is associated with the initiation of a critical cascade of endocrine events in the fetus that result in readiness for birth and an ability to adapt to extra-uterine life. Cortisol stimulates an increase in the neutrophil:lymphocyte (N:L) ratio and a rise in thyroid hormones that in turn have a positive impact on skeletal muscle tone, body temperature regulation, and glucose homoeostasis. Maturation of the fetal hypothalamic-pituitary-adrenal (PHA) axis is essential for triggering parturition and ensuring the final phase of fetal maturation.

It is appealing to surmise that pregnancies jeopardized by placental anomalies or fetal compromise will have altered concentrations of progestagens because of disrupted or altered metabolic pathways within the feto-placental unit. A number of trials have studied mares with either naturally occurring high-risk pregnancies or with experimentally induced placental disease. Theses studies have documented wide variations in maternal concentrations of plasma progestins including premature elevations and precipitous declines.1,6,10,15,16

Several patterns of progestagen activity during late pregnancy begin to emerge. The worst scenario is a pattern of rapidly declining progestagen concentrations with values approaching zero. In pregnancies complicated by acute fetal distress, there is a dramatic decline in progestagen production, which reemphasized the importance of a healthy feto-placental unit for normal production and metabolism of progestagens.1 Most of these pregnancies were associated with fetal death and abortion. The second pattern is one of precociously elevated levels of nearly all progestagen metabolites that is often associated with bacterial placentitis, enhanced fetal adrenocortical activity, and promising neonatal survival.1,6,10 A few pregnancies compromised by placental anomalies other than
bacterial placentitis, such as placental edema or villous atrophy, exhibited a slightly different pattern. Levels of certain progestagens such as P4 were elevated, but other metabolites, including P5, were decreased, which possibly reflects a lack of functional placenta. A third pattern of progestagen activity occurs when maternal progestins fail to show the normal pre-partum rise. Mares experiencing prolonged gestations because of fescue toxicosis or other causes fall into this category.

Clinical Implications
Progestagen supplementation is a popular, yet controversial, treatment for mares with placentitis and other at-risk pregnancies. Oral altrenogest, a synthetic progestin, has been administered at doses of 0.088 mg/kg once daily to help prevent abortion and premature delivery in mid- to late-term mares. Alternatively and anecdotally, some clinicians prefer using injectable progesterone (300 mg, q 24 h, IM). The author recommends using a short-acting form of progestin supplementation rather than preparations claiming longer duration of action. This allows for daily adjustments in therapy as warranted. It has been the author's experience that mares can deliver live foals as well as abort while receiving oral altrenogest at doses up to 0.044 mg/kg (q 24 h, orally). If mares on progestin supplementation do reach their anticipated foaling dates, then it is recommended to decrease the dose of altrenogest gradually rather than discontinuing therapy abruptly.

Advocates of progestagen supplementation cite its ability to promote uterine quiescence and inhibit prostaglandin-mediated abortion. Anecdotal reports report on the apparent ability of progestagen supplementation to prevent pre-term labor in late gestational mares with placentitis. Critics of such therapy question the benefit of using progestagen supplementation in mares that may already have elevated concentrations of progestone metabolites. Most mares at risk for premature delivery are also receiving other therapy including antibiotics, non-steroidal medication such as flunixin meglumine, and anti-cytokine drugs such as pentoxifylline. Therefore, it is difficult to separate the impact of altrenogest administration from the effects of other concurrently administered medications. Researchers are beginning to provide answers to this dilemma by studying mares with experimentally induced bacterial placentitis and evaluating the impact of administering or withholding altrenogest supplementation as well as other therapeutic agents.

Pre-term birth is a leading cause of neonatal infant morbidity and mortality in the developed world. Progestosterone supplementation has been used in women with a history of pre-term birth since the 1970s. In reviews of multicentric trials, women receiving progesterone were statistically and significantly less likely to experience recurrent miscarriage and prema-

Estrogens
There are two groups of estrogens in the mare: the common phenolic estrogens, estrone and estradiol 17ß, and the ring unsaturated estrogens, equilin and equilenin that are unique to the horse. The fetal gonads provide the precursors that are ultimately converted by the uteroplacental tissues to estrogens. Plasma-estrogen concentrations peak during months 7 and 8 of gestation; this is followed by a gradual decline thereafter, which parallels the rise and fall in the size of fetal gonads. Between days 150 and 280 days of gestation, estrone levels >1000 ng/ml are considered normal, and levels <1000 ng/ml are indicative of fetal stress. Estrone levels <500 ng/ml are associated with severely compromised or dead fetuses. The significance of elevated estrogen concentrations has not received much attention, although higher than normal levels of estradiol-17β have been reported in late-term mares exposed to endophyte-infected tall fescue. Higher than normal concentrations of estradiol-17β may contribute to the agalactia observed in mares suffering from fescue toxicosis.

The role of estrogen in the late-term mare remains uncertain. One frequently referenced study evaluated the effect on pregnancy outcome of removing estrogen precursors by gonadectomizing horse fetuses in mid to late gestation. Mares experienced dramatic decreases in plasma estrogen concentrations accompanied by prolonged, effective labor, decreased prostaglandin production, and the birth of dysmature foals. In other species, estrogen has an effect on uterine contractility and uterine blood flow. Proposed mechanisms of action for estrogen include promoting formation of uterine oxytocin receptors, increasing uterine gap junction formation, and altering uterine blood flow, which may help explain the weak labor in estrogen-deficient mares. Limited studies in late-term mares stressed by medical or surgical disease or induced abortion concluded that maternal serum concentrations of estrone sulfate (ES) were not a sensitive indicator of fetal compromise or death. Maternal ES concentrations declined only after severe fetal stress or abortion had occurred.

Clinical Implications
There are no controlled clinical trials examining the effects of estrogen supplementation in the late gestational mare. Therefore, no specific recommendations regarding the form of estrogen, the dosage, or
the route of administration can be offered for its use in the late-term mare.

Relaxin

In the horse, the peptide hormone relaxin is produced primarily by the placenta. Relaxin promotes uterine and cervical growth and remodeling that is essential for normal fetal growth and parturition. Relaxin decreases the collagen content in the extracellular matrices of the pubic symphysis and cervix, inhibits uterine contractility, and plays a role in mammary gland development. Relaxin has angiogenic and vasodilatory effects on endometrial and mammary tissues. This effect may be mediated through up-regulation of vascular endothelial growth factor (VEGF). The maternal concentration of relaxin begins to increase after day 75 of gestation and peaks at day 175. It remains elevated until day 200 of gestation and then, it declines precipitously post-partum. Low maternal concentrations of relaxin during late gestation have been associated with high-risk pregnancies and complicated deliveries. Some of the periparturient problems associated with low relaxin levels have included premature placental separation, placentalitis, hydrops, symptomatic maternal pituitary neoplasia, oligohydramnios, and fescue toxicosis.

Clinical Implications

Currently, there are no commercially available assays for equine relaxin. Perhaps with the recent production of recombinant equine prorelaxin, there will be new research reevaluating relaxin as a marker of uteroplacental function in the mare.

Domperidone, Fescue Toxicosis, and Post-Term Pregnancy

As a dopamine receptor antagonist, domperidone represents an interesting therapeutic intervention to treat fescue toxicosis and potentially other periparturient complications involving prolonged gestation and agalactia in the mare and lack of readiness for birth in the foal. Fescue toxicosis is an intriguing model of maternal and fetal disease. In the mare, it is characterized by a lack of readiness for parturition that leads to prolonged gestation, abortion, dystocia, and agalactia accompanied by placental abnormalities that include premature placental separation, thickening, and edema. In the foal, the lack of readiness for birth is associated with an increased incidence of sepsis, peripartum asphyxia syndrome, failure of passive transfer, and dysmaturity or failure “to adapt” after delivery. Late-term mares grazing endophyte-infected tall fescue show decreased concentrations of prolactin and relaxin and fail to exhibit the normal late gestational surge in progestins. Late-term mares grazing endophyte-infected tall fescue show decreased concentrations of prolactin and relaxin and fail to exhibit the normal late gestational surge in progestins. Some studies report increased levels of estrogens and decreased levels of thyroxine (T3) in exposed mares. Foals exposed to ergopeptide alkaloids in late gestation have decreased plasma levels of immunoassayable progestins, cortisol, T4, and tri-iodothyronine (T3).

Insight into the pathophysiology of this condition may help improve our understanding of endocrine events associated with other causes of prolonged gestation and lack of readiness for delivery in the mare and maladaptation/dysmaturity in the foal. Some of the specific therapies used to ameliorate the endocrine abnormalities and clinical signs of fescue toxicity may find application in other periparturient conditions.

Ergopeptide alkaloids are the predominant toxins associated with fescue toxicosis and are believed to cause the impaired reproductive function and agalactia through stimulation of D2-dopamine receptors. Dopaminergic stimulation results in decreased prolactin secretion. Prolactin plays an active role in the endocrine regulation of steroidogenesis and lactogenesis. The initiation of parturition in the mare involves proper maturation and function of the fetal hypothalamic-pituitary-adrenal (HPA) axis. Prolonged gestation length associated with fescue toxicosis may be caused by hypoprolactinemia-induced changes in uterofoetalplacental steroid metabolism or inhibition of D2-dopamine receptors on corticotrophs in the fetal anterior pituitary gland.

The ideal management strategy for mares consuming infected tall fescue is strategic withdrawal of mares from infected pasture or hay 60–90 days prepartum. If this is not possible or practical, the administration of D2-dopamine receptor antagonists including domperidone (1.1 mg/kg, q 24 h, orally), sulpiride (3.3 mg/kg, q 24 h, orally), or perphenazine (0.3–0.5 mg/kg, q 12 h, orally) have been used successfully, beginning on day 300 of gestation, to prevent the endocrine alterations and clinical signs of fescue toxicosis in late-term mares. Unlike the other D2 antagonists, domperidone does not cross the blood-brain barrier.

Domperidone (1.1 mg/kg, q 12–24 h, PO) has also enjoyed success in treating post-partum mares suffering from agalactia not caused by fescue toxicosis. A treatment protocol to induce non-pregnant mares to lactate and become foster dams for orphan foals also incorporates the use of domperidone. The regimen consists of a minimum 7-day course of domperidone (1.1 mg/kg, q 24 h, PO), altrenogest (44 mg, q 24 h, PO), and estradiol-benzoate-in-oil (10 mg, q 24 h, IM). In the author’s experience, this protocol has been used effectively to treat certain post-partum mares that are rejecting their foals and showing varying degrees of agalactia.

Another poorly characterized syndrome in the mare is prolonged gestation length not caused by obvious fescue toxicosis. There are benign causes that are usually associated with normal parturition and the birth of a healthy foal of average size. Explanations include human error and miscalculation of the foaling date based on an inaccurate breeding date. Prolonged gestation has also been
attributed to delayed embryonic development, especially during the first 2 mo.\textsuperscript{47} Duration of gestation is partly controlled by nutrition and genotype of the foal.\textsuperscript{48,49} Colts tend to have longer gestation lengths than fillies. Mares due to foal earlier in the year may have longer gestation lengths as a result of the shorter photoperiod. Older mares tend to have longer gestations.\textsuperscript{50} However, the mare’s reported range of “normal” gestation lengths is quite elastic, and some references describe normal pregnancies that endure for up to 374 days or longer.\textsuperscript{47,48} Therefore, it is difficult to define what constitutes a post-term pregnancy by days of gestation alone.

In the mare, there seems to be three types of foals associated with prolonged gestations: (1) foals that are normal in size and adaptation, (2) large “post-mature” foals that are thin with long hair coats, ineffective suckle reflexes, erupted incisors, poor muscle development, and overgrown hooves with or without concurrent limb contracture, and (3) small, dysmature foals that are thin with weak suckle reflexes, underdeveloped musculature, short, fine hair coats, periarticular laxity, and varying degrees of incomplete ossification. Dysmature and post-mature foals may exhibit poor thermoregulation, gastrointestinal dysfunction, glucose instability, renal immaturity, and other endocrine abnormalities. Some of these individuals may be stillborn. In western Canada, prolonged gestations have been associated with the birth of foals suffering from congenital hypothyroidism, dysmaturity, and a variety of musculoskeletal lesions including mandibular hypoplasia, forelimb contracture, rupture of the common digital extensor tendons, and incompletely ossified cuboidal bones.\textsuperscript{51,52} Affected mares have significantly longer gestation lengths, and \textasciitilde 25\% of these mares experience premature lactation and dystocia.\textsuperscript{51}

Post-term pregnancies in female humans have been associated with two types of outcomes: (1) an aging placenta and “post-mature” fetus that continues to grow in utero and is unusually large but thin at birth, and (2) an unfavorable uterine environment and placental insufficiency associated with the birth of a small, dysmature infant suffering from in utero growth retardation (IUGR).\textsuperscript{53} Both post-mature and dysmature infants are at increased risk for perinatal morbidity and mortality. Many post-term human pregnancies are complicated by decreased amniotic fluid volume (oligohydramnios)\textsuperscript{54} and meconium staining/aspiration. Management strategies vary for human females with prolonged pregnancies exceeding 42 wk, but induced delivery is often pursued if gestation dates are accurate and there is a favorable cervix.\textsuperscript{55} If gestation dates are uncertain or there is lack of cervical ripening, then management strategies vary and often focus on continued fetal surveillance using biophysical scoring, evaluation of fetal activity and heart rate acceleration in response to fetal movement, and uterine contractions.\textsuperscript{53} More recently, with the use of prostaglandin E (PGE) to induce cervical relaxation, more aggressive management of post-term pregnancies has been recommended.

In cattle, fetal adenohypophyseal aplasia has been associated with prolonged gestation in the cow and skeletal immaturity in the calf.\textsuperscript{56} In this case, the absence of fetal cortisol secretion as the endocrine trigger to initiate parturition is the proposed mechanism for prolonged gestation. Other cases of prolonged gestation in cattle have been ascribed to fetal adrenocortical hypoplasia and primary fetal adrenal insufficiency, both of which are associated with glucocorticoid deficiency.\textsuperscript{57}

Using the diagnostic tools available to us, more of these post-term equine pregnancies should, at the very least, be evaluated. Transrectal and/or transabdominal ultrasound can be used to assess fetal size and activity, fetal heart rate reactivity in response to fetal movement, placental thickness and integrity, and quality and quantity of fetal fluids. Maternal hormone concentrations, including progestins, estrogen, and possibly prolactin and relaxin, can be monitored, and electrolyte profiles in mammary secretions can be evaluated using commercially available milk or water-hardness test kits. A multiparous mare, with an uneventful past history of normal pregnancies, can serve as her own control. If she begins to exceed previous gestation lengths by more than several weeks, reevaluation of the pregnancy is justified, especially if there are other concerning signs such as agalactia.

A mare with a post-term pregnancy associated with a large fetus, agalactia, low maternal progesterin levels, or unfavorable milk electrolyte profile would be a candidate for domperidone therapy based on the suspicion that there is a lack of the normal stimulus for parturition and fetal maturation as is reported with fescue toxicosis. In the author’s experience, this category of mare has responded favorably to domperidone therapy with udder development, cervical relaxation, and spontaneous delivery of a viable foal. Little is known about the cause of many prolonged equine pregnancies, because they are not investigated and are simply allowed to take their own course; many end in neonatal demise of undetermined cause.

3. Biophysical Parameters

Transrectal and Transabdominal Ultrasonography

This topic is covered in detail in presentations\textsuperscript{58} and other review articles.\textsuperscript{59,60}

Doppler Velocimetry

Another diagnostic tool that has had minimal application in the pregnant mare is Doppler velocimetry.\textsuperscript{61} This technique is used in women to examine fetoplacental circulation in an attempt to identify pregnancies at risk for fetal IUGR and maternal toxemia. Using a hand-held Doppler transducer, umbilical and uterine arteries can be
evaluated and displayed as wave forms. Different vessels have different wave-form profiles based on the dynamics of blood flow during systole and diastole. To evaluate relative flow velocity and placental perfusion, the systolic to diastolic ratio (S/D) in the umbilical and uterine vessels is measured. In normal pregnancies, the S/D ratio decreases; advancing gestation reflects decreasing placental vascular resistance and increasing umbilical blood flow required by the growing fetus. McGladdery et al.\(^7\) used this technique to examine a small group of pregnant pony mares. Preliminary results showed a similar decline in S/D ratio with advancing gestation.\(^6\)

Umbilical and uterine circulations are high-flow, low-resistance systems, and their wave forms are characterized by a persistent diastolic component. Disappearance of flow during diastole is abnormal and indicates increasing vascular resistance. Changes in flow dynamics may proceed for many weeks until changes in fetal wellbeing are detected by transabdominal ultrasonography. Increases in placental vascular resistance have been associated with infants suffering from IUGR or small size for gestational age as well as maternal hypertension, toxemia, and other perinatal complications.\(^32-44\) Doppler velocimetry has also been used to evaluate the effect of various treatment strategies, including low-dose aspirin therapy, to improve uteroplacental perfusion by reducing vascular resistance. This technique still offers promise for clinical application in equine perinatology.

Placental Function
The placenta is more than just a blue print of the intrauterine environment. It is a dynamic organ in its own right. It has long been appreciated as the gatekeeper of nutrient delivery and oxygen exchange throughout pregnancy, but it also synthesizes a number of hormones, including steroids, peptides, glycoproteins, and eicosanoids. The placenta also inactivates other hormones such as catecholamines, glucocorticoids, thyroxine, and prostaglandins. In the horse, the growth of the placental exchange surface is controlled by both the maternal and fetal genome.\(^65\) When the genetic potential for placental growth is constrained (illustrated when a horse fetus is placed in a smaller surface density of microcotyledons in a pony mare uterus), the chorionic villi elongate, which increases the total surface area of fetomaternal contact. This results in a larger fetus than would be produced by a pony genotype within a pony uterus.\(^66\) However, very little is known about the factors that regulate placental growth or the critical windows in gestation when placental structure and function can be modified by interventional therapies.

The equine placenta is 5–7 times more efficient in nutrient transfer per unit area than either the cow or sheep placenta.\(^67\) This may be attributed to the countercurrent blood-flow exchange mechanism in the equine placenta. The high transplacental glucose gradient that exists between dam and fetus across the equine placenta results in efficient glucose transfer between mare and fetus.\(^66,68\) Oxygen exchange between maternal and fetal circulations is also very effective.\(^66,69\)

Fasting of the late-term mare for 12–30 h has been shown to increase production of uterine prostaglandin F metabolites (PGFM). Likewise, refeeding or infusion of glucose produces a rise in plasma glucose and immediate fall in uterine PGFM concentrations. This fasting-induced surge in PGFM was greatest in late-gestational mares. In one study, five of eight fasted mares delivered prematurely within 1 wk of the period of food withdrawal.\(^70\)

Clinical Implications
Hypoglycemia in the pregnant mare can adversely affect placental metabolism and glucose delivery to the fetus. Late-term mares that must be fasted, as is often prescribed after abdominal surgery, should be maintained on glucose infusions to prevent hypoglycemia and to reduce the risk of prostaglandin-mediated pre-term labor. IV infusions of 2.5% or 5.0% dextrose in 0.45% saline administered at fluid rates of 1–2 mg/kg/min of dextrose are recommended. Pregnant mares that are anorexic because of systemic illness should be supplemented through nasogastric intubation or through parental nutrition to prevent a similar cascade of prostaglandin-mediated events.

Oxygen therapy for pregnant mares with compromised placental function has been advocated to reduce the risk of fetal hypoxia before and during parturition. Effective oxygen administration using intranasal insufflation and oxygen flow rates of 10–15 l/min has been documented.\(^71,72\)

Parturition
Delivery is divided into three stages. Stage I is variable in length and associated with subtle clinical signs in the mare that include restlessness, nesting, frequent urination and defecation, loss of appetite, and separation from the herd. It is associated with the critical but under appreciated period of fetal repositioning in preparation for delivery. Stage II labor commences with the rupture of the allantochorion at the cervical pole. It is short in duration and is characterized by strong uterine contractions. Stage III labor is associated with milder post-partum uterine contractions and the passage of the fetal membranes.

In a study using direct radiography to monitor the position, posture, and presentation of the equine fetus during late gestation and delivery,\(^73\) the important sequence of events during stage I was clearly shown. During naturally occurring stage I labor, the full-term fetus undergoes purposeful movements to rotate the head and forelimbs into the dorsal position; this is followed by extension of the forelimbs and neck into the pelvic canal. The stimulus for initiation of these movements is not known.
Given the relatively low incidence of dystocia in spontaneously foaling mares, the mechanism that controls this in utero fetal “dance” is normally quite efficient. The increased incidence of dystocia and premature placental separation associated with various methods of induction\textsuperscript{74–76} stresses the importance of limiting chemical induction of the mare to a select group of periparturient emergencies.

The optimal dose of oxytocin and route of administration for induction remains controversial. Some researchers and clinicians believe that the use of low doses of oxytocin are more physiologic and less likely to induce untoward delivery complications.\textsuperscript{77,78}

Clinical Implications

Whenever possible, induction should only be undertaken in late-term mares that are close to their own physiologic foaling dates. Indications for induction should be limited to conditions that would seriously threaten maternal or fetal health if the pregnancy were allowed to continue or if unsupervised, spontaneous delivery would occur. Examples of such conditions include hydropros, pre-pubic tendon rupture, imminent death of the mare because of colic or other systemic illness, and maternal history of severe dystocia requiring mandatory assistance during delivery. Criteria used to assess readiness to foal include normal udder development, the presence of colostrum in the teats, a favorable electrolyte profile in pre-partum mammary secretions,\textsuperscript{79} and a dilated or softening cervix.

Pre-foaling mammary secretion electrolytes are related to fetal readiness for birth in normal pregnancies.\textsuperscript{80} Calcium concentration increases were accompanied by an inversion of sodium and potassium concentrations.\textsuperscript{81} Mature, term foals are accompanied by an inversion of sodium and potassium concentrations alone are commercially available. \textsuperscript{c,d} Mares with precocious udder development and lactation because of placentalitis may have early, and misleading, elevation of mammary secretion calcium concentration.\textsuperscript{82}

The optimal dose of oxytocin and route of administration for induction remains controversial.\textsuperscript{74–76,78,81,83} Some researchers and clinicians promote the use of low doses of oxytocin (2.5–5.0 IU, q 15–30 min, IV) as being more physiologic and less likely to induce untoward delivery complications.\textsuperscript{77,79} Some clinicians advocate a continuous infusion of oxytocin at a rate of 1 IU/min. Maintaining a continuous infusion can be problematic in some mares that pace and roll during stage I labor. Regardless of the oxytocin method selected, induced deliveries are associated with an increased risk of delivery complications including premature placental separation and dystocia. If induction is imperative and the cervix is unfavorable, topical instillation of prostaglandin E2 gel to the cervix should be considered. Intra-cervical application of prostaglandin E2 has been used in female humans\textsuperscript{84} and mares\textsuperscript{85} to induce cervical ripening before induction of parturition.

If medical conditions warrant induction or if premature delivery seems imminent despite therapy, then the delivery of the foal becomes the next focus of therapy. Fetal organ maturation is regulated by the HPA axis, and a rise in fetal plasma cortisol concentrations usually occurs during the last 2–3 days before delivery.\textsuperscript{86} Administration of ACTH directly to the equine fetus in utero promotes precocious fetal maturation and early delivery but is too invasive a technique to use safely in practice.\textsuperscript{87} ACTH administration to late-term mares stimulated fetal maturation in some but not all mares.\textsuperscript{88} In 1975, Alm et al.\textsuperscript{89} used high doses of dexamethasone (100 mg, q 24 h, IM for 4 days) to induce mares to foal. Maternal glucocorticoid administration significantly reduced gestation length and resulted in the birth of foals that were small but reportedly mature. Another study performed using the same pre-partum dose of steroids resulted in dystocia and fetal death.\textsuperscript{74} Anecdotal reports from clinical practice suggest that varying doses of dexamethasone administered pre-partum to mares resulted in improved fetal survival. Evaluation of the potential benefits of maternal steroid therapy was revisited recently by Ousey et al.\textsuperscript{90} Five Thoroughbred mares received 100 mg of dexamethasone one time daily from 315 to 317 days of gestation. Dexamethasone-treated mares delivered significantly earlier than control mares. Duration of second- and third-stage labor did not differ between treated and control mares. One steroid-treated mare experienced premature placental separation, but the alantochorion ruptured spontaneously before manual intervention. All of the foals seemed healthy and mature and exhibited normal post-partum behavior. Steroid-treated mares had poorer quality colostrum at the time of delivery, and four foals in the treated group required colostrum supplementation.

Administration of dexamethasone to pre-partum mares remains an attractive and inexpensive method of inducing precocious fetal development. However, caution is urged before using this therapy. The number of mares treated under controlled conditions has been small, and the few studies examining this induction strategy have differed in their results. The optimal dose of dexamethasone and the frequency and timing of administration require further research. In particular, the time of gestation at which this therapy is initiated may be critical in terms of fetal endocrine development and response to treatment. Antenatal steroid administration has been used in human females at risk for premature delivery, and its use remains controversial.

The Placenta

The mare should pass her placenta within 3 h of delivery. A normal placenta weighs ~10–11% of the foal’s birth weight. Heavier than normal fetal
membranes may be caused by edema associated with placentitis and/or insufficiency. Detailed reviews of the systematic examination of the equine placenta are presented elsewhere.91–95 If placental pathology or dysfunction is suspected, tissue samples should be submitted for histopathology from representative areas of the chorionallantois, including the fetal and non-fetal horns, body of the placenta, cervical star, umbilical cord, and amnion. Pathological lesions that might be missed on gross inspection alone include hypoplastic or atrophic changes in the microcotyledons associated with placental insufficiency, acute bacterial placentitis, and Equine Herpes Virus 1 (EHV-1)-induced vascular changes.

Umbilical cord anomalies may be overlooked but can contribute to fetoplacental compromise. Average cord length in Thoroughbreds is between 36 and 83 cm.94 Unusually long cords (>80 cm) have been associated with hypoperfusion of the allantochorion. They may be prone to cord torsion, which may contribute to fetal strangulation, hypoxia, death, and abortion.94,96,97 Excessively short cords place increased traction on the placenta during delivery and may predispose the mare to premature placental separation.

Clinical Implications
Clients and foaling attendants should be trained to save and weigh the placenta. Unusually heavy or light placentas are a reason to prompt an earlier than normal veterinary examination of the foal and fetal membranes. Heavy placentas may be associated with edema, congestion, and/or infection, and they may increase the risk of sepsis and hypoxic-ischemic encephalopathy in the neonate. A thin, light placenta often corresponds to villous atrophy or hypoplasia, and it may be associated with smaller than normal foals with increased susceptibility to metabolic and endocrine instabilities during early post-natal life.

Late Pregnancy and Immunosuppression
Because of the stress and/or immunosuppressive effects of pregnancy, late-term mares may be at increased risk to experience recrudescence of EHV-1 infection with subsequent abortion and/or to begin nasal shedding of Streptococcus equi or fecal shedding of Salmonella sp if they are inapparent carriers of these pathogens. Pregnant mares also show inconsistent or unpredictable immune responses when immunized for the first time against novel antigens that they have never been exposed to either by natural infection or previous vaccination.

Clinical Implications
Pregnant mares should be maintained on a regular vaccination schedule against EHV-1 during months 5, 7, and 9 of pregnancy and should be protected from unnecessary stress, such as shipping or showing, during late pregnancy. They should be regarded as possible sources of infectious diseases should unexplained cases of strangles infection, EHV-1 abortion, or Salmonella diarrhea show up on a breeding farm or other facility where pregnant mares are in residence. All incoming mares should be quarantined for a minimum of 21–28 days, and they should be monitored for signs of fever and infectious diseases before allowing them entry into the resident mare population.

If mares have never been vaccinated against rabies, it is recommended that they receive their initial priming dose pre-breeding rather than during pregnancy to ensure a consistent immune response.

Other selected therapies used in late-term mares with complicated pregnancies are presented in Table 1.

The Newborn Foal
Healthy full-term foals are precocious neonates that have an effective suckle reflex and can sit sternal within 20 min of birth. Tactile stimulation inside the pinnae or inside the nares should elicit a vigorous attempt at avoidance with an ear twitch and grimace, respectively. Immediately post-partum, the foal’s heart rate is relatively slow at 50–60 beats/min, but then, it rises steadily to >100 beats/min within the first 1 h. The neonate’s respiratory rate is rapid, shallow, and >50–60 breaths/min, because the lungs that were filled with amniotic fluid only minutes before are now being expanded. Body temperature should stabilize between 99°F and 102°F. Most foals should be standing within 1 h and nursing from the udder within 2 h of delivery. Thereafter, they should remain bright and inquisitive when approached and be able to return to the udder to nurse consistently.

Clinical Implications
Clients and foaling attendants should be familiar with the above sequence of post-partum events. Foals suffering from in utero sepsis, periparturient asphyxia, serious forms of dysmaturity, or a variety of congenital musculoskeletal disorders will often deviate from this simple, but important, behavioral time line. If this occurs, a veterinarian should be contacted, and a complete examination should be performed on the foal, placenta, and mare as soon as possible.

Colostrum and Passive Immunity
Colostrum ingestion is critical not only for passive transfer of IgG but for many other reasons. Colostrum is a rich source of calories, vitamins A and E, white blood cells, cytokines, growth factors, and other hormones and enzymes.98,99 Laxative properties have also been ascribed to its ingestion. The predominant immunoglobulins in equine colostrum are IgG(T), IgGa, and IgGb, and there are lesser amounts of IgM and IgA in colostrum. At parturition, normal colostrum should have an IgG concentration of >3000 mg/dl. The colostral IgG
concentration may exceed 9000 mg/dl in some mares. However, colostral immunoglobulin concentrations may decline rapidly to negligible levels within 12 h of delivery in mares that are being nursed regularly by healthy foals. The ability of the newborn foal’s intestinal tract to non-selectively absorb these large immunoglobulins peaks immediately after delivery and decreases dramatically within the first 3–6 h of life. Absorptive efficiency is only 22% within 3 h of delivery. Maternally derived antibodies can be detected in foal blood within 6 h of colostrum ingestion.

Healthy foals consuming adequate amounts of good-quality colostrum should have serum IgG concentrations of 800–1200 mg/dl by 12–24 h of age. Failure of the foal to ingest or absorb adequate colostral immunoglobulins is termed failure of passive transfer (FPT). A foal with FPT is defined as a foal with a serum IgG concentration of <400 mg/dl at 24 h of age. Partial FPT is defined as a foal with a serum concentration between 400 and 800 mg/dl. The reported incidence of complete or partial FPT in foals varies from 3% to 37.8%.

Clinical Implications
Colostral quality can be evaluated immediately after delivery by measuring specific gravity using a colostrometer or by measuring refractive index using a sugar refractometer. Poor-quality colostrum may be caused by a variety of factors including premature lactation, poor maternal immune or nutritional status, exposure to endophyte-infected pasture, advancing maternal age, and breed. If poor-quality colostrum is detected, an alternate source of colostrum can be administered in a timely fashion.

Radioimmunoassay (RIA) has long been considered the gold standard used to measure and validate IgG concentration. The disadvantage is that the test requires 18–24 h to obtain results. A variety of screening tests are available to measure serum IgG in foals. These tests include glutaraldehyde coagulation, zinc sulfate turbidity, and semiquantitive ELISA. For a more complete discussion of FPT, the diagnostic tests available, and recommended therapies, the reader is referred to several excellent review articles. Many veterinarians prefer to use commercial kits based on either glutaraldehyde coagulation or ELISA. In a recent comparison of glutaraldehyde coagulation and ELISA, both tests were appropriate screening tests with high sensitivity and negative predictive value. However, the ELISA was better than the glutaraldehyde coagulation in specificity and positive predictive value, meaning that foals with FPT were correctly identified. Therapy for FPT includes colostrum administration if the foal has normal gut function and is still young enough to absorb colostral antibodies. Older foals and those neonates with compromised gastrointestinal tracts benefit from plasma administration.

4. Conclusion
Equine perinatology has evolved rapidly over the last two decades. However, most mares will con-
References and Footnotes

IN-DEPTH: PERINATOLOGY—END OF PREGNANCY THROUGH BEGINNING OF LIFE


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