Equine Pregnancy and Clinical Applied Physiology

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1. Introduction
The ability to produce a viable foal is critical to the brood mare. Maintenance of pregnancy entails almost a year of physiological “work” on the part of the gravid mare. This article reviews the physiology of pregnancy and applies it in the veterinary management of the mare.

2. Basics of the Endocrinology of Normal Pregnancy, From Ovulation to Parturition
An understanding of the endocrinology of equine pregnancy is helpful when considering administration of supplemental hormones to pregnant mares. We will begin with a basic review and continue on to applying this information in practical therapeutic situations.

Progesterone begins to rise after ovulation in diestrus, irrespective of pregnancy status, with the development of the corpus luteum (CL). This initial rise of progesterone is approximately linear over the first several days; by day 5 after ovulation, serum progesterone is up to approximately 4 ng/mL. If the mare is pregnant, progesterone produced by this CL (or corpora lutea if the mare has double-ovulated) maintains the pregnancy. This CL is called the primary CL of pregnancy. Early progesterone secretion is essentially the same, irrespective of whether the mare is pregnant or is in diestrus. If pregnant, luteolysis does not occur as it would in the nonpregnant mare, and this primary CL is maintained and continues to secrete progesterone. Ginther has termed these two phases of progesterone secretion by the primary CL as “output D” and “output 1,” for diestrous production and first luteal response of pregnancy.

Embryo migration between days 11 to 15 is necessary for maternal recognition of pregnancy, which keeps the early pregnant mare from returning to estrus. The signal for maternal recognition of pregnancy is poorly understood in the mare, but embryo migration within the uterus is clearly required. At day 16 or 17 after ovulation, the mobile embryo stops migrating within the uterus, and fixation, normally at the base of one of the uterine horns, occurs. Fixation is thought to be caused by a combination of increasing embryo size (diameter) as well as increased uterine tone, possibly caused by estrogen secreted by the embryo. Maternal recognition of pregnancy by the equine uterus prevents prostaglandin release by the endometrium, thus allowing the continued function of the primary CL. Interestingly, by approximately day 30, progesterone production from the primary CL decreases, resulting in somewhat lower circulating serum progesterone.
concentrations. Progesterone as low as 2.5 ng/mL can even be seen at this stage of normal pregnancy, although somewhat higher concentrations between 4 and 10 ng/mL are often considered the “normal range” for the first trimester. ^3 Fluctuations in peripheral progesterone levels have been shown to occur throughout the day, though not with a specific diurnal pattern. ^5

In the pregnant mare, unique structures known as the endometrial cups form by approximately day 35 after ovulation. ^1 The cells that form the basis of the endometrial cups are from the embryo, specifically from the trophoblast chorionic girdle. These embryonic cells invade the maternal endometrium in a ring-like fashion around the developing umbilicus at the base of the uterine horn. There may be as many as 30 or more grossly visible, small, raised, whitish endometrial cups on the endometrial surface. The embryonic cup cells produce a hormone called equine chorionic gonadotropin (eCG), formerly known as pregnant mare’s serum gonadotropin. This hormone is first detectable systemically between days 35 to 40 of pregnancy. The cups are mature and robustly secreting eCG at approximately days 50 to 60, but they will subsequently undergo sloughing by days 100 to 150 in most mares. This hormone is stimulatory to the ovary and causes follicular development, followed by either ovulation or luteinization (without ovulation) of these follicles. New luteal structures, called supplementary corpora lutea, are thus produced. As the result of the increased number of corpora lutea now present on the ovaries, systemic progesterone rises. The primary CL is also stimulated by eCG; therefore it remains active and secretes even more progesterone as well. This resurgence phase of progesterone secretion by the primary CL is termed the “secondary luteal phase” or “output 2,” whereas the production by supplementary corpora lutea is termed the “third luteal phase” or “output 3.” ^1

To summarize, progesterone rises after ovulation (diestrous phase) as the result of the primary CL. Because of maternal recognition of pregnancy, the primary CL does not undergo luteolysis but continues to secrete progesterone after day 14 of diestrus (first luteal phase). Subsequent to the stimulation by eCG, the primary CL increases production (second luteal phase), combined with production from the supplementary corpora lutea (third luteal phase). ^1,4

Progesterone from ovarian sources is required for early pregnancy maintenance to day 45. If pregnant mares are ovariectomized between days 50 to 70, many but not all will abort. It is during this stage that the feto-placental unit begins taking over the role of pregnancy maintenance by ramping up its progesterone production. The production of feto-placental estrogens also begins at this time. ^1,2

The corpora lutea continue to produce large quantities of progesterone, with high systemic concentrations (approximately 10–15 ng/mL) peaking at approximately 60 to 120 days of gestation; they are active until regression begins at approximately 150 to 180 days after ovulation. Actual progesterone is quite low in the pregnant mare after approximately 180 days of gestation. By this time, the feto-placental unit has taken over the production of all progestogens. The term “progestogen” means progesterone-like substances or metabolites. The term “progestin” is also often used in a similar fashion, or “progestin” may be reserved for medications having progesterone-like function. All ovarian luteal structures will regress by approximately 200 days of gestation. ^1,2

Feto-placental progestogens, especially 5-α-pregnanes, are detectable in maternal serum/plasma by 60 days of gestation when measured by means of advanced laboratory techniques (gas chromatography/mass spectrometry, which are not commercially available). ^3 The substrate for these progestogens is maternal cholesterol. Cholesterol is metabolized to pregnenolone (P5) and then to 5-α-pregnanes and other progestogens. The sites of progestogen conversion include utero-placental tissues as well as the fetal gonads and adrenals. It is thought that the fetal adrenals play a critical role in progestogen metabolism through their production of P5. Total progestogen concentrations are relatively high in the second and third trimesters; they will then increase dramatically during the last few weeks of gestation and peak in the last days of gestation, only to drop precipitously near term. ^1,2

Although sometimes overlooked, estrogen plays an endocrinological role in early pregnancy. The embryo produces small amounts of locally active estrogens. However, it is not until approximately day 35 that systemic estrogen rises. The source of this estrogen is the ovary, more specifically, the corpora lutea and possibly follicles. The stimulation of the ovaries by eCG is responsible for the timing of this increase in estrogen. It appears that estrogen is not actually necessary for pregnancy maintenance, because ovariectomized mares administered only exogenous progestins will maintain pregnancy without the administration of estrogens. ^1,2

At approximately 80 days of gestation, the feto-placental unit increases the production of estrone, estradiol-17β, estradiol-17α, and the equine-specific estrogens equilin and equilenin. The gonads of both male and female fetuses produce estrogen precursors, such as dehydroepiandrosterone, which are then metabolized at the level of the placenta into the various estrogenic hormones. The fetal gonads are grossly hypertrophied during gestation when large quantities of these estrogen precursors are being made. High levels of these estrogenic compounds will be present throughout much of the remainder of pregnancy, decreasing only in the last 2 to 3 months of gestation. These estrogens are postulated to increase blood flow to the fetal compartment and to promote uterine tonicity. ^1,2

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To summarize, during the second and third trimesters, the feto-placental compartment produces large amounts of progestogens and estrogens. Hormone production occurs through the teamwork of fetal adrenals and gonads as well as the placental tissues. Total estrogens gradually decline during the last trimester. Total progestogens continue to rise and increase greatly during the last several weeks of gestation, finally peaking before parturition.8,9

The equine mechanism of parturition is not completely understood, but general concepts have been elucidated and reviewed.8,9 As discussed above, high progestogens and low total estrogens are the hormone milieu of late gestation. With the rapid fetal growth of late gestation, the uterus becomes “stressed” by physical stretch, making the myometrium more contractile. The effect of stretch is “stressed” by physical stretch, making the myometrium more contractile. The effect of stretch is thought to be countered by the high and increasing progestogens that characterize late gestation. The high progestogens are necessary for continued uterine quiescence until just before the time of parturition. These progestogens promote enzymes that inactivate prostaglandins, thus “blocking” their ecbolic (contractile) effects.8,9

At the end of gestation, a dramatic change in the hormonal milieu occurs, and progestogens fall precipitously. This drop coincides with maturation of the equine fetal hypothalamic-pituitary-adrenal axis, which occurs very late in gestation and is necessary for the fetus to signal its preparedness for parturition. As noted above, equine fetal adrenals produce the precursor P5, which is metabolized by the placenta to progestogens. As fetal adrenocorticotrophic hormone (ACTH) rises, adrenal enzymatic pathways are modified, and concomitantly the fetal adrenal decreases P5 production and instead produces cortisol. Thus, less fetal adrenal P5 substrate is produced and progestogens fall, normally occurring as late as 1 to 2 days before parturition.8,9

We think of corticosteroids as being anti-inflammatory; however, in the late-term fetus, the recently produced fetal cortisol activates enzymes that actually synthesize more prostaglandins. As the degree of progestogen “block” falls, prostaglandins continue to rise and myometrial contractions begin to occur. In association with periods of evening myometrial contractions, estradiol-17β rises at night in the week before parturition. This estrogen increases uterine responsiveness to prostaglandins and may even promote further prostaglandin production. Finally, the neuroendocrine Ferguson reflex, resulting from fetal distention of the cervix and vagina, causes large amounts of oxytocin release. Oxytocin and prostaglandin peak with rupture of the choriovalli ("water breaking") and expulsion of the fetus.8,9

3. Evidence-Based Applied Endocrinology and Practical Therapeutics

Progestogen supplementation can be used as treatment for early-bred or known pregnant mares if the mare’s endogenous progesterone production is suspected of being low.10 For instance, altrenogest or natural progesterone may be administered beginning in early diestrus (commonly at or after day 5 after ovulation, theoretically not to have the treatment interfere with embryonic passage through the oviduct). Ovariectomy studies with the use of progestosterone supplementation have shown that serum progesterone concentrations of 2 ng/mL were considered the minimum endogenous amount necessary to support pregnancy. In addition, when concentrations above 4.0 ng/mL were maintained consistently, no study mares aborted.11 Note that altrenogest does not cross-react with progesterone assays; therefore endogenous progesterone production may be monitored while mares are supplemented with this product.12 A commercial altrenogest assay to determine circulating altrenogest levels is not readily available. If supplementing with a parenteral natural progesterone, a serum progesterone determination will show the cumulative effect of both the exogenously administered product and endogenous production by the mare.13

Little research has addressed the question of whether altrenogest administration suppresses endogenous progesterone production. Two studies, one in earlier gestation12 and one in late gestation,13 concluded that altrenogest administration did not suppress endogenous progesterone production.12,13 When eight mares were administered 22 mg of altrenogest orally daily from day 40 to 105 of gestation, no changes in serum progesterone were identified when compared with the eight control mares.12 In this study, progesterone was not monitored daily but only on days 40 to 46, 69 to 75, and 99 to 105 of gestation.12 On the other hand, a recent study14 that evaluated the effects of nonsurgical embryo transfer and altrenogest administration on serum progesterone concentrations found lower progesterone in altrenogest-treated mares. Altrenogest, 19.8 mg, was administered orally from days 6 to 21 after ovulation. In nonpregnant, sham embryo–transferred mares, progesterone was lower at postovulatory days 10, 12, and 13 in the eight mares administered altrenogest, when compared with the eight similar sham controls. In early pregnant mares (that did not have sham or actual embryo transfers performed), progesterone was lower at days 14 to 18 and 21 in the eight altrenogest-treated mares compared with the eight control pregnant mares.14 The researchers speculated that the altrenogest may be feeding back negatively at the level of the pituitary, with subsequent decrease in luteinizing hormone release.14 The first study12 was performed during the period of endometrial cup secretion of eCG, a luteotropic hormone, whereas the recent study was performed at stages without eCG support.14 Thus, the specific hormonal milieu at 40 to 105 days of gestation may have stimulated enough endogenous progesterone production to minimize any potential negative...
feedback effects of altrenogest. Often, when discontinuing altrenogest treatment, veterinarians will gradually lower, over a week or so, the daily altrenogest dose administered before its complete cessation. The theory behind this “weaning” practice is that it will allow time for the gravid mare’s endogenous endocrine systems to gradually adapt to altrenogest withdrawal.

Endotoxin experiments provided good evidence for the practical use of altrenogest supplementation during early pregnancy, before formation of endometrial cups, in the mare. Endotoxin stimulates endogenous prostaglandin release, thus causing luteolysis, with resulting pregnancy loss. Mares between 21 to 35 days of pregnancy were administered systemic endotoxin. All seven mares that were concomitantly administered 44 mg of altrenogest orally once daily until day 70 maintained their pregnancies. In mares that were administered altrenogest only to day 40 of gestation, six of seven mares had fetal death within 4 days of altrenogest cessation. Thus, altrenogest administered at the time of insult could maintain early pregnancy despite a toxic insult and subsequent luteolysis. In addition, the altrenogest treatment needed to be maintained until the fetoplacental unit was producing adequate progesterone for subsequent pregnancy maintenance. The 44 mg of altrenogest per mare used in this study corresponds to a dose of approximately 0.088 mg/kg, which is commonly called a “double dose.” By comparison, the standard dose of altrenogest labeled for suppressing estrus is 0.044 mg/kg (“single dose”) orally every 24 hours. These same researchers also addressed whether flunixin meglumine could prevent luteolysis and maintain pregnancy in mares that were administered endotoxin. Flunixin meglumine, a non-steroidal anti-inflammatory cyclo-oxygenase inhibitor, interferes with the production of prostaglandin. When flunixin meglumine was administered to mares between days 21 and 44 of gestation intravenously 10 minutes before endotoxin administration, endogenous progesterone production was maintained and none of the seven mares lost their pregnancy. In those mares in which flunixin meglumine was administered 1 hour after endotoxic insult, systemic progesterone fell to below 2 ng/mL for several days, and pregnancy was lost in one of three mares. When flunixin meglumine was administered 2 hours after endotoxic insult, progesterone fell to below 0.5 ng/mL, and all three pregnancies were lost. Likewise, the 12 pregnant mares administered only endotoxin had very low progesterone concentrations, and all lost their pregnancies. Thus, flunixin meglumine was most useful when administered before endotoxin was given, but it was also of benefit in maintaining pregnancy in two of three mares when administered within 1 hour of the insult.

Other work supports the administration of progesterone or altrenogest to maintain pregnancy in the face of prostaglandin-induced abortion. In one study, six mares between 82 and 102 days of gestation were administered 250 µg of cloprostenol (q 24 h, IM) to induce abortion. Systemic progesterol concentrations rose, whereas progesterone concentrations fell, and fetuses were expelled spontaneously by the third day of cloprostenol administration. Subsequently, the ability of progesterone or altrenogest and flunixin meglumine administration to inhibit abortion induced by cloprostenol administration was examined. Mares were either administered progesterone 300 mg (q 24 h, IM) or 44 mg altrenogest (q 24 h, PO; “double dose”) beginning either 18 or 12 hours, respectively, after the first cloprostenol injection. The progesterone regimen was used in eight mares between 98 to 153 days of gestation, and, of these mares, only three aborted. When altrenogest was used in similar fashion in mares between 93 to 115 days of gestation, none of the mares aborted. In contrast, when 500 mg flunixin (q 8 h, IV) was administered beginning 15 minutes before the first daily cloprostenol injection, all mares aborted. Thus, progesterone or altrenogest supplementation but not flunixin administration blocked cloprostenol-induced abortion at these gestational ages. Taken together, these studies support the concept that progestin supplementation can maintain equine pregnancy when the mares were submitted to prostaglandin F2α insults.

If there is fetal demise after formation of the endometrial cups, the mare will normally have a phase of pseudopregnancy. Even without a live pregnancy, the endometrial cups will not regress until approximately days 120 to 150 after ovulation. The cups continue to secrete eCG, subsequently causing the ovarian luteal structures to secrete progesterone, which inhibits resumption of cyclicity. Loss of pregnancy during the endometrial cup phase will generally prevent the mare from becoming pregnant again during that season. Therefore, in cases in which a pregnancy must be terminated early (ie, presence of twins), it is important to perform elective abortion before endometrial cup formation, which is approximately 35 days of gestation but subject to individual mare variation. Before eCG production, a single dose of prostaglandin administered to the pregnant mare will result in luteolysis and pregnancy termination. Return to estrus and ovulation are normal after this procedure when performed before the eCG phase. After eCG production is present, and hence after the formation of supplementary corpora lutea, multiple doses of prostaglandin are necessary to terminate pregnancy. Although some mares may return to estrus when fetal demise (termination or spontaneous) occurs during the eCG phase, others will not. The eCG production that continues after the fetal loss affects ovarian function, in which case follicles develop but then may luteinize, without ovulating properly.
To illustrate the use of prostaglandin for elective pregnancy termination, 185 abortions were induced with once-daily intramuscular injections of cloprostenol administered during the period of eCG production. Three to four daily injections were necessary. Reportedly, in 90% of the abortions, no manual veterinary intervention was necessary. Exogenous prostaglandin treatment caused luteolysis and increased endogenous progastalgin production, altogether causing uterine contractions, subsequent cervical softening, and expulsion of the fetus.

Once eCG production subsides, multiple daily doses of prostaglandin are still necessary to achieve abortion. Approximately 66% to 75% of 21 pony and 25 horse mares, respectively, aborted within the first week of administration of daily prostaglandin (product not specified) when it was administered at 100 to 245 days of gestation. Some mares required up to 4 weeks of daily prostaglandin to achieve abortion. Later in gestation, at approximately 10 months of gestation until near to term, both natural prostaglandin and the analogue fluprostenol did not reliably cause parturition when administered several times in one day. It is also worthwhile to note that, depending on stage of gestation, dystocia may occur.

4. Late-Gestation Progestogen and Estrogen Monitoring

Systemic diseases that affect the gravid mare can affect hormone production by the fetus and placenta. Serial serum progestogens can be periodically monitored in mares as an indicator of pregnancy health. Commercially available progesterone assays cross-react considerably with the pregnanes and other progestogens produced by the feto-placental unit. Thus, diagnostic laboratories will use their progesterone assay to measure total progestogens, which is the sum of both progesterone and other cross-reacting feto-placental progestogens. Note that laboratory assays for progesterone vary in their ability to cross-react and quantify the various equine progestogens. Thus, total progestogens determined on a serum specimen from a gravid mare and assayed at two different laboratories, running two different progesterone assays, may show considerable differences in the total values. It is best to stay with one laboratory when submitting serial specimens for pregnant-mare total progestogen determination. Normal reference ranges have been determined by means of the assay at BET Laboratories in Kentucky. Total progestogens normally ranged from 4 to 10 ng/mL until approximately 300 to 320 days of gestation. After this time, progestogens may increase to above 40 ng/mL. Total progestogen concentrations are generally performed in a serial fashion so that a trend of rising, stable, or falling, becomes evident. Progestogens have been shown to rise abnormally and prematurely in the compromised mid- to late-gestation pregnancy. In severe cases of pregnancy compromise, in which fetal death is imminent, acute decreases in progestogens have been identified both in naturally occurring pregnancy conditions and in experimentally induced placenitis. Increases in progestogens before that normally identified in the last several weeks of gestation are a cause for concern and indicate ongoing fetal stress and compromise, with premature activation of the fetal pituitary adrenal axis. The mechanism for this occurrence is the increased fetal adrenal production of the precursor P5, which is metabolized by the placenta to more progestogens. Response to treatment may be assessed indirectly. For example, if progestogens fall back to a normal range, then improvement in the clinical condition of the fetus and placenta is suggested. Alternatively, failure of progestogens to rise can be identified in mares with fescue toxicity or uterine pathology and prolonged gestation.

Estrogen production can likewise be determined in serum obtained from the mare and used as an indicator of feto-placental health. Total estrogen concentrations may also be taken serially but can be helpful if only a single specimen is assayed. As discussed above, the fetal gonads produce estrogen precursors that are then metabolized at the level of the placenta into various estrogens. Estrogens peak in the second trimester and then fall gradually. Normal reference ranges have been determined by means of the assay at BET Laboratories in Kentucky. Total estrogens normally were at least 1000 pg/mL from approximately 150 to 300 days of gestation. After this time, estrogens will normally be lower as term approaches.

Low total estrogens have been found in cases of placenitis. Retrospectively, Douglas found that in naturally occurring cases of placenitis at gestational ages between 150 and 280 days, it was common to find both abnormally elevated total progestogens and low total estrogens in mares that aborted. Mares that maintained their pregnancy (with various treatments administered) had normally low progestogen and normally high estrogen.

5. High-Risk Mares and Reproductive Hormone Supplementation

The discussions above lead to the question of hormone supplementation for the high-risk pregnant mare with a compromised feto-placental unit. Questions one might ask are: If progestogens are elevated in abnormal pregnancies, then why administer additional progestins to the mare? What is the argument for this administration? Furthermore, is progestin supplementation safe for the fetus? The argument for administration of progestins to later-term pregnant mares with at-risk pregnancies is that the treatment maintains uterine quiescence. As was discussed above, progestogens continue to...
rise in late pregnancy and help maintain uterine quiescence up until just before parturition. In normal pregnancies, progestogens actually upregulate a placental enzyme, 15-hydroxy prostaglandin dehydrogenase that breaks down prostaglandins. Prostaglandin F will cause smooth muscle contraction. Thus, it is postulated that higher progestogens lower the effects of prostaglandins and quiet the myometrium. In addition, progestogens have immune modulating effects critical for pregnancy maintenance.

Although exogenous progestins were shown to be effective in maintaining early pregnancy in the face of attempted cloprostenol-induced abortion, similar studies have not been performed in late pregnancy. However, the efficacy of progestin treatment has been demonstrated when used in combination with trimethoprim sulfamethoxazole (30 mg/kg, q 12 h, PO) and pentoxifylline (8.5 mg/kg, q 12 h, PO) to treat experimentally induced bacterial placentitis. Altrenogest at a dose of 0.088 mg/kg (q 24 h, PO; “double dose”) was used in both the placitcitis and cloprostenol studies. Regarding the safety of supplemental progestogen administration, safety studies presented on the altrenogest label indicate that the only untoward sign was increased clitoral size in fillies born to normal mares that were administered 0.088 mg/kg (q 24 h, PO), beginning at 20 days of gestation and ending at 325 days. Thus, it seems reasonable to discontinue altrenogest by approximately 325 days of gestation.

Altrenogest crosses the placenta and is present in the foal at birth. A recent study compared parturition and foal health parameters in normal pony mares maintained on the 0.088 mg/kg dose of altrenogest through foaling and those that were not administered altrenogest. In six healthy pony mares supplemented with altrenogest through parturition, stage II active labor was more than 10 minutes in duration in four of the five treated mares, and one additional treated mare required a cesarean section. Foals from treated mares had lower respiratory rates and higher blood pH; one foal died at 30 minutes, and another needed intensive supportive care. Finally, these researchers found that there were differences in the neutrophil-to-lymphocyte ratio, suggesting dysmaturity, in foals born to altrenogest-treated pony mares.

Some progestins have been shown to alter mental arousal status. When progesterone was administered systemically to pregnant ewes, fetal lamb mental status was lessened as determined by monitoring of fetal neurologic and electromyographic responses. Regarding its effect in horses, one case report describes a foal that became stuporous and obtunded after being administered the progesterone metabolite allopregnanolone. However, it is currently not known if administration of progestins to the pregnant mare causes any noticeable alteration in fetal mental status. Interestingly, progesterone therapy has been used in humans with acute traumatic brain injury, in which case the progesterone is thought to have neuro-protective effects and to lessen cerebral edema. Additionally, a rodent model of pediatric brain trauma with the use of progesterone as a treatment has shown some positive neuro-protective effects. Finally, human pediatric studies evaluating progesterone treatment effectiveness in head trauma are planned or ongoing.

Another consideration is whether administration of progestogens to the late-gestation pregnant mare can alter gestational length. Progestogens rise near term and then fall off precipitously in the last 1 to 2 days before foaling. If progestogens are administered to the late-pregnant mare, could this treatment mimic what is happening in late gestation and inadvertently shorten gestational length? Only a few studies have addressed this pertinent question. When natural progesterone was administered daily to healthy mares from 318 days of gestation to foaling, gestational length was shortened from a mean of 344 days in nine untreated controls to a mean of 332 days in the nine treated mares. Reported, these foals were healthy at birth. As discussed above, six healthy, late-gestation pony mares were administered a double dose of altrenogest through foaling. The gestational length of ponies administered altrenogest tended to be shorter but was not statistically significant from the untreated controls. Finally, groups of six pregnant pony mares were administered either altrenogest, progesterone, or placebo daily from 300 days of gestation for 10 days. Gestational length was not different between groups, and all foals were reportedly healthy. In this study, progesterone supplementation increased total progestogens as measured in the mare serum, but altrenogest did not increase total progestogens. With such small sample sizes, the possibility of normal gestational length variability negating any effects between groups might be considered. Additionally, if one considers that equine gestation is normally variable between 320 to 365 days, then there is the chance that progestin administration did nothing to shorten gestation in early studies. Nevertheless, the administration of progesterone or altrenogest did not reliably prevent equine parturition.

Limited work has been performed looking at the administration of estrogens to the pregnant mare. In one study, clinical cases of mares assumed to have placentitis and medically managed with various antibiotic and medical regimens were either administered no estrogens or either estrogen cypionate or estradiol 17b. The mares were not administered progestins. The live foal rate of 70% was higher in the group given either of the two estrogen preparations compared with the live foal rate of 20% in mares not given estrogen. In this study, the live foal rate was 87% for a control group of normal.
mares not affected by placentitis. Further studies regarding estrogen treatment have not been performed. With such limited information available, general recommendations regarding estrogen administration cannot be made.

6. Dexamethasone Induction

Since the 1970s, it has been known that administration of high doses of dexamethasone to healthy, late-gestation mares will induce parturition. Dexamethasone, 100 mg per mare (approximately 0.2–0.25 mg/kg; q 24 h, IM), from 321 to 324 days of gestation in 12 mares, shortened gestation and resulted in the birth of viable foals. Mean gestation length in treated mares was 328 days versus 340 days in controls. Parturition, fetal membrane expulsion, mammary gland development, and lactation were normal, and the mares remained healthy. Foals were described to be initially “weak in the fetlock area,” but the problem resolved by 7 to 10 days of age. Although dexamethasone-induced foals were smaller, foal growth rate was similar to that in foals born to untreated mares.

Similarly, in five healthy mares administered this same dexamethasone treatment at days 315 through 317 days of gestation, healthy foals were born at a mean gestational age of 322 days, compared with five control mares at a mean of 335 days. One mare foaled within 15 hours of the last dexamethasone injection. A parturition range of 1 to 8 days after last dexamethasone administration was reported. This group did not find joint laxity or poor ossification of the foals’ fetlock or carpal joints. Most (four of five) foals produced from the dexamethasone treatment group required administration of supplemental colostrum to ensure adequate passive transfer. The foals responded adequately to an ACTH challenge test. This group specifically noted that other than slight depression, mild inappetence, and poor mammary gland development at foaling, the mares were healthy and showed no evidence of laminitis. Maternal total progestagens rose, whereas cortisol and a metabolite of progestagens fell, during dexamethasone treatment. This group cautioned that although the foals and mares remained healthy during this treatment with dexamethasone, this treatment protocol could not be directly or safely extrapolated to the mare with a compromised pregnancy in which the fetal hypothalamic pituitary axis was already activated because of fetal distress. In both studies, administration of dexamethasone was begun before the spontaneous maturation and activation of the fetal hypothalamic pituitary adrenal axis.

The association between dexamethasone treatment and subsequent dystocia has also been reported. In an early report, two healthy pony mares were administered 100 mg of dexamethasone (mean, 0.3 mg/kg; q 24 h, IM) for 3 or 4 days beginning approximately 344 to 347 days of gestation, and no outward signs of initiation of labor were identified. However, both mares subsequently had dystocia, with dead foals delivered. Both mares also retained their placentas. A third pony mare was administered 100 mg dexamethasone for 3 days beginning at 327 days. On day 331, oxytocin was administered, and, in this case, parturition was normal but the placenta was again retained.

Clinical data are limited regarding the use of dexamethasone for induction of parturition in healthy mares, much less in compromised pregnancies. One study used smaller doses of dexamethasone in mares with experimentally induced streptococcal placentitis. Several treatment approaches combining various combinations of trimethoprim sulfamethoxazole, aspirin, altrenogest, and dexamethasone were used in the mares once clinical signs consistent with placentitis had developed. Trimethoprim sulfamethoxazole (30 mg/kg, q 12 h, PO) and dexamethasone were administered to one group of six light horse mares. Dexamethasone was given as follows: 40 mg, 35 mg, 25 mg (q 24 h, IV), with each successively lower dose administered for 2 days. Four of the six mares delivered viable foals at a gestational age of approximately 308 ± 4 days (mean ± SEM). Likewise, four of six mares administered only trimethoprim sulfamethoxazole had viable foals but at approximately 319 ± 5 days. It is not clear from the report if both groups of mares were inoculated at similar gestational ages. In this study, aggressive antibiotic treatment was deemed most useful in improving fetal outcome. Reportedly, the mares were not systemically ill and did not show signs of laminitis.

High-dose dexamethasone treatment has been reported to cause laminitic complications in mares affected by bacterial placentitis.

7. Conclusions

Studies to elucidate equine fetal physiology and that of normal pregnancy continue to this day. In addition, work on pathological mechanisms of diseased pregnancy and how to best treat the high-risk gravid mare is ongoing. Not everything is known, and pieces of the puzzle are being added. There is often no easy answer to the difficult clinical presentation. My hope is that this article has provided you with knowledge that will help you in your clinical decision-making.

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References and Footnotes


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