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Short Communication

How to Use Oxytocin Treatment to Prolong Corpus Luteum Function for Suppressing Estrus in Mares

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ABSTRACT

Prolonging function of the corpus luteum (CL) is a method of suppressing estrus that uses continued secretion of endogenous progesterone to keep mares out of heat naturally. The most common method of prolonging CL function has been intrauterine insertion of a glass ball (i.e., marble). However, several recent reports have described deleterious complications associated with their use, including the presence of multiple glass balls, fragmentation of the glass ball(s), and/or pyometra. Therefore, the use of other methods for prolonging CL function is warranted. Alternatives to using an intrauterine glass ball for prolonging CL function include (1) oxytocin treatment, (2) inducing a late-diestrus ovulation, (3) intrauterine infusion of plant oils, and (4) manual reduction of the conceptus after day 16 of gestation. Of these, oxytocin treatment is the most practical and efficacious method of prolonging CL function. As described here, one oxytocin protocol involves administering 60 units of oxytocin intramuscularly (IM) once daily on days 7 to 14 after ovulation, which induces prolonged CL function in 60% to 70% of treated mares. Alternatively, by extending the duration of oxytocin treatment to 29 days, administration of 60 units of oxytocin IM can be initiated randomly at any point in the estrous cycle with no loss in efficacy (i.e., over 70% response).

1. Introduction

Suppression of estrous behavior is commonly performed in mares to prevent real and/or perceived/anticipated effects of the behavior from adversely affecting performance activities such as racing or showing [1]. General methods of suppressing estrous behavior include (1) administration of exogenous progesterone or synthetic progestins, (2) extending the duration of corpus luteum (CL) function, (3) suppressing ovarian follicular activity, and (4) ovariectomy [2]. Of these, daily administration of the FDA-approved, orally active, synthetic progestin altrenogest (ReguMate, Intervet, Millsboro, DE 19966) (Altresyn, Ceva Animal Health, Lenexa, KS 66215), has historically been the most widely used method of suppressing estrous behavior, making it the de facto "gold standard." Although altrenogest treatment is highly effective, its expense, need for long-term daily administration, and safety risks for personnel during handling [3] are drawbacks to its use. In addition, because of increased scrutiny/concern regarding the use of exogenous steroid hormones in performance horses, there has been considerable interest in the development of nonpharmacologic (i.e., nonhormonal) methods of estrus suppression.

One method of suppressing estrus that does not require administration of exogenous progesterone/progestins is prolonging function of the CL, which allows continued secretion of endogenous progesterone to keep mares out of heat naturally. In nonpregnant mares, the CL secretes progesterone for approximately 2 weeks after ovulation and then stops functioning as a result of endometrial secretion

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of prostaglandin F2α (PGF2α), which causes regression of the CL (i.e., luteolysis) by destroying its progesterone-producing cells [4]. In response to luteolysis, the blood progesterone concentration falls below 1.0 ng/mL and the mare returns to estrus. Therapeutically preventing luteolysis to maintain secretion of progesterone from the CL has been exploited as an alternative method of suppressing estrus in mares, by capitalizing on the fact that when luteolysis does not occur (for any reason) in a nonpregnant mare, the CL has an inherent functional life span of 2 to 3 months [5], during which the progesterone concentration remains sufficiently elevated to block estrous behavior.

The most common method of prolonging CL function in mares has been intrauterine insertion of a glass ball (i.e., marble). In 2003, Nie et al [6] reported that placement of a 25- or 35-mm sterile glass ball into the uterine body immediately after ovulation resulted in prolonged CL function in approximately 40% of the mares that retained the glass ball (50% of the smaller glass balls were expelled soon after insertion). In mares that developed prolonged CL function after placement of a glass ball, CL function was maintained for approximately 90 days, during which time blood progesterone remained elevated and estrous behavior was not displayed. Given the ease and apparent efficacy of the glass ball protocol, it provided an attractive option for estrus suppression, leading to its widespread use in performance mares over the past 10+ years. Although the original report describing the use of an intrauterine glass ball for estrus suppression found no adverse effect of the glass ball on the endometrium or subsequent fertility [6], it is becoming evident there are significant risks associated with their use. That has been made patently clear by a rash of recent reports documenting extremely deleterious complications associated with the use of intrauterine glass balls, including the presence of multiple glass balls, fragmentation of the glass ball(s), and/or pyometra (Fig. 1) [7–11]. An apparent contributing factor in all these cases was long-term retention of the glass ball (i.e., for years), such that the presence of the glass ball was not known by the individuals working with the mare. That seems to explain why some mares had two glass balls in their uterine lumen (i.e., a second glass ball was apparently inserted without knowledge of the first and/or not checking for it). These recent developments provide a compelling reason to reconsider the use of intrauterine glass balls for estrus suppression in mares and instead use alternative methods of prolonging CL function [12].

Fig. 1. Two glass balls removed from the uterus of a mare. One glass ball was mostly intact, but the other one had fragmented into multiple pieces. Reproduced with permission from Turner et al [10].

Alternatives to using an intrauterine glass ball for prolonging CL function include (1) oxytocin treatment, (2) inducing a late-diestrus ovulation, (3) intrauterine infusion of plant oils, and (4) manual reduction of the conceptus after day 16 of gestation [8]. Of these, oxytocin treatment is the most practical and efficacious method of prolonging CL function, and its use will be discussed here. However, when discussing the use of oxytocin for estrus suppression in mares, it is important to note the diametrically opposed effects of oxytocin on luteal function at differing times of the estrous cycle. In nonpregnant mares, endogenous oxytocin stimulates PGF2α secretion from the endometrium during spontaneous luteolysis [13,14], illustrating that oxytocin is "pro-luteolytic" at that stage of the estrous cycle. The ability of the endometrium to secrete PGF2α in response to oxytocin (endogenous or exogenous) increases markedly between days 10 and 15 after ovulation due to an increase in the concentration of oxytocin receptors [15,16] and PGF2α synthetic enzymes [17] in the endometrial cells. In contrast, before day 10, the concentration of endometrial oxytocin receptors [15,16] and PGF2α synthetic enzymes [17] is low, which effectively blocks the ability of oxytocin (endogenous or exogenous) to stimulate PGF2α secretion. Not only does exogenous oxytocin fail to stimulate PGF2α secretion when it is administered before day 10, but it can also paradoxically disrupt subsequent luteolysis leading to prolonged CL function [18]. It is this "anti-luteolytic" effect of oxytocin during middiestrus that forms the basis for using it as a method of estrus suppression in mares.

2. Clinical Technique

In 2007, we reported [19] that administration of 60 units of oxytocin, q 12 hours, intramuscularly (IM) on days 7 to 14 after ovulation reliably induced prolonged CL function in mares. In 2012, we reported [20] that once daily administration of the 60-unit dose IM was as effective as twice daily administration, simplifying the treatment protocol (CL function was prolonged in 60% to 70% of mares in both groups). Also in 2012, Gee et al [21] reported that administering 10 units of oxytocin IM once daily on days 7 to 14 did not reliably induce prolonged CL function; therefore, the critical threshold IM dose of oxytocin needed to disrupt luteolysis is between 10 and 60 units. Given that 60 units of oxytocin IM once daily is consistently effective, it is the recommended dose for blocking luteolysis. In 2013, Keith et al [22] reported that when IM treatment with 60 units of oxytocin was initiated on day 8 after ovulation and continued through days 10, 12, or 14, the proportion of mares experiencing prolonged CL function significantly increased as the number of days of oxytocin administration increased through day 14, demonstrating the need to continue oxytocin treatment until the expected time of luteolysis for maximum effectiveness. Importantly, in both