Review of Management of Anestrus and Transitional Mares

Erin L. Oberhaus, MS; and Dale Paccamonti, DVM, MS, Diplomate ACT*

Authors' addresses: School of Animal Sciences, Louisiana State University Agricultural Center (Oberhaus); and Department of Veterinary Clinical Sciences, School of Veterinary Medicine (Paccamonti), Louisiana State University, Baton Rouge, LA 70803; e-mail: pacc@lsu.edu. *Corresponding and presenting author.

Although mares are regarded as seasonally polyestrous animals, great individual variation exists regarding the onset of fall transition and duration of ensuing winter anestrus, as well as the onset of spring transition. Although most mares transition to a period of reproductive quiescence, approximately 10% to 20% of mares continue to exhibit estrous cycles throughout the year.[1] The onset of winter anestrus and subsequent spring transition are primarily dependent on photoperiod or day length.[1] Day length varies by latitude, and mares are more likely to enter winter anestrus in more extreme latitudes and more likely to cycle year-round in the lower latitudes nearer the equator. Changes in photoperiod are detected by the retina and processed by the pineal gland. During periods of darkness, the pineal gland releases melatonin.[1] Melatonin appears to play a pivotal role in seasonality of reproduction; however, the mechanism by which melatonin exerts its action in the mare is unclear. In the autumn, as day length decreases, the duration of melatonin secretion increases. During the spring, as day length increases, the duration of melatonin secretion decreases, and a concurrent increase in gonadotropin-releasing hormone (GnRH) release is observed. In response, the anterior pituitary increases secretion of gonadotropins, and follicular activity begins. It appears that luteinizing hormone (LH) plays a more critical role than follicle-stimulating hormone (FSH) in initiating the onset of cyclicity. During anestrus, when GnRH is low, LH is at basal levels, whereas FSH does not change dramatically throughout the year.[2] Although other factors, both systemic and local at the ovarian level, appear to be involved in the onset of anestrus and the resurgence of cyclicity, many questions remain unanswered, (as reviewed in Donadeu and Watson[3]).

Whether or not a mare transitions to winter anestrus and the duration of her anestrus may be influenced by factors such as nutrition, age, breed, and temperature. Studies have shown that mares in good body condition are more likely to cycle year around, and mares in good body condition that do enter into anestrus begin cycling on average 1 month earlier than mares in poorer body condition.[4,5] Similarly, an increasing plane of nutrition or grazing on green grass is associated with an earlier return to cyclicity.[6,7] Older mares tend to begin cycling slightly later than young mares,[8,9] and po-

NOTES

nies tend to be more seasonal than horses.[10,11] Ambient temperature is considered a modulating factor during the spring transition. A warm spring seems to initiate earlier cyclicity.[12,13] Conversely, breeders will often report that a sudden cold snap during spring transition will cause mares to revert back to an anestrous-like state. This is especially true in conditions of extreme cold that create a demand for energy to maintain the core body temperature. Temperature probably modulates the effectiveness of dopamine antagonists such as sulpiride, used in an attempt to initiate cyclicity.[14] It is often difficult to separate out confounding variables when examining the effect of one variable on the onset of cyclicity. For example, in the spring, as the day lengthens, temperatures are usually on the rise and horses tend to be turned out to graze on spring pastures rather than be kept indoors. All three factors probably are conducive to mares emerging from winter anestrus into a transitional state.

For many breeds of horses, an industry imposed birthdate of January 1 has created an incentive to produce early season foals. This is advantageous in breeds in which horses compete in athletic events at a relatively young age because an earlier foal is of course more mature than another foal born later in the season that year. To produce maximally competitive foals, breeders strive to deliver them as close to January 1 as possible; however, this becomes difficult because the mare has an 11-month gestation period, and an early delivery necessitates an early conception. Therefore, it is important that mares begin regular, fertile estrous cycles as early in the year as possible. However, mares are not typically reproductively active at the time of desired breeding; therefore, many resources have been invested in the effort to induce earlier cyclicity. There are two targets at which to aim when attempting to induce earlier cyclicity: (1) shorten the anestrous period and (2) shorten the transition period. Artificial light to supplement the photoperiod is commonly used by breeders to induce earlier cyclicity in anestrous mares. Providing artificial light to simulate increased day length earlier in the year is a relatively easy, inexpensive, and effective method to initiate an earlier return to cyclicity; however, mares still go through a period of transition.[15] Photoperiod adjustment is usually begun around December 1 in the Northern hemisphere. A common protocol is to provide a period of light for 15 to 16 hours per day (followed by 8 to 9 hours of darkness). This is best accomplished by turning the lights on at the end of the day for a few hours. Alternatively, a short (1 to 2 hours) period of light can be provided during the night (usually 8 or 9 hours after onset of darkness) to interrupt the duration of the melatonin influence (as reviewed by McCue et al[16]).

As mares come out of anestrus and enter the transitional period, multiple waves of follicular growth and regression will be seen if the mares are observed closely through ultrasonography. Sharp et al[15] reported that pony mares in Florida had, on average, 3.7 follicular waves before the first ovulation of the year. The early follicles are not steroidogenically competent and do not produce sufficient quantities of estrogen to alter concentrations of estrogen in the serum. They can, however, produce low levels of estrogen that can result in estrous behavior. During this transitional period, estrous behavior exhibited by a mare can be very erratic. Transition typically lasts for weeks, and mares may exhibit prolonged periods of estrus, interspersed with variable periods of passivity or rejection of the stallion. This presents a frustrating and sometimes confusing situation for horse owners who desire to breed their mare early in the season. When a mare is in obvious estrus, it would seem advisable to breed her; however, if she is still in transition, that display of estrus is probably not accompanied by a fertile cycle. Therefore, breeding a mare in transition is a waste of time and resources. Furthermore, breeding during transition can actually decrease the chances of getting a problem mare in foal. For example, the repeated deposition of semen into the uterus of a mare with impaired fertility and the resulting inflammation from each breeding can exacerbate an already tenuous situation.

As the period of transition progresses and the developing follicles increase in size, they eventually become steroidogenically competent and produce detectable levels of estrogen approximately 1 week before the first ovulation.[17] The estrogen stimulates production of LH from the pituitary, and the eventual LH surge will result in maturation and ovulation of a dominant follicle.

Researchers have investigated many ways to shorten transition and advance the onset of cyclicity in the effort to produce early season foals. Some techniques have included follicle aspiration, use of ovulatory inducing agents such as human chorionic gonadotropin (hCG) or recombinant LH, and various schemes of administering GnRH or GnRH analogues in the form of pumps or slow-release formulations. Ultrasound-guided aspiration of the dominant follicle during transition resulted in a shortening of transition in studies performed in our lab. Mares that underwent follicular aspiration had a rise in progesterone 10 days after a 35-mm follicle was observed, compared with 35 days in control mares.[18]

Attempts to induce ovulation during transition by pharmacological means have not been routinely successful. Studies on the use of either exogenous GnRH or GnRH analogues to induce cyclicity have had conflicting results. Most researchers have observed an increase in both FSH and LH in response to exogenous GnRH treatment in anovulatory mares; however, the effects on follicle dynamics and ovulation vary. Deep anestrous mares were administered varying dosages (0, 50, or 100 ng/kg/h) of

GnRH through osmotic minipumps.[19] Ovulation did not occur in control mares; however, in both groups receiving 50 or 100 ng GnRH, ovulation in three of 10 and seven of 10 treatment mares occurred 20 and 19 days after treatment, respectively. A dose-dependent increase in LH was also observed.[19] Similarly, Allen et al[20] increased GnRH in anestrous pony mares and light horse mares by injecting either one or two slow-release polymer implants impregnated with either 0.9 or 1.8 mg of GnRH agonist (ICI 118 630). The implants delivered either 30 or 60 μg GnRH analogue, respectively, for 28 days. Thirteen pony mares (76%) and 120 horse mares (88%) ovulated within 3 to 18 days after treatment. Seventy of the 100 horse mares bred during that time conceived.[20] Conversely, Mumford et al[21] did not observe an increase in follicle development (number or size) after fitting anestrous mares with subcutaneous implants containing varying dosages of the GnRH analogue goserelin and observed only a 35% increase in ovulation rate. The increased ovulation rate depended on dosage as well as ovarian status before treatment.

The success of treatment with GnRH or its analogues appears to depend on how deep into anestrous a mare is. The use of the GnRH agonist deslorelin in late-transitional mares advanced the date of first ovulation by approximately 2 weeks, but repeated injections were needed.[22] Any treatment is less likely to be effective if a mare is in deep anestrus. As spring progresses and the more advanced a mare is into transition, the more likely a treatment is to be successful. Thorson et al[23] found that if mares received a continuous infusion of GnRH (100 μg/h for 28 days) beginning in February, they would return to acyclicity when treatment was stopped. However, if treatment was begun in March, mares would continue to cycle. Recently, Newcombe et al[24] were successful in initiating earlier cyclicity with deslorelin in mares pre-treated with intravaginal progesterone (CIDR). Ninety-six percent (143/149) of the mares treated with deslorelin pumps ovulated earlier, but that rate of ovulation depended on the size of the largest follicle at time of treatment.[24] The use of GnRH and its analogues appears to have limited advantages in inducing earlier cyclicity, and, of those methods that have been successful, repeated injections were needed and timing was crucial. Frequent, repeated administration of GnRH analogues has not yet proven practical and/or inexpensive for breeders.

In another approach to hasten the onset of the ovulatory season, Schauer et al[25] supplemented growing follicles with equine LH (eLH) (from pituitary extracts) during early transition to stimulate development of steroidogenically active dominant follicles with the ability to respond to an ovulatory stimulus. Mares received eLH, q 12 h IV, until a follicle reached 32 mm, at which time they received hCG, 3000 U IV. Although eLH treatment stimulated follicle growth, it failed to produce steroidogenically active follicles responsive to hCG. Furthermore, eLH did not hasten the onset of the ovulatory season because the treated mares that did ovulate subsequently returned to an anovulatory transition state.[25]

Progesterone has also been used in various approaches, including slow-release formulations, oral progestogens, and intravaginal devices.[26] Staempfli et al[27] administered a single dose of a slow-release formulation of progesterone to early- and late-transitional mares. Treatment had no effect on the early-transition mares but resulted in ovulation in 10 to 24 days in 10 of 12 mares treated in late transition, versus only three of 12 control mares during the same time period. Many other studies, dating back to the 1970s, have found similar results. Mares in anestrus or early transition do not respond to progesterone therapy, whereas ovulation may be advanced in mares in late transition (as reviewed by McCue et al[28]). When a mare has reached the stage of transition in which follicles of 30 mm or larger are detected, she can usually be successfully "normalized" into regular estrous cycles by daily feeding of the oral progestogen, altrenogest[a] or an injection of a long-acting formulation of progestin.[b14]

One of the most promising approaches to inducing earlier cyclicity in mares has been to manipulate endogenous prolactin. Prolactin administered to anestrous mares has been shown to stimulate ovarian activity and to induce ovulation in seasonally anovulatory mares.[29,30] Another way of manipulating prolactin is through the use of dopamine antagonists such as domperidone or sulpiride. Dopamine antagonists counteract the effects of hypothalamic dopamine on the adenohypophysis and enhance prolactin secretion in the winter, when plasma concentrations are normally very low.[30,31] It is assumed that the dopaminergic antagonists cause their effect by stimulating prolactin secretion. Early studies examining the effects of dopamine antagonists in anestrous mares found that sulpiride, either 1 mg/kg, q 24 h IM, begun in late January and continued until ovulation,[32] or 200 mg, q 24 h IM, begun in early February and continued until ovulation or for a maximum of 58 days,[33] advanced the first ovulation of the year by 21 d or 33 days, respectively. However, Donadeu and Thompson[34] administered sulpiride 1 mg/kg, q 24 h SC, for 32 days beginning in mid-January and failed to see an effect on ovarian activity or ovulation, indicating the importance of prolonged administration when treatment is initiated very early in the year in anestrous mares.

As previously stated, many factors undoubtedly affect the onset of cyclicity in a mare. For example, Gentry et al[5] fed mares to achieve a high or low body condition. Whereas those mares with low body condition ceased follicular activity and entered ovarian quiescence in the winter, all mares in the high body condition group except one continued to cycle or had significant ovarian activity. Therefore, it is not unreasonable to expect factors such as body condition, nutrition, environmental temperature, photoperiod, and so forth, to affect the response to dopamine antagonists and play a role in the onset of cyclicity. Duchamp and Daels[35] first put mares under 14.5 hours of light beginning on January 10, for 2 weeks before administering sulpiride (1 mg/kg, q 12 h IM) until ovulation or for a maximum of 21 days. Treated mares ovulated almost 17 days earlier than controls. Nearly 73% ovulated within 28 days of the beginning of sulpiride treatment.

Kelley et al[36] showed that pretreatment with estrogen greatly enhanced the prolactin response to daily treatment with sulpiride. Mares received 10 injections of estradiol benzoate (11 mg, q 48 h IM) or vegetable oil as a control, beginning on January 11. Sulpiride treatment (250 mg, q 24 h SC) was begun 11 days after initiation of the estradiol treatment. Mares that received estradiol ovulated 45 days earlier than mares receiving sulpiride alone. Similarly, Mitcham et al[37] used estrogen to prime mares before treatment with domperidone. In January, mares in anestrus received a single injection of domperidone (3 g, in biodegradable particles, IM) either alone or after a single injection of estradiol cypionate (ECP) (100 or 150 mg IM), whereas another group also received progesterone (1.5 g, long-acting formulation, IM), and another group received ECP (150 mg IM) and progesterone (1.5 g, long-acting formulation, IM), without domperidone. Mares receiving ECP before domperidone ovulated earlier than those not receiving ECP. Of the mares that received ECP, 14 of 31 ovulated within 35 days, whereas of those that did not receive ECP, only three of 36 ovulated within 35 days, including none of nine that received domperidone alone. Timing of pretreatment with ECP relative to administration of domperidone (1, 6, or 11 days apart) was also assessed. Administration of domperidone 1 day after treatment with ECP provided the most positive response on prolactin compared with day 6 or day 11. The addition of progesterone did not affect the date of first ovulation. Likewise, estrogen and progesterone without domperidone did not advance ovulation. A second experiment examined the effect of varying doses of ECP (0, 75, or 150 mg IM) followed by 1.5 g or 3 g domperidone. Estradiol cypionate had a positive effect on advancing ovulation in domperidone-treated mares in a dose-independent manner.[37]

In a recent report, transitional mares with a follicle ≥25 mm received sulpiride (1 mg/kg, q 24 h IM) until ovulation or for a maximum of 21 days.[38] Mares receiving sulpiride ovulated 25 days earlier than did control mares. Of the mares receiving sulpiride, 46% ovulated within 20 days, and 85% ovulated within 30 days versus 27% and 37%, respectively, for control mares.

Mari et al[39] compared sulpiride (1 mg/kg, q 24 h IM) and domperidone (1 mg/kg, q 24 h PO) administered to anestrous mares for 25 days during February. Of the sulpiride-treated mares, three of 10 ovulated during treatment; another three ovulated within 7 days of the last sulpiride treatment, and two more ovulated within 14 days of the last treatment, for a total of eight of 10 ovulating within 38 days of the beginning of treatment. The remaining two ovulated more than 30 days after sulpiride treatment ended. Of the domperidone-treated mares, only two ovulated during treatment, whereas eight ovulated 64 to 108 days after treatment ended. The control mares ovulated 53 to 113 days after the treatment period. The authors concluded that sulpiride was effective in advancing ovulation, whereas domperidone was effective only in some mares. It is possible that the lack of effect with domperidone was due to the dose or route of administration in this study.

Most recently, Mitcham[c] compared domperidone (1.5 g in biodegradable microparticles, IM) with varying doses (0.75 and 1.5 g, IM) of a new, non-particle formulation of sulpiride in ECP-treated mares. Treatment with domperidone took place 1 day after treatment with 100 mg ECP; treatment with sulpiride took place 1, 6, and 11 days after treatment with 100 mg ECP. Domperidone-treated mares as well as control mares received vehicle on days 6 and 11. The addition of 50 mg thyroxin 6 days before ECP treatment was also used to assess the prolactin response to domperidone or sulpiride. The prolactin response was greatest in mares treated with 100 mg ECP and 1.5 g sulpiride formula. Mares that received domperidone or 0.75 g sulpiride did not ovulate earlier compared with controls; however, of the mares treated with the higher dose of sulpiride (1.5 g), seven of the nine ovulated earlier relative to controls. Previous results showed that the effect of sulpiride on prolactin is quick but does not persist as well as the effect of domperidone. Therefore, repeated injections of sulpiride provided maximal results. The response to domperidone was greater than in control mares but significantly lower than in mares treated with sulpiride. Thyroxin did not have an effect on either the prolactin response to dopamine antagonists or the mean date of first ovulation. The preparation of sulpiride in a non-particle, slow-release formula may be less expensive (non-particle compared with microparticles) and more useful for breeders in the future.

The differing results reported in the various studies that used dopamine antagonists may be due to any number of factors, including when treatment was initiated—during anestrus or transition; the route of administration—intramuscular, subcutaneous, or oral; the dose and frequency of administration, body condition, and adjunct treatments such as pretreatment with increased photoperiod or administration of estrogen. Treatments beginning when mares are in mid-late transition probably would require a shorter duration to achieve an effect compared with treatment begun during deep anestrus. If pretreatment with estrogen can significantly affect the results, it could prove to be a valuable adjunct therapy. Formulations that enable effective treatment with as few injections as possible would certainly meet with greater acceptance and improve client compliance compared with treatment regimens requiring daily injections for weeks or months.

Many recent advances have been made in the ability to induce earlier cyclicity in mares; however, no single protocol yet exists to provide an infallible method of bringing mares into cyclicity earlier and shortening the duration of the vernal transition. The use of artificial lights beginning in December remains a widely used and trusted tool for inducing earlier cyclicity, but mares still have the erratic signs of transition. The use of pharmacological agents such as GnRH analogues, progestogens, and dopamine antagonists has been successful, but with variable results. The most promising of these therapies is the use of a dopamine antagonist, either sulpiride or domperidone, after pre-treatment with estradiol. Although studies have clearly shown the value of dopamine antagonists for advancing the onset of cyclicity, work remains to be done to determine the best compound to use, the best formulation, the best route of administration, and the best adjunct therapy to achieve the greatest benefit while at the same time maximizing ease of use and minimizing cost.

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