Review Report

Effects of buserelin on the reproductive performance in transitional and anestrous mares

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Abstract

Breeding mares early in the year can alleviate economic pressure by increasing the number of estrous cycles per season, recovery of embryos per season or recovery of embryos prior to the beginning of performance season. Pharmacological manipulation of anestrus and transition periods is managed indirectly by increasing the photoperiod or directly using exogenous GnRH, GnRH agonists, pituitary extracts, gonadotropins, dopamine antagonists, progesterone, and estrogens. Efforts to evaluate the effectiveness of GnRH and its agonists (goserelin, deslorelin, historelin, and buserelin) to induce ovarian follicular development and return to cyclicity in anestrous and transitional mares have had conflicting results. However, specific buserelin protocols appear to actively stimulate folliculogenesis under the influence of a short-duration lighting program. Additionally, buserelin treatment is effective in producing adequate ovulatory, pregnancy, and return to estrus rates.

Keywords: GnRH agonist, mare, transition, anestrus, buserelin

Introduction

The natural breeding season in the mare is timed to maximize the foal's chances of survival during the winter. This adoption has led the mare to be a long-day, seasonally polyestrous animal with regular ovulatory cycles occurring in response to increasing day length.[1,2] During winter, in response to an increased period of darkness, the pineal gland releases melatonin.[3] Melatonin has a pivotal role in seasonality of reproduction; however, the mechanism by which it exerts its action is still unclear.[4] Regardless, the mare's hypothalamic-pituitary axis changes with decreased GnRH secretion, leading to baseline concentrations of LH and cessation of ovarian follicular waves in most mares.[3,5] As day length and photoperiod increase the transitional period ensues; this lasts for 60-80 days and culminates in season's first ovulation.[1] As melatonin decreases, there is a concurrent increase in GnRH.[1] The anterior pituitary increases secretion of gonadotropins, most importantly LH, since FSH concentrations do not change remarkably throughout the year.[5] Ovarian activity increases with growth and regression of follicles, causing erratic estrous behavior.[1,6,7]

There can be a great variation between and within mare groups regarding the onset of fall transition, duration of winter anestrus, and onset of spring transition due to variable latitude, climate, age, body condition, and nutrition.[2,3,6,7] Young mares, lower latitudes, warmer ambient temperatures, green grass, and an upward plane of nutrition appear to hasten transitioning out of the winter anestrous period.[8–10] The early transition phase is characterized by the development of numerous smaller follicles (> 20 mm) that develop and become atretic.[3,11] During late transition, 1-3 anovulatory follicular waves occur each with a larger dominant follicle (> 35 mm) that often regresses before, finally, a dominant follicle is selected and proceeds to ovulate.[3,11] Cyclicity returns with the first ovulation.

In the horse industry there is economic pressure to produce foals early in the year since as weanlings, yearlings, and performance horses, they will have a developmental advantage compared to their younger counterparts. Additionally, breeding mares early in the year increases the number of estrous cycles with potentially higher recovery of embryos per season or recovery of embryos prior to the beginning of a mare's performance season. Unfortunately, mares are not typically reproductively active at desired breeding (late winter); therefore, many resources have been invested in the effort to induce earlier cyclicity.[4]

Pharmacological manipulation of anestrus and transition periods is managed indirectly by increasing the photoperiod[12] or directly using exogenous GnRH, GnRH agonists, pituitary

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extracts, gonadotropins, dopamine antagonists, progesterone, progestagens, or estrogens.[6] Efforts to evaluate the effectiveness of GnRH and its agonists (goserelin, deslorelin, historelin, and buserelin) to induce ovarian follicular development and return to cyclicity in anestrous mares have had conflicting results.[13–16] It appears that dose, route of treatment, frequency, and most importantly date of onset of treatment and the pretreatment status of the ovary have an influence on the efficacy of the treatment.[17] This review focuses on the specific use of buserelin, as it appears to have clinical and economic benefits.

In a study, 45 nonlactating, seasonally anestrous mares were assigned randomly to 1 of 3 groups (n = 15 per group): 1. untreated controls; 2. intramuscular buserelin at 12-hour intervals (40 pg/injection) for 28 days or until ovulation; 3. GnRH agonist (buserelin) as a subcutaneous implant designed to release ~ 100 pg/12 hours for 28 days.[18] Injected or implanted buserelin hastened ovulation in transitional mares compared to control mares. Seven of 15 (47%) mares in group 2 responded to twice-daily injections of GnRH agonist (40 pg/injection) and ovulated mean 18.3 ± 5.2 days after initiation of treatment. Implant mares ovulated 60% (9/15) of the time, with a mean of 15.8 ± 9.2 days.[18] Response interval and number of mares responding to GnRH agonist treatment were not different ($p > 0.05$) between treated groups. No control mares versus 53% of treated mares ovulated within 30 days after initiation of treatment.[18] An increased response to buserelin over time indicated that the GnRH agonist increased pituitary stores of LH by day 7 in mares given the implant and by day 21 for mares injected with GnRH agonist. The implant resulted in a better response than the twice-daily treatment, with greater LH peak and daily serum concentrations and a more rapid and larger decline in FSH response parameters. This correlated with mares' response to GnRH-induced biphasic LH profiles with peaks at ~ days 6 and 16-20 after initiation of treatment, with ovulations occurring near the second peak.[19] Mares that failed to ovulate exhibited the first peak, but not the second, with LH declining to baseline concentrations.

The implications from the above study were that buserelin can induce ovulation in anestrous mares more frequently than control mares; however, some mares did not respond. It was hypothesized that due to a failure to cause sufficient decline in FSH concentrations and/or sufficient increase in concentrations of LH failing to result in a reciprocal relationship between the gonadotropins. Therefore, they concluded that the doses used may have been too high or low and further studies are needed to determine the best dose and treatment route.[18]

A further study in which subcutaneous buserelin (10 µg) was given twice daily in January, February, and March was compared to a native GnRH (10 µg/hour) pump in seasonally anestrous mares; both produced ovarian follicular growth and induced ovulation. Additionally, buserelin was more effective in February and March.[17] Building on that study, 2 experiments were designed with 60 anestrous mares.[20] The first utilized 26 primiparous or seasonally anestrous (follicles < 20 mm, no edema, small ovaries) maiden mares were assigned to 3 groups. Group 1A (n = 9) received subcutaneous injections of 10 µg buserelin twice daily, beginning February 15 for a maximum of 28 days plus a single injection of hCG (2,500 IU) when a follicle > 35 mm in diameter was noted. Group 1B (n = 9) mares received 1 intravenous hCG (2,500 IU) when a spontaneously developed follicle > 35 mm in diameter was detected. Group 1C (n = 8) mares were untreated and not bred. Mares were bred every other day until the day of ovulation. Pregnancy was diagnosed (via ultrasonography) on days 14, 25, 35, 45, 60, and 180 after ovulation. The second experiment included a random assortment of 34 mares on private farms that were placed on buserelin twice daily beginning in early February for a maximum of 21 days, plus 1 hCG (2,500 IU) injection when a follicle > 35 mm was detected. Group 2B (n = 18) mares were given hCG (2,500 IU) when a spontaneously developed follicle ~ 35 mm was detected. Mares with a follicle > 35 mm were bred by natural service or inseminated (semen from a stallion of known fertility). Pregnancy was diagnosed (via ultrasonography) on days 14, 25, and 40 after ovulation. Both buserelin plus hCG treatment in anestrous mares and hCG treatment alone in transitional mares significantly advanced the date of the first ovulation of the year compared to untreated mares. The mean interval from onset of GnRH treatment and detection of a follicle > 35 mm was 10.6 ± 2.2 days. The percentage of mares ovulating in response to GnRH plus hCG in Experiment 1 (7 of 9; 77.8%) and Experiment 2 (11 of 16; 68.8%) was not significantly different. Pregnancy rates for ovulations induced by GnRH plus hCG for Experiments 1 (71.4%) and 2 (81.8%) were similar. No significant differences in pregnancy rates were noted between buserelin plus hCG (77.8%) or transitional mares treated only with hCG (85.2%),[20] further supporting the concept that buserelin protocols are suitable for inducing fertile ovulations in anestrous mares early in the breeding season.

Most recently a larger study used 79 anestrous (< 20 mm follicles) or transitional (> 20 mm follicles without prior ovulation) mares with a specific buserelin treatment protocol and the efficacy of inducing ovarian follicular development, ovulation, pregnancy, and return to estrus were documented.[21] Mares were placed under 16 hours of day light for a minimum of 2 weeks. As this was a clinical situation, it was not possible to have a control group that was not placed under lights and therefore, if there was no follicular development, they were placed on 12.5 µg intramuscular buserelin twice daily. When a 35-40 mm follicle was present, ovulation was induced with intravenous hCG (3,000 IU), the mare was bred and buserelin treatment ceased after ovulation was identified. The average length of treatment was 10.42 days, with anestrous mares requiring longer treatment compared to transitional mares (12.20 versus 9.96 days, respectively). There was no significant effect of length of treatment on ovulation, pregnancy outcome, or twinning. Overall, 71% of mares developed follicles large enough to induce ovulation. Transitional mares were more likely to ovulate than anestrous mares (94 versus 64%, respectively).[21] Of the mares that ovulated, 72% became pregnant, 24% of which were twins.[21] Mares that did not become pregnant returned to estrus within the normal 18-21 days interval. The buserelin protocol described above appeared to actively stimulate folliculogenesis in both anestrous and transitional mares under the influence of a short-duration lighting program and regardless of length of treatment. The authors concluded that buserelin treatment at this dose should be considered effective in producing adequate ovulatory, pregnancy, and return to estrus rates in anestrous and transitional mares.[21]

Conclusion

Buserelin, a GnRH agonist, can be used successfully to advance the onset of cyclicity during anestrus and transitional periods.

Conflict of Interest

None to declare.

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