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Short Communication

Preliminary Evaluation of Treatment With Long-Acting Estradiol Cypionate and Sulpiride for Advancing First Ovulation of Year in Postpartum Acyclic Mares

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ABSTRACT

Two preliminary trials were performed to evaluate the efficacy of long-acting estradiol cypionate plus sulpiride treatment for hastening the first ovulation in postpartum acyclic mares. In 2010 (year 1) and 2012 (year 2), mares that had foaled in January or February and that were ≥7 ± 1 day postpartum were teased to a stallion to detect estrus and examined by transrectal ultrasonography 3 times weekly. Mares identified as acyclic were alternately assigned to treatments as follows: year 1—group ECP-SUL (n = 5)—same day intramuscular (IM) injection of 50-mg long-acting estradiol cypionate (ECP) plus 1.5-g long-acting sulpiride (SUL), or CON (n = 5)—control; year 2—ECP-SULX2 (n = 4)—IM injection of 100-mg ECP, followed 2 and 7 days later with IM injection of 1.5-g SUL, or CON (n = 5). When a follicle ≥35 mm in diameter, prominent uterine edema and a relaxed cervix were detected, an ovulation-inducing agent was administered. Examinations continued at 2- to 3-day intervals until ovulation was detected. Median (range) interval to ovulation did not differ in year 1 between SUL-ECP (76 days; 31–90 days) and CON mares (74 days; 35–98 days; $P = 1.00$), or in year 2 between ECP-SULX2 (48 days; 36–66 days) and CON mares (39 days; 39–71 days; $P = .91$). The injection of the dopamine antagonist sulpiride in a sustained release form in conjunction with the estrogen ECP failed to shorten the interval to the first ovulation of the year in these two groups of postpartum acyclic mares.

1. Introduction

Most mares undergo a fertile onset of estrus in 5–12 days, with ovulation within 20 days after foaling [1,2]. Yet, some early foaling mares fail to have this ovulatory estrus and may revert to anestrus or transitional estrus, if they have not been maintained under artificial lighting conditions during late gestation [3–5]. Mares with postpartum acyclicity will have corresponding delays in the interval between foaling and conception and reduced probability of maintaining yearly foal production. Developing effective treatments to ensure postpartum cyclicity would be beneficial for the equine breeding industry.

Ginther [2] suggested that either ovarian inactivity immediately after foaling or reversion to inactivity after the first postpartum ovulation was strongly associated with seasonal influences. Whether the mechanism(s) resulting in postpartum acyclicity differs from that contributing to seasonal acyclicity in nonlactating mares remains to be confirmed. Prolactin may be involved in vernal transition of seasonally anovulatory nonlactating mares [6], and stimulation of prolactin with dopamine antagonist administration has been recommended for treatment [6,7]. Because estradiol treatment increases pituitary prolactin content and secretion, therapy that includes adding estrogen to

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administration of a dopamine antagonist may be beneficial [8–10]. Whether concurrent treatment or pretreatment with estrogen, in conjunction with administration of a dopamine antagonist, could be used to stimulate earlier ovulation in postpartum acyclic mares has not been reported. Therefore, these preliminary trials were performed to investigate efficacy of administration of estradiol cypionate and a dopamine antagonist (sulpiride) in acyclic postpartum mares.

2. Materials and Methods

2.1. Animal Use

All experimental procedures were performed according to the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training (http://history.nih.gov/research/downloads/US_Principles.pdf) in accordance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.).

2.2. Animals

Quarter Horse and Quarter Horse–cross mares, aged 4–18 years that foaled in January or February on one farm in Southeast Texas during 2010 and 2012 were used in this study. Mares were maintained on Bermuda grass pasture and fed additional Bermuda grass hay and grain to maintain good body condition (condition score ≥ 5). Mares foaled on pasture, unattended. Only mares with no history of retained placenta, whose uteri were involuting normally, that had a well-developed udder and appeared to be lactating normally, were included in the study.

2.3. Examinations and Assignment to Treatment

Data for this trial were obtained from a production herd that was visited Tuesdays, Thursdays, and Saturdays (3 times weekly) for performing routine veterinary reproductive examinations for breeding purposes beginning February 16. Foaling mares $\geq 7 \pm 1$ day postpartum were exposed to a stallion to detect behavioral estrus on Sunday, Monday, Wednesday, and Friday. Mares were examined by transrectal palpation and ultrasonography on Tuesdays, Thursdays, and Saturdays. Mares that failed to show behavioral estrus, had no evidence of a corpus luteum on ultrasound examination, and that failed to undergo follicular growth ($\leq$10–25 mm diameter, or regressing in size) on at least three successive examinations at 2–3 days intervals, were alternately assigned to treatment: year 1—2010; ECP-SUL (n = 5; 10–25 days postpartum on day of treatment)—intramuscular (IM) injection of 50-mg long-acting estradiol cypionate (BioRelease Estradiol Cypionate LA, BET Pharm, Lexington, KY) plus IM injection of 1.5-g long-acting sulpiride (microparticle polymer sulpiride complex; BET Pharm, Lexington, KY), or CON (n = 5; 17–46 days postpartum on day assigned to control)—no treatment; year 2–2012; ECP-SULX2 (n = 4; 19–32 days postpartum on first day of treatment)—IM injection of 100-mg long-acting estradiol cypionate followed 2 and 7 days later with IM injection of 1.5-g long-acting sulpiride, or CON (n = 5; 14–34 days postpartum on day assigned to control)—no treatment.

Mares were subsequently examined at 2- to 7-day intervals until a dominant follicle $\geq$ 30 mm diameter was detected and then examined at 2- to 3-day intervals until an ovulation-inducing agent was administered (1.5-mg BioRelease Deslorelin IM, BET Pharm, Lexington, KY; or 2500 i.u. Chorulon [hCG] intravenously, Merck Animal Health, Madison, NJ) when a $\geq$35-mm–diameter follicle was detected. Examinations continued at 2- to 3-day intervals until ovulation was detected. Days from foaling to the day that first ovulation was detected were recorded.

2.4. ECP and Sulpiride Treatments

ECP treatment: 1 (2010) or 2 (2012) mL estradiol cypionate (50 mg/mL; BioRelease Estradiol Cypionate LA) was injected IM in the right neck using an 18-gauge needle. Sulpiride (SUL) treatment: Biorelease microparticle formulation was prepared as previously described [8,9] and contained 1.5-g sulpiride, which was injected (20 mL) IM in the left or right (alternated in 2012) semimembranosus muscle using a 16-gauge needle.

2.5. Blood Collection and Assays

In year 2 (2012), a subset of mares (two ECP-SULX2 and two CON mares) had serum samples obtained at intervals (ECP-SULX2 mares at Day 0, before treatment with ECP; Day 2, before the first SUL treatment; Day 7, before the second SUL treatment; and approximately 4–5 days later) to monitor circulating prolactin concentrations. Blood samples were collected from two untreated (CON) acyclic postpartum mares on similar days postpartum for comparison. Blood samples were obtained by jugular venipuncture into sterile vacutainer tubes, allowed to clot, and serum was separated and frozen (-80°C) until assayed for progesterone concentration to confirm absence of a functional corpus luteum (i.e., $<$1 ng/mL) and for prolactin concentration. The concentrations of plasma progesterone were measured by a validated RIA as previously described [11]. Assay sensitivity was 0.2 ng/mL, and intra-assay and interassay coefficients of variation were 3.73% and 8.42%, respectively. Prolactin concentrations were determined by a modified homologous, double antibody radioimmunoassay according to methods previously described [12]. Assay sensitivity was 0.125 ng/mL, and intra-assay and interassay coefficients of variation were 2.52% and 6.93%, respectively.

2.6. Data Analysis

Due to a lack of normal distribution, intervals from parturition to first ovulation for treatment groups were compared using the Mann–Whitney rank sum test.

3. Results

For combined years, 19 acyclic postpartum mares were identified for evaluation from mares foaling in late January or February. Follicle diameters recorded during the first 2 to