AUSTRALIAN VETERINARY JOURNAL
AUSTRALIA'S PREMIER VETERINARY SCIENCE TEXT
EQUINE

SHORT COMMUNICATION

Sustained-release deslorelin acetate implants disrupt oestrous cyclicity in the mare

CJ Joonè* and J Cavalieri

There is a need for a safe, effective and practical method of oestrus suppression in the mare. The aim of this study was to monitor ovarian activity in mares exposed to either 9.4 or 28.2 mg deslorelin acetate, a GnRH agonist, in the form of a sustained-release implant. Following oestrus synchronisation, mares were randomly assigned to one of three groups ($n = 4$ per group) and administered either one (Des1 group; 9.4 mg) or three (Des3 group; 28.2 mg) implants of deslorelin acetate (Suprelorin-12, Virbac Australia) or one blank implant (Control group; Virbac Australia). Mares underwent weekly blood sampling for 12 weeks following implant placement (Day 0–Day 84), with transrectal palpation and ultrasonography of the reproductive tract at all sampling timepoints except Days 56, 70 and 77. All mares showed baseline serum progesterone concentrations (SPC; ≤1.3 nmol/L or 0.4 ng/ml) on Day 0. Cycling Control mares showed typical oestrous cyclicity characterised by peaks and troughs in SPC over time. Four of eight treated mares demonstrated a sustained elevation in SPC after the initial ovulation after implant placement; SPC declined to baseline levels (Des1 group; 2 mares) or remained elevated (Des3 group; 2 mares) at the final sampling timepoint on Day 84. Oestrous cyclicity was erratic in three of the remaining four treated mares. In total, 87.5% (7 of 8) of treated mares showed atypical oestrous cyclicity after implant placement. These results suggest that deslorelin acetate disrupts oestrous cyclicity in the mare, which warrants further research.

Keywords contraception; gonadotrophin-releasing hormone; horse; oestrus suppression; persistent corpus luteum

Aust Vet J 2023;101:275–278 doi: 10.1111/avj.13244

Suppression of oestrus in the mare is frequently requested in clinical practice, with the aim of improving temperament and performance. Progestogens are commonly used to prolong dioestrus but registered formulations require frequent re-administration at significant cost and carry risks to persons exposed to the drug.[1] A variety of other methods to suppress oestrus in the mare have been developed, each with their own advantages and limitations.[2]

In a number of species, chronic exposure to GnRH agonists down-regulates the hypothalamic–pituitary–gonadal axis and inhibits reproductive function.[3] Recently, Kaps et al. reported transient effects on ovarian function in Shetland mares administered one implant of either Suprelorin-6 or Suprelorin-12[4] and in Haflinger mares administered one implant of Suprelorin-12.[5]

The aim of the current study was to investigate the effects of up to three implants of Suprelorin-12 on oestrous cyclicity in domestic mares. Ethical approval was granted by the Animal Ethics Committee, James Cook University (A2462). Nine Standardbred and three Thoroughbred mares (median age 15 years; range 7–19 years) were administered up to two doses of prostaglandin-F2α (PGF2α; 500 µg cloprostenol; Jurox Pty Ltd, New South Wales, Australia) intramuscularly, 14 days apart, to synchronise oestrus. Mares found to be in oestrus at initial examinations were exempt from the first PGF2α treatment. All mares received the second PGF2α treatment on the same day. Three days later, mares were stratified according to age and breed and randomly assigned to one of three treatment groups ($n = 4$ per group). Each Des1 mare received one implant of deslorelin acetate (9.4 mg; Suprelorin-12; Virbac Australia Pty Ltd), each Des3 mare received three implants of deslorelin acetate (28.2 mg; Suprelorin-12) and each Control mare received one blank implant (Virbac Australia Pty Ltd). Implants were placed under desensitized vulvar mucosa, using aseptic technique. The day of implant placement was designated as Day 0.

All mares underwent weekly blood sampling for the next 12 weeks, from Day 0 (5 February 2018, latitude 19.3° S) to Day 84 (30 April 2018), with gynaecological examinations, including transrectal palpation and ultrasonography of the reproductive tract, at all sampling points except Days 56, 70 and 77. Blood samples were collected by jugular venipuncture into plain vacutainer tubes and allowed to clot at room temperature before centrifugation. Serum was stored at −20°C until assayed as a single batch within 6 months of collection. Serum progesterone concentrations (SPC) were determined using chemiluminescence immunoassay (Immulite 1000, Siemens Healthcare Pty Ltd, Victoria, Australia). The intra-assay coefficient of variation was 5.54%.

All mares showed baseline SPC (mean 0.77 nmol/L; range 0.635–1.3 nmol/L) and either nil or regressing (based on subsequent examinations) luteal structures on the day of implant insertion (Day 0). Over the trial period, cycling Control mares showed typical peaks and troughs in SPC over time, correlated to the presence or absence of corpora lutea on gynaecological examinations, respectively. One mare showed signs typical of seasonal anoestrus from Day 49 of the study, with another entering seasonal anoestrus from Day 70. Serum

*Corresponding author.
College of Public Health, Medical and Veterinary Sciences, James Cook University, Townsville, Queensland, Australia; carolynne.joone@jcu.edu.au

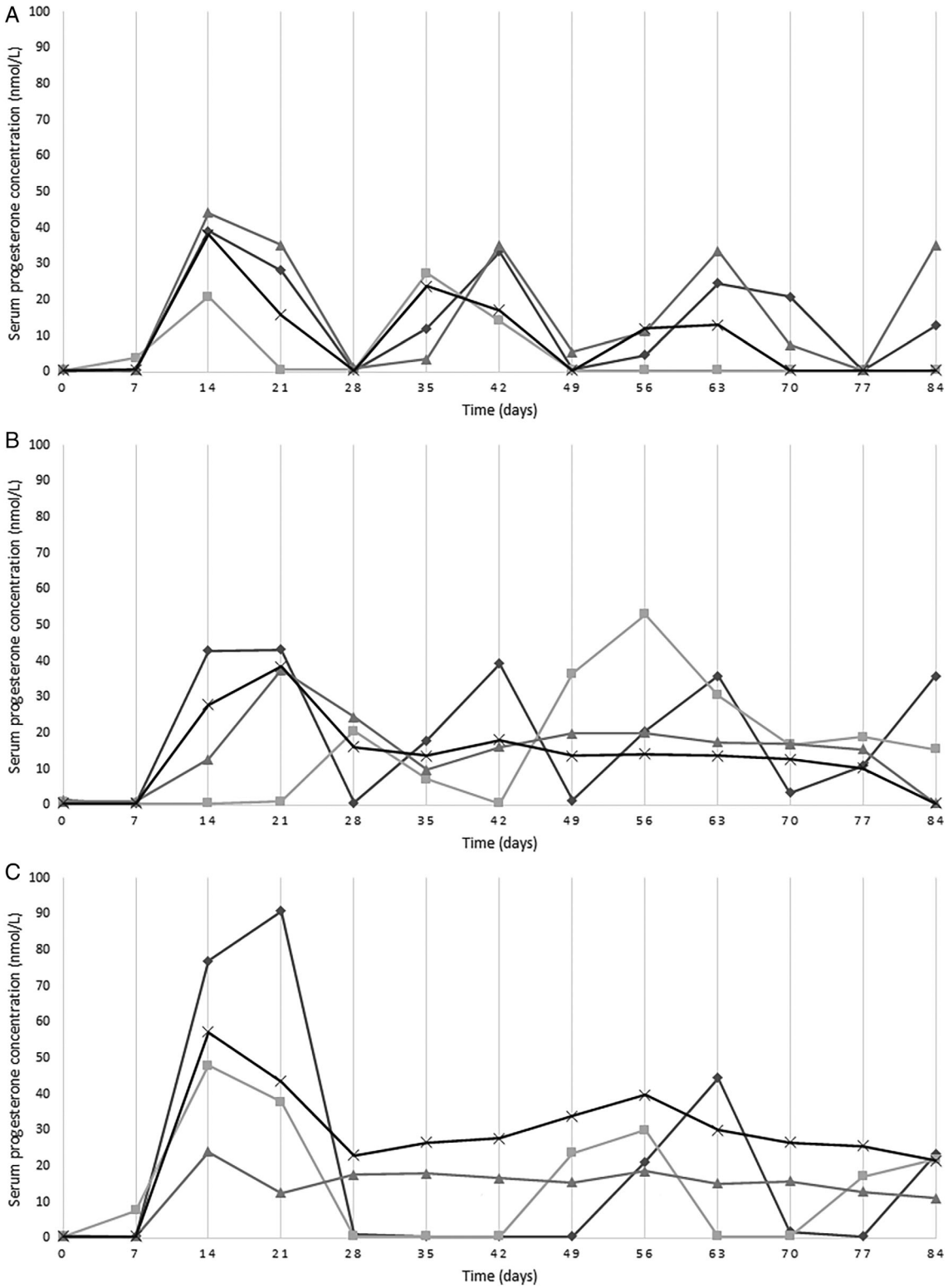

Figure 1. Graphs of serum progesterone concentrations over time in individual mares from each trial group: (A) Control mares (one blank implant), (B) Des1 mares (one Suprelorin-12 implant; 9.4 mg deslorelin acetate) and (C) Des3 mares (three Suprelorin-12 implants; 28.2 mg deslorelin acetate). The day of implant placement corresponds to Day 0.

progesterone profiles from individual Control mares are shown in Figure 1A.

Two mares from Des1 (1 implant) showed persistently elevated SPC (≥9.8 nmol/L) after the initial ovulation after oestrus synchronisation and implant placement, up to and including Day 77. Luteal structures were confined to a single ovary in both mares throughout sequential gynaecological examinations during this period. Of the remaining two mares in this group, one showed erratic oestrous cyclicity characterised by a prolonged period of baseline SPC as well as at least 6 weeks of persistently elevated SPC. Serum progesterone profiles from individual Des1 mares are shown in Figure 1B.

Somewhat similarly, two mares in Des3 (3 implants) showed persistently elevated SPC (≥12.6 nmol/L) after the initial ovulation after oestrus synchronisation and implant placement. Progesterone levels in serum in these mares remained elevated at the conclusion of the trial (Day 84). Luteal structures were confined to a single ovary in both mares throughout sequential gynaecological examinations during this period. The two remaining mares in this group showed brief periods of baseline SPC over the trial period. Serum progesterone profiles from individual Des3 mares are shown in Figure 1C.

If normal progesterone profiles compatible with normal interovulatory intervals are defined as peak concentrations of progesterone >12 nmol/L occurring every 21–28 days with declines to basal concentrations between peaks, then for the Control, Des1 and Des3 treatments, 75.0% (3 of 4), 25% (1 of 4) and 0% (0 of 4) mares, respectively, experienced normal progesterone profiles ($\chi^2 = 5.25$; $P = 0.072$).

The current study demonstrates atypical serum progesterone profiles including transient to prolonged suppression of oestrous cyclicity in seven of eight (87.5%) mares treated with either one or three implants of Suprelorin-12 (9.4 or 28.2 mg deslorelin acetate, respectively). Previous studies have suggested that horses, particularly stallions, are relatively resistant to the down-regulatory effects of GnRH agonists.[6–8] Various studies on the use of low-dose GnRH agonist implants (2.1 mg deslorelin acetate) for ovulation induction in mares describe moderately prolonged interovulatory intervals following treatment.[9–12] Blunted pituitary responsiveness to the administration of GnRH during the first luteal phase following a GnRH-agonist-induced ovulation, consistent with a temporary down-regulation of the anterior pituitary, has also been shown.[13,14]

Few studies have investigated the effects of prolonged exposure to higher doses of GnRH agonists in mares.[4–6,15] Fitzgerald et al.[15] administered the GnRH-agonist goserelin acetate for 28 days via biodegradable depots. Thirteen of 16 mares demonstrated interovulatory intervals in excess of 30 days. In five of these mares, prolonged anovulation was linked to a persistent corpus luteum. In the current study, persistently elevated SPC correlated to the detection of one or more corpora lutea confined, consistently, to the same ovary over consecutive examinations. Although this suggests persistence of corpora lutea in these mares, further study using a larger sample size and more frequent gynaecological examinations is required. Worth noting is that persistent corpora lutea are common in mares, affecting 6.1% of interovulatory intervals[16] and becoming more frequent as mares approach the autumn transition.[17,18] Persistent corpora lutea were not reported in the studies by Kaps et al.[4,5]

In conclusion, the current study demonstrates persistent (≥9 weeks) elevation of SPC in four of eight mares (50%) subsequent to the first ovulation after administration of either one or three Suprelorin-12 implants. Transient suppression of oestrous cyclicity occurred in three of the remaining four treated mares (37.5%). Further research on the use of sustained-release deslorelin acetate implants to suppress oestrus in the mare is warranted.

Acknowledgments

The authors would like to thank Virbac Pty Ltd (New South Wales, Australia) for provision of the Suprelorin-12 and blank implants. Open access publishing facilitated by James Cook University, as part of the Wiley - James Cook University agreement via the Council of Australian University Librarians.

Conflicts of interest and sources of funding

The authors have no conflicts of interest to declare.

References

1. U.S. Food and Drug Administration. FDA Animal Drug Safety Communication: FDA highlights potential health risks to people exposed to altrenogest products for horses or pigs. 2018. https://www.fda.gov/animal-veterinary/cvm-updates/fda-animal-drug-safety-communication-fda-highlights-potential-health-risks-people-exposed.
2. Crabtree J. A review of oestrus suppression techniques in mares. *Equine Vet Ed* 2022;34:141–151. https://doi.org/10.1111/eve.13405.
3. Stout T, Colenbrander B. Suppressing reproductive activity in horses using GnRH vaccines, antagonists or agonists. *Anim Reprod Sci* 2004;82:633–643. https://doi.org/10.1016/j.anireprosci.2004.04.009.
4. Kaps M, Okada C, Gautier C et al. Transient suppression of ovulatory ovarian function in pony mares after treatment with slow-release deslorelin implants. *Domest Anim Endocrinol* 2021;74:106505. https://doi.org/10.1016/j.domaniend.2020.106505.
5. Kaps M, Okada CT, Gautier CM et al. Deslorelin slow-release implants delay ovulation and increase plasma AMH concentration and small antral follicles in Haflinger mares. *Animals* 2021;11:1600. https://doi.org/10.3390/ani11061600.
6. Montovan S, Daels P, Rivier J et al. The effect of a potent GnRH agonist on gonadal and sexual activity in the horse. *Theriogenology* 1990;33:1305–1321. https://doi.org/10.1016/0093-691X(90)90049-Y.
7. Falomo ME, Normando S, Zanibellato E et al. Sexual behavior and serum testosterone concentration in stallions treated with slow-release implants of deslorelin acetate. *J Vet Behav* 2013;8:278–284. https://doi.org/10.1016/j.jveb.2013.02.001.
8. Gautier C, Schmidt K, Aurich J et al. Effects of implants containing the GnRH agonist deslorelin on testosterone release and semen characteristics in Shetland stallions. *Anim Reprod Sci* 2018;195:230–241. https://doi.org/10.1016/j.anireprosci.2018.05.027.
9. Mumford E, Squires E, Jöchle E et al. Use of deslorelin short-term implants to induce ovulation in cycling mares during three consecutive estrous cycles. *Anim Reprod Sci* 1995;39:129–140. https://doi.org/10.1016/0378-4320(95)01383-B.
10. Morehead J, Blanchard T. Clinical experience with deslorelin (Ovuplant™) in a Kentucky Thoroughbred broodmare practice (1999). *J Equine Vet Sci* 2000;20:358–402. https://doi.org/10.1016/S0737-0806(00)80381-0.
11. Vanderwall D, Juergens T, Woods G. Reproductive performance of commercial broodmares after induction of ovulation with hCG or Ovuplant™ (deslorelin). *J Equine Vet Sci* 2001;21:539–542. https://doi.org/10.1016/S0737-0806(01)70158-X.

12. Blanchard TL, Brinsko SP, Rigby SL. Effects of deslorelin or hCG administration on reproductive performance in first postpartum estrus mares. *Theriogenology* 2002;58:165–169. https://doi.org/10.1016/S0093-691X(02)00912-3.
13. Farquhar VJ, McCue PM, Nett TM et al. Effect of deslorelin acetate on gonadotropin secretion and ovarian follicle development in cycling mares. *J Am Vet Med Assoc* 2001;218:749–752. https://doi.org/10.2460/javma.2001.218.749.
14. Johnson C, Thompson D, Cartmill J. Pituitary responsiveness to GnRH in mares following deslorelin acetate implantation to hasten ovulation. *J Anim Sci* 2002;80:2681–2687. https://doi.org/10.1093/ansci/80.10.2681.
15. Fitzgerald B, Peterson K, Silvia P. Effect of constant administration of a gonadotropin-releasing hormone agonist on reproductive activity in mares: preliminary evidence on suppression of ovulation during the breeding season. *Am J Vet Res* 1993;54:1746–1751.
16. Santos VG, Bettencourt E, Ginther O. Long-term characteristics of idiopathic persistent corpus luteum in the mare. *Theriogenology* 2015;84:242–251. https://doi.org/10.1016/j.theriogenology.2015.03.015.
17. King S, Douglas B, Roser J et al. Differential luteolytic function between the physiological breeding season, autumn transition and persistent winter cyclicity in the mare. *Anim Reprod Sci* 2010;117:232–240. https://doi.org/10.1016/j.anireprosci.2009.04.012.
18. King S, Neumann K, Nequin L et al. Time of onset and ovarian state prior to entry into winter anestrus. *J Equine Vet Sci* 1993;13:512–515.

(Accepted for publication 9 April 2023)