Proceedings of the
18th Annual Meeting of the
Italian Association of Equine Veterinarians
SIVE

Feb. 3-5, 2012 - Bologna, Italy

Next SIVE Meeting:

Feb. 1-3, 2013 – Arezzo, Italy

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Although mares are seasonally polyestrous animals, great individual variation exists regarding the onset of spring and fall transition and the occurrence and duration of winter anestrus. The onsets of winter anestrus and subsequent spring transition are primarily dependent on photoperiod or day length. Day length of course varies by latitude and mares are more likely to enter anestrus during winter in more extreme latitudes and more likely to cycle year-round in the lower latitudes nearer the equator. The effect of photoperiod is via the pineal gland and through release of melatonin during periods of darkness. Melatonin inhibits secretion of GnRH from the hypothalamus in the mare. In the autumn, as day length decreases, the duration of melatonin exposure increases and GnRH output is reduced. During the spring, as day length increases, the duration of melatonin secretion decreases, thus leading to an increase in GnRH release.

In response, the anterior pituitary increases secretion of gonadotropins and follicular activity begins. It appears that LH plays a more critical role than FSH in initiating the onset of cyclicity. During anestrus when GnRH is low, LH is at basal level, while FSH does not change dramatically throughout the year. 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 3).

Whether a mare goes into winter anestrus, and the duration of anestrus, is 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 those mares in good body condition that do enter into anestrus begin cycling on average a month earlier than mares in poorer body condition. Similarly, an increasing plane of nutrition or grazing on green grass is associated with an earlier return to cyclicity. Older mares tend to begin cycling slightly later than young mares, and ponies tend to be more seasonal than horses. Environmental temperature may modulate the effectiveness of dopamine antagonists, such as sulpiride, used in an attempt to initiate cyclicity. 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 lengthsen, temperatures are usually on the rise and horses tend to be turned out to graze on spring pastures rather than be kept indoors.

For many breeds of horses, it is important that mares begin regular fertile estrous cycles as early in the year as possible, allowing earlier breeding and hence, earlier foaling, in the following year. This is advantageous in those breeds where 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 in the same year. There are two targets at which to aim when attempting to induce earlier cyclicity. The first is to shorten the anoestrous period; the second is to shorten the transition period. For those mares that do enter winter anestrus, manipulating the photoperiod by providing artificial light to simulate in-
creased 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. Photoperiod adjustment is usually begun around December 1 in the northern hemisphere. A common scheme is to provide a period of light for 15 to 16 h (followed by 8 to 9 h 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 h) period of light can be provided during the night (usually 8 or 9 h after onset of darkness) to interrupt the duration of the melatonin influence (as reviewed in 11).

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 via ultrasonography. Sharp et al. (1993) 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 may last for months 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 that desire to get their mare bred early in the season. When a mare is in obvious estrus, it would seem to be advisable to breed her if you want her to become pregnant. However breeding a mare in transition is a waste of the stallion’s semen and farm personnel’s time. An additional problem is that repeated breeding during transition can actually decrease the chances of getting a problem mare in foal. 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 a week prior to the first ovulation. 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 order to expedite getting mares pregnant earlier in the year including follicular aspiration, use of ovulatory inducing agents such as hCG or recombinant LH, and various schemes of administering GnRH or GnRH analogues such as 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 d after a 35 mm follicle was observed, compared to 35 d in control mares. Attempts to induce ovulation during transition by pharmacological means have not been routinely successful. Use of deslorelin in late transitional mares advanced the date of first ovulation by approximately two weeks, but repeated injections were needed. 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. found that if mares received a continuous infusion of GnRH (100 ug/h for 28 d) beginning in February, they would return to acyclicity when treatment was stopped. However, if treatment was begun in March, mares would continue to cycle.

In another approach to hasten the onset of the ovulatory season, Schauer et al. supplemented growing follicles with LH during early transition to stimulate development of steroidogenically active dominant follicles with the ability to respond to an ovulatory stimulus. Treatment resulted in ovulation occurring 45 d earlier in a small group of treated mares.
Progesterone has also been used in various approaches, including slow release formulations, oral progestogens, and intravaginal devices. Staempfli et al. 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 d in 10 of 12 mares treated in late transition, vs. only 3 of 12 control mares during the same time period. Many other studies, dating back to the 1970’s have found similar results. Mares in anestrus or early transition do not respond to progesterone therapy, while ovulation may be advanced in mares in late transition (as reviewed in 19).

One of the most promising approaches is the use of dopamine antagonists such as domperidone or sulpiride. Early studies examining the effects of dopamine antagonists in anoestrous mares found that sulpiride, either 1 mg/kg, q 24 h, IM, begun in late January and continued until ovulation, or 200 mg, IM, q 24 h, begun in early February and continued until ovulation or for a maximum of 58 d, advanced the first ovulation of the year by 21 d or 33 d, respectively. However, Donadeu and Thompson administered sulpiride, 1 mg/kg, SC, q 24 h for 32 d 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 anoestrous mares. As previously stated, many factors undoubtedly affect the onset of cyclicity in a mare. For example, Gentry et al., fed mares to achieve a high or low body condition. While 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, etc., to affect the response to dopamine antagonists and play a role in the onset of cyclicity. Duchamp and Daels first put mares under 14.5 h of light beginning on January 10, for 2 wk before administering sulpiride (1 mg/kg, q 12 h, IM) until ovulation or for a maximum of 21 d. Treated mares ovulated almost 17 d earlier than controls. Nearly 73% ovulated within 28 d of the beginning of sulpiride treatment.

Kelley et al. showed that pretreatment with estrogen enhanced the effect of 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 d after initiation of the estradiol treatment. Mares that received estradiol ovulated 45 days earlier than mares receiving sulpiride alone. Similarly, Mitcham et al. used estrogen to prime mares before treatment with domperidone. In January, mares in anoestrus 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), while 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 d while of those that did not receive ECP, only 3 of 36 ovulated within 35 d, including 0 of 9 that received domperidone alone. 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. ECP had a positive effect on advancing ovulation in domperidone treated mares in a dose-independent manner.

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 d. Mares receiving sulpiride ovulated 25 d earlier than control mares. Of the mares receiving sulpiride, 46% ovulated within 20 d, and 85% ovulated within 30 d vs. 27% and 37%, respectively, for control mares. Mari et al. compared sulpiride (1 mg/kg, q 24 h, IM) and domperidone (1 mg/kg, q 24 h, PO)
administered to anoestrous mares for 25 d during February. Of the sulpiride treated mares, 3 of 10 ovulated during treatment; another 3 ovulated within 7 d of the last sulpiride treatment and 2 more ovulated within 14 d of the last treatment for a total of 8 of 10 ovulating within 38 days of the beginning of treatment. The remaining 2 ovulated more than 30 d after sulpiride treatment ended. Of the domperidone treated mares, only 2 ovulated during treatment while 8 ovulated 64 to 108 d after treatment ended. The control mares ovulated 53 to 113 d after the treatment period. The authors concluded that sulpiride was effective in advancing ovulation, while domperidone was effective in only some mares. It is possible that the lack of effect with domperidone was due to the dose or route of administration in this study.

The differing results reported in the various studies may be due to any number of factors, including when treatment was initiated—during anoestrus or transition; the route of administration—IM, SC, or PO; the dose and frequency of administration, body condition, and adjunct treatments such as pretreatment with increased photoperiod or administration of estrogen. Treatment begun when mares are in mid-late transition would likely require a shorter duration to achieve an effect compared with treatment begun during deep anoestrus. If pretreatment with estrogen can significantly impact the results, it could prove to be a valuable adjunct therapy. Formulations that enable effective treatment with a single injection would certainly meet with greater acceptance and improve client compliance compared with treatment regimens requiring daily injections for weeks or months. While studies have clearly shown the value of dopamine antagonists for advancing the onset of cyclicity, much work remains to be done to determine the best drug 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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REFERENCE LIST

22. Donadeu FX, Thompson DL. Administration of sulpiride to anovulatory mares in winter: effects on prolactin and gonadotropin concentrations, ovarian activity, ovulation and hair shedding. Theriogenology 2002 Jan 15;57(2):963-76.