Mares behaving badly: a review of methods for estrus suppression in the mare*

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Abstract

Mares are seasonally polyestrus and based on the presence or absence of reproductive hormones, specifically estrogen and progesterone, their behavior can vary throughout the year. Concerns pertaining to mare behavior are often attributed to their estrous cycle, however undesirable mare behaviors need to be differentiated from other non-reproductive causes of undesirable behavior. While behaviors consistent with estrus are described as increased frequency of approaching the stallion, leaning hindquarters toward the stallion, relaxed facial muscles, slightly lowered head, ears turned toward the side, posturing, clitoral eversion, and passive urination, common client complaints such as kicking, tail swishing, or poor attitude may be related to the diestrus phase of the estrous cycle. Display of these behaviors alone may not directly relate to the issues with the estrous cycle and, in particular, if not displayed under controlled teasing conditions with a stallion. Multiple treatments have been utilized by veterinarians for estrus suppression and manipulation, however some of them are poorly effective while others may actually promote estrous behavior. Treatments can be categorized as progestogen supplementation, extension of the luteal phase, suppression of ovarian follicular activity, ovariectomy, and non-traditional or alternative therapies. This review details the individual therapies available for the potential treatment of estrous behavior and each therapy's associated efficacy.

Keywords: Estrus behavior, mare, estrus suppression, review

Introduction

Mares are frequently presented by owners and trainers for undesirable behavior perceived to correlate with cyclicity. However, a variety of other issues may result in declining mare performance, including musculoskeletal, gastrointestinal, behavioral, and urinary tract disorders. Thus, it is important to combine a baseline knowledge of the normal mare estrous cycle and associated reproductive behaviors with a complete physical examination and potential ancillary tests (endoscopy, lameness examination, etc.) before attributing the behaviors to stages of the reproductive cycle. We will therefore briefly review normal estrous cycle and associated behaviors in the mare. Following this, various treatment options will be discussed while focusing on their individual level of empirical evidence of success, advantages, and disadvantages.

The equine estrous cycle

Mares are long-day, seasonally polyestrous breeders. The mare's reproductive seasonality is regulated by photoperiod and can be broken down into four phases throughout the year: anestrus, spring transitional period, the ovulatory season (further divided into estrus and diestrus), and autumn transitional period. However, a small percentage of mares will ovulate year round and never enter the remaining three phases.[1,2]

The beginning of the ovulatory season is marked by the first ovulation which may be detected by regular examinations by ultrasound per rectum or serial determination of serum progesterone concentrations. As stated above, each cycle thereafter is divided into two stages: estrus and diestrus. Estrus averages 6.5 days in length and is characterized by sexual receptivity, dominant follicle emergence, basal concentration of plasma progesterone (<2 ng/ml), and ovulation. Estrogen begins to rise 6 to 8 days prior to ovulation and its presence is due to increased follicular growth. High concentrations of estrogen with baseline progesterone concentrations are positively correlated to expression of estrus behavior. The length of this estrus period becomes abbreviated as day length increases and summer solstice approaches. Ovulation marks the end of estrus (day 0), however, mares

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can still exhibit estrus behavior up to 24-48 hours following ovulation. Diestrus averages 15-16 days, is initiated after ovulation, and extends through luteolysis. This stage is characterized by the presence of a corpus luteum (CL) in the ovary, high concentrations of plasma progesterone, and non-receptive behavior toward the stallion.

Estrogen is not the main dictator for reproductive behavior but rather behavior is regulated by the concentration of progesterone; basal concentrations of progesterone will allow for varying degrees of behavior consistent with estrus. It should be noted that the ovulatory season is the only period of the year during which there is endogenous progesterone by the CL a structure present in the ovary as a result of ovulation of one or more follicles. This concept needs to be understood in order to be able to determine whether or not a behavior is associated with a cyclical pattern and, if it is, what the dominant hormone is at the time the behavior is expressed. Moreover, in most mares, these phases are differentiated by the distinct behaviors when mares are teased under controlled conditions to a stallion. It is only when using a stallion to tease a mare that one can attribute a particular behavior to a particular stage of the estrous cycle. In addition, findings from reproductive ultrasound examination and serum progesterone concentrations can aid in determining in which phase of the estrous cycle is the mare.

Anestrus occurs during the time of year when shortened day length increases pineal melatonin production and a subsequent decrease in hypothalamic gonadotropin releasing hormone (GnRH) production. During this time of low GnRH production, most mares are anovulatory and generally reproductively quiescent. Although ovulation does not occur during this phase, some follicular growth is sustained. There is no luteal source of progesterone during this phase and as a result mares may exhibit varying degrees of estrus behavior and stallion receptivity.

Spring transition occurs during the period of increasing daylight, whereas autumn transition occurs during the period of decreasing daylight. Both periods are characterized by estrus without ovulation. It is during these timeframes that owners will become frustrated with unpredictable periods of estrus behavior since mares will produce follicular waves without ovulation which may extend for many days to weeks. During the spring transition there is a progressive increase in follicular activity with development of up to three anovulatory follicular waves prior to the ovulatory wave.[3] It has been hypothesized that failure of ovulation during spring transition is due to insufficient stores of pituitary luteinizing hormone (LH) or lack of steroidogenic competence of ovarian follicles.[4,5] During the autumn transition there is a progressive decline in luteal and follicular activity marked by a decrease in steroidogenesis. Thus in this regard, the autumn transition can be characterized by a long anovulatory follicular phase or a shortened luteal phase. Lastly, anovulatory hemorrhagic follicles are more common in autumn transition. These occur when a dominant follicle fails to ovulate and subsequently, the follicular lumen fills with blood. Some anovulatory hemorrhagic follicles appear to luteinize and synthesize progesterone, however do not appear to be responsive to prostaglandin F2-alpha as the average interovulatory interval is 38.5±15 days.[6] In summary, autumn transition is accompanied by erratic estrous cycles characterized by long follicular phase/short luteal phase or anovulatory hemorrhagic cycles. This transition can take up to 60 days or more.

Estrus behavior

It is important to understand the range of behavior in normal mares during estrus in order to assess whether or not a behavior is attributable to ovarian hormone production (or lack thereof). These behaviors can only be objectively evaluated in the presence of a stallion under controlled teasing conditions. Such estrous behaviors include increased frequency of approaching the stallion, leaning hindquarters toward the stallion, relaxed facial muscles, slightly lowered head, ears turned toward the side, posturing, clitoral eversion, bent forelimb, vulvar winking, and urination. Posturing is the most significant sign of receptivity and is characterized by a full body response: arched tail, flexed stifles and hocks, tipped pelvis, and weight distribution to the front limbs; this posture allows the mare to support the weight of a stallion during breeding.[1] In the absence of a stallion, estrus behavior may be directed towards inanimate objects or other animals including geldings and mares, and even cattle, however one cannot truly conclude the mare is in heat based on her behavior in the absence of a stallion. In contrast,

during diestrus and thus under the influence of progesterone, mares are non-receptive to stallion advances and may squeal, bite or kick. Other non-receptive behaviors include pinned ears and tail swishing.

Given that the absence of progesterone is a pre-requisite for displaying estrus behavior in mares, behaviors consistent with estrus are observed in anestrus mares and even ovariectomized mares. In fact, the adrenal gland serves as a small source of sex steroid production (estradiol, progesterone, and testosterone) and it is hypothesized by some to play a role in facilitating paradoxical estrus behavior.[7] Paradoxical estrus behavior is unique to the mare and is thought to be important for maintaining a bond between a stallion and his harem of mares in the wild, as they band year-round. This phenomenon is of vital importance clinically because bilateral ovariectomy may not improve estrus behavior, actually the objectionable behavior may be exacerbated. In fact, bilateral ovariectomy may be performed to make a "jump" or "teaser" mare for use in situations of semen collection from stallions. While some "jump" mares are useful just after ovariectomy and require no supplemental estrogen to display estrus behavior, some mares may require estrogen therapy.

Behavior problems in the performance mare: etiology and clinical evaluation

Often mares are presented to veterinarians for complaints of estrus behavior affecting performance. Common complaints from owners that are not associated with estrus behavior include kicking, biting, squealing, stomping in the trailer, tail swishing, and poor attitude. Not all owners can rightfully discriminate actual estrus behavior from other behavioral issues associated with poor discipline or medical problems. Described behaviors by some owners will be the result of inadequate training e.g. the inability of an owner to catch a mare in a pasture is likely not estrus related. However, some mares do fail to perform at their best due to strong estrus behavior and may become difficult to manage, perform erratically, or appear lame.[8] Estrogen has also been associated with laxity in ligaments so lameness may be exacerbated during estrus.[8] Common complaints from owners associated with estrus include elevating tail or winking during performance, leaning on fences toward other horses or stimuli, slowing or stopping at other horses while riding, wet stall/legs/tail due to excessive urination, posturing in the arena, or intermittent colic. Intermittent colic can occur due to 'mittelschmerz', which is pain associated with ovulation.

Whereas estrus behavior can interfere with performance or be an inconvenience, it is important to exclude other causes of poor performance and undesirable behavior before assigning a diagnosis. It is important to obtain a thorough history of the types of behaviors observed, when these behaviors are occurring, and whether they are cyclic in nature. Some mares may possess a desirable demeanor during estrus and exhibit undesirable behaviors during diestrus. A thorough physical examination along with reproductive and lameness examinations should be performed to diagnose whether the mare's behavior/demeanor is truly reproductive in origin. A complete reproductive examination should include trans-rectal palpation, trans-rectal ultrasound, external examination, vaginal speculum examination, serum progesterone concentration, and teasing behavior to a stallion. Granulosa-theca cell tumors can be characterized by variable unwanted behavior depending on the predominant hormone. Undesirable behavior and back soreness can also occur with 'mittelschmerz'. Mares that exhibit pain at the time of ovulation can be painful on palpation of the ovary, painful when touching their flanks, or painful while riding. These mares may show resistance if saddling occurs near the time of ovulation. Mares may require serial reproductive examinations to determine the frequency of the behavior and the relationship to the estrous cycle. If the behavior is deemed not related to the estrous cycle, it is important to systematically evaluate other organ systems to determine other medical problems that may be occurring. Musculoskeletal conditions such as joint and/or back pain should be ruled out as a primary cause of poor performance. Gastrointestinal abnormalities such as enteroliths or gastric ulcers must be considered as a cause for intermittent pain. While urogenital conditions such as uroliths, vaginitis, and pneumovagina can be confused as causes of estrus associated behaviors due to increased frequency of urination or vulvar winking, these conditions can be ruled out during a thorough urogenital examination.

Treatment for estrus suppression can be pursued once other causes of poor performance and undesirable behavior are ruled out and it is determined the mare is free from ovarian pathology. It is

important to emphasize to owners that estrus behavior is a normal behavior, some mares exhibit it more intensely than others and that there are several treatment options available to suppress estrus behavior with varying efficacy. Depending on the owner's goals mares with overt estrus behavior may need to be treated either for a prolonged period of time, or only short-term (i.e. to get through a show). Some treatment options are superior to others, with each having associated advantages and disadvantages. Not all treatments may be suitable for all mares given that behavioral problems may occur at different stages of the estrous cycle.

Progestogen therapy

Progesterone has a strong negative feedback effect on LH secretion by the adenohypophysis[9,10] and can be implemented throughout the year as a therapy for estrus suppression. Exogenous progestogens can be administered to bind to and activate progesterone receptors thereby suppressing estrus behavior. Plasma progesterone concentrations greater than 1 ng/mL need to be maintained to block estrus behavior.[11] Progesterone has a stronger negative impact on LH secretion than it does on follicle stimulating hormone (FSH) secretion, therefore, follicular activity is present due to incomplete FSH suppression, and ovulations are still possible.[12] Mares that demonstrate misbehavior associated with 'mittelschmerz' pain may not benefit from exogenous progestogens as ovulation, and thus ovulatory pain, is still possible. In humans, progesterone has a tranquilizing effect on the central nervous system,[13] thus it can be argued that progestogen administration may not be ideal for high performance athlete mares.

Natural progesterone

Natural progesterone can be compounded in an intramuscular injectable oil-based form. One hundred milligrams of progesterone per day is sufficient to block estrus behavior in mares.[14] Anecdotally, this is the quickest acting therapy available and achieves adequate suppression within 1-2 days of administration. A long-acting intramuscular formulation is available that is given every 7-10 days for suppression of estrus behavior by maintaining concentration of serum progesterone greater than 2ng/mL.[15]

Advantages of natural progesterone include its high efficacy at suppression of estrus behavior, its rapid onset, and its capacity to be administered year-round for estrus suppression. Disadvantages of natural progesterone include associated injection site swelling and pain which is not ideal for performance mares, the need for multiple injections, and the associated human safety issues due to liposolubility and ease of trans-dermal absorption.

Altrenogest

Altrenogest (Regumate®; Merck Animal Health; Summit, NJ) is a progestin considered to be the 'gold-standard' therapy for the suppression of unwanted estrus behavior. It has been FDA approved for the use in horses and is administered orally once daily. Estrus suppression is accomplished within 3 days of treatment initiation. Because of its high efficacy, administration of altrenogest and observation for behavioral improvement may be used as a diagnostic trial when it is unclear whether a particular behavior is due to reproductive cyclicity.

Altrenogest has been recently compounded into an intramuscular injectable.[16] There are two formulations available: a 12 day formulation (Altrenogest BioRelease LA150,BETPharm, Lexington, KY) and a 30 day formulation (MP500, BETPharm, Lexington KY). However, these injectable forms are not FDA approved and the studies available have only been completed by the compounding drug company.[16] MP500 contains 500mg altrenogest encapsulated in lactide-glycolide microparticles and is designed to release approximately 16.6mg altrenogest/day over a 30 day period.[16] A similar amount of altrenogest (450mg) is formulated as a long release LA150 form which inhibited the onset of estrus for approximately 15 days, indicating a greater availability and more rapid release in the LA150 formulation when compared to the MP500 formulation.[16] Thus, MP500 would be more useful for longer-term suppression of estrus in performance mares, whereas LA150 would be suited for shorter suppression (approximately 2 weeks duration).[16]

Advantages of oral use of Regumate® include its high efficacy, ability to be implemented as therapy year-round, absence of reported long-term adverse consequences on mare fertility and body condition, and oral administration.[17] Disadvantages of Regumate® include the associated human safety issues with ease of trans-dermal absorption, the daily dosing regimen, and the cost of the product. The advantages of formulated, intramuscular altrenogest include its reduced frequency of administration when compared to its oral formulation, its progestogenic effect to successfully block return to estrus, and its ability to be implemented year-round. Disadvantages of injectable altrenogest include injection site soreness, cost, and lack of long-term fertility studies.

Synthetic progestin implants

Various hormone implants are available for use in other species and have been unsuccessfully used in mares for estrus suppression.[18,19] Synovex®S (Zoetis Inc.; Kalamazoo, MI) is a bovine growth promotor implant. This implant was developed for use in steers and heifers to promote weight gain and feed efficiency. One subcutaneous implant consists of 8 pellets containing 200mg progesterone and 20mg estradiol, which are slowly absorbed over a period of 100-150 days. Assuming a constant rate of degradation, these implants would release 1.3-2.0 mg progesterone daily.[20] Implanting 1, 4, and 10 devices subcutaneously in mares resulted in return to estrus within the expected timeframe as determined by behavior when teased to a stallion; accordingly, serum progesterone concentrations returned to <0.5ng/ml following cessation of the natural luteal phase.[18] In conclusion, the Synovex®S implant does not provide the minimum amount of progesterone required to prevent estrus behavior in the mare and therefore it is not an efficacious therapy for estrus suppression in mares.

Other injectable progestins

Numerous injectable progestins, including synthetic progestins, formulated for human use have been administered off-label to mares in an attempt to suppress estrus behavior. The perceived advantage of these preparations is that they may be administered periodically instead of daily. However, use of these products does not ensure that the compound will bind the mare's progesterone receptors and result in suppression of estrus behavior. The most common progestins available are the human contraceptive medroxyprogesterone acetate (Depo-Provera® Pfizer Injectables; New York, NY), hydroxyprogesterone caproate (Makena®, AMAG Pharmaceuticals, Inc; Waltham, MA), and megestrol acetate (MGA 200 Premix®, Zoetis; Parsippany, NJ). All three of these progestins have been examined with regard to their ability to maintain pregnancy in the mare as an indicator of maintaining adequate blood progesterone concentrations.[21] All three failed to maintain early pregnancy when administered daily beginning on day 16 of gestation following prostaglandin administration on day 18.[21] Medroxyprogesterone acetate is the only one that has been studied in regards to its ability to suppress estrus behavior in mares and failed to do so.[22] The above studies support the notion that none of these progestins can suppress estrus behavior in mares, likely due to their inability to bind to the equine progesterone receptors.[21] However, many owners and veterinarians continue to use these products with the perception that they are effective. This further indicates that many perceived misbehaviors are likely unrelated to reproductive hormones or cyclicity. Currently, the only effective synthetic progestogen in mares is altrenogest.

Prolongation of the luteal phase

Extending the function of the CL will prolong the luteal phase (diestrus) and the production of endogenous progesterone. Because estrus suppression methods based on this mechanism of action relay on ovulation and subsequent CL formation, they can only be used in cycling mares.

Pregnancy and pseudopregnancy

Prior to pharmacological methods of estrus suppression becoming available, pregnancy was used as a method for suppressing estrus behavior. The gestation length in a mare is quite variable and can range from 320-380 days in length. During the early period, the primary CL is responsible for endogenous progesterone production and subsequent pregnancy maintenance and suppression of estrus

behavior. By day 35, the endometrial cups begin forming and produce equine chorionic gonadotrophin (eCG) which is responsible for luteinization of ovarian follicles. Equine chorionic gonadotropin is continually secreted and progesterone reaches maximal concentrations at 90-120 days gestation, when the placenta begins to maintain pregnancy via placental progestogen production. Pregnancy is currently not recommended as a method of estrus suppression. In addition, an important disadvantage to pregnancy is the regulations by differing sports governing bodies regarding the stage of pregnancy during which a mare can compete.

Pseudopregnancy, or false pregnancy, is accomplished when an embryo is reduced after the period of maternal recognition of pregnancy. Embryos can be reduced via the trans-rectal pinching technique after day 16. Manual reduction of embryos between day 16-22 resulted in prolonged interestrus interval (mean 82 days) in ten of eleven mares.[23] This method is effective at suppressing estrus behavior due to maintenance of endogenous progesterone production for at least 60 days.[23] However, this method may present ethical issues by termination of a viable pregnancy and cost accompanying breeding and cycle management. Similar to the above recommendations pertaining to pregnancy and estrus suppression, this is also not a currently recommended method to suppress estrus.

Intrauterine marble

The intrauterine marble is a well-known method for attempting estrus suppression among clients and veterinarians. However, its efficacy is questionable. The use of an intrauterine marble for the suppression of estrus was first reported in the Netherlands with a success rate of 75%,[24] and its presence was thought to mimic a conceptus or induce a low-grade endometrial inflammation, resulting in prostaglandin depletion and subsequent prevention of luteolysis.[24] A 25- or 35-mm marble was placed in the uterine lumen during early diestrus (within 24 hours of ovulation) and resulted in prolonged luteal function up to 90 days; however, the reported success rate of 75% did not account for the 6 of 24 mares that expelled the marble and included mares who did not respond for multiple cycles. If the 24 mares that started the study are included, only 4/24 (16%) responded on their first cycle. This is very similar to the reported incidence of spontaneous persistent CL (13%) formation from that same study.[24] However, intrauterine placement of a 20mm water filled polypropylene ball inserted 2 to 4 days after ovulation did not produce evidence of continuous prostaglandin release.[25] T hey reported that 9 of 12 mares (75%) had a prolonged luteal phase (44-75 days) which is a different efficacy than that which had been previously reported. The advantages to the intrauterine marble technique are its ease of administration and relatively low cost, leading to its widespread use despite varying degrees of efficacy. The biggest disadvantage to using the intrauterine marble technique is that there is a high probability of failure with the potential for marble expulsion in a majority of mares. In addition, there are well-documented cases of diffuse endometrial damage induced from glass shards embedded into the endometrium, in addition to cases of pyometra.[26] Therefore intrauterine marbles have been shown to be unreliable by a number of studies, with numerous significant complications reported. There are other superior methods available to suppress estrus.

Exogenous oxytocin

Serial oxytocin administration is a practical and efficacious method of prolonging CL function in the mare. Administration of 60 units of oxytocin in the muscle twice daily on days 7 to 14 prolonged CL function in 6 out of 6 mares through day 30.[27] It was later reported that 60 units of oxytocin in the muscle once daily on days 7-14 was equally effective.[28] A lower dose of 10 units of oxytocin in the muscle or intravenously once daily on days 7 to 14 was unsuccessful.[29] A later study found the effectiveness of suppressing estrus behavior following administration of 60 units of oxytocin in the muscle once daily on day 7 to 14 of the mare's cycle.[30] This study concluded that CL function was prolonged for about 2 months in 2 of 3 treated mares with weak expression of estrus behavior noted.[30]

Administration of 60 units of oxytocin in the muscle once daily is effective at prolonging CL function in 60-70% of treated mares when administered on day 7-14. This is the most common protocol implemented clinically.[28] The advantages associated with this method of estrus suppression include its

efficacy, low cost, and reversibility with administration of exogenous prostaglandin. The disadvantages of this method include the requirement of reproductive cyclicity, multiple injections, and cycle management to accurately identify the day of ovulation. If the owner wants to forgo cycle management costs, one option is to initiate treatment with 60 units of oxytocin in the muscle once daily for 29 consecutive days.[31] This option resulted in prolonged CL function in over 70% of treated mares, and cost to the owner is minimal.[31] With once daily or twice daily treatments of 60 units of oxytocin, there were no adverse effects or reactions observed in any of the mares.[31]

Diestrual ovulation

In contrast to other species, mares can ovulate during diestrus in the presence of high circulating concentrations of progesterone. The frequency of diestrus ovulations varies according to breed, with Thoroughbreds and Quarter Horses having as many as 20% of ovulations occurring during diestrus, while the frequency is very low in ponies[32,33] Diestrual ovulations that occur 1-4 days prior to luteolysis may cause a prolonged luteal phase, as the immature CL does not undergo luteolysis in the face of endogenous endometrial prostaglandin production. Induction of a diestrual ovulation using 3000 IU of human chorionic gonadotropin (hCG) intravenously successfully resulted in a prolonged luteal phase (2-3 months) in 4 of 5 treated mares that developed a follicle >30mm in size.[34] However, not all mares developed a large enough follicle to induce ovulation on their first cycle; 2 of five mares developed inducible follicles on their first cycle (both responded to hCG), one mare developed an inducible diestrual follicle on her second cycle (responded to hCG), one mare developed one inducible diestrual follicle on her third cycle (did not respond to hCG), and one mare never developed an inducible diestrual follicle.[34] In that same study, 1 of 4 control, saline-treated mares had a spontaneous diestrual ovulation and developed a prolonged luteal phase.[34] Advantages of this option for treatment of estrus suppression include its effectiveness if conditions are met (30mm late diestrual follicle that responds to hCG treatment). However, a major disadvantage is that only a small percentage of mares will be presented with a diestrual follicle large enough to respond to treatment and they may or may not respond to hCG treatment. Another limitation that hinders its use in practice includes the necessity of multiple reproductive tract ultrasonograms to identify an appropriately-sized diestrual follicle capable of responding to an ovulation induction agent.

Intrauterine plant oil

In 2011 it was reported that the intrauterine infusion of 1mL of either coconut or peanut oil on day 10 after ovulation prolonged the luteal phase in 11 of 12 treated mares as assessed by concentrations of progesterone above baseline for 30 days.[35] Estrus behavior was not documented. A follow-up study found that when 1mL fractionated coconut oil was infused into the uterus on day 10 in 12 mares, all 12 mares returned to estrus as expected with a normal decline in progesterone at the time of luteolysis.[36] Based on the conflicting data, more work is needed to determine whether intrauterine plant oil administration is an effective method for estrus suppression in mares and whether there are any associated side effects with its administration. If effective, it would require some cycle management to identify the day of ovulation with resultant prolongation of endogenous progesterone production. As with other methods of prolongation of luteal function, reproductive cyclicity must be present.

Suppression of ovarian follicular activity

Suppressing ovarian function is done by targeting and subduing the hypothalamic-adenohypophyseal-ovarian axis. By down-regulating the hypothalamic production of GnRH, there is a subsequent reduction in pituitary gonadotropin production and a resultant suppression of ovarian activity. By employing these methods the reduction in follicular growth and subsequent lack of ovulation result in a decrease in endogenous estrogen production and no endogenous progesterone production. Typically mares that undergo these therapies exhibit behavior similar to their anestrus behavior; therefore, it may not suppress or solve behavior problems if mares are reported to exhibit estrus behavior in the winter

months. The therapies listed below may be a useful test of the likelihood of the efficacy of ovariectomy for behavioral modification.

GnRH agonist

When a GnRH agonist is administered, it is postulated that the adenohypophysis becomes hyperstimulated and eventually desensitized.[37] With desensitization, there is a reduction in gonadotropin release and a subsequent lack of ovulation (due to reduced LH) and reduction in follicular growth (due to reduced FSH). Ovuplant™ (Peptech Animal Health Pty Limited; North Ryde NSW 2113, Australia) is a deslorelin-containing, slow-release implant that functions to hasten ovulation in mares. Field reports indicate that Ovuplant™ is associated with a delayed return to estrus in mares following implantation,[38] with a prolonged interovulatory interval when compared to induction of ovulation with intravenous hCG.[39] In addition, administration of prostaglandin to induce luteolysis following Ovuplant™ resulted in a prolonged interovulatory period compared to mares without the implant by an average of 6.2 days.[38,40,41] As expected, plasma concentration of LH and FSH were lower in treated compared to control mares.[38] However, removal of the deslorelin implant within 48 hours after administration resulted in normal interovulatory intervals and FSH secretion.[40] When Ovuplant™ is used with the goal of estrus suppression, the implant is left in place in order to maintain a decrease in gonadotropin production with a resultant suppression of ovarian activity. Although this option offers ease of administration, the duration of estrus suppression is short-lived (until follicular growth resumes) and dose dependent. This method does hold an increased cost associated with cycle monitoring, unpredictable return to estrus, and problems with availability of the implant (not available in the USA).

GnRH antagonist

Gonadotropin releasing hormone antagonists act by inhibiting the action of GnRH and thereby inhibiting gonadotrophin secretion and subsequent ovarian activity. The advantage of a GnRH antagonist over GnRH agonists in that they have a more rapid onset.[42] For this reason, administration of GnRH antagonists is more frequent that their agonist counterparts.[42] Antarelix™ ([N-Ac-D-Nal(2)‘, D-pCl-Phe*, D-Pa1(3)3, D-(HCi)6, Lys(iPr)*, D-Ala”] GnRH; 100 pg/kg in 10 mL of 5% mannitol, Europeptides, Argenteuil, France) is a GnRH antagonist that has been shown to postpone ovulation in mares, thereby increasing the interovulatory interval.[43] When a single subcutaneous dose of Antarelix™ (100ug/kg) was administered to mares on day 8 following ovulation, the estrous cycles of treated mares were significantly longer than control mares (33.5±3.8 days vs. 24.0±1.1 days).[44] The prolongation was attributed to a delay in the development of a large preovulatory follicle due to a reduction in FSH and LH concentrations.[43] Although ovarian activity can be suppressed, behavioral estrus can be inconsistent with this treatment; in addition, frequent administration, short-term effect, and highly variable responses among mares also reduce the indications for clinical application of this treatment option.

GnRH vaccine

Vaccination with a GnRH carrier protein and adjuvant can induce an immune response to a GnRH protein, resulting in neutralization of the deca-peptide via production of anti-GnRH antibodies. By neutralizing GnRH, there is a decrease in gonadotropin production and a subsequent reduction in ovarian activity. Mare response, as indicated by antibody titers to GnRH immunization, is variable and estrus-related behavior may correlate with the achieved level of ovarian suppression.[44] There are several GnRH vaccines available on the market.

For instance, Equity® (Zoetis Australia Pty Ltd.; Rhodes NSW, Australia) is perhaps the most widely applied. It requires two doses administered four weeks apart and is labeled for use in Australia for estrus suppression in mares and fillies not intended for breeding. In a study done by Pfizer Animal Health, all treated mares exhibited increased GnRH antibody titers, reduction in ovarian size, decreased folliculogenesis, and anestrus-like behavior (average of 3 months duration) within two weeks of the second immunization.[45] The length of ovarian shutdown following the second immunization varied from 4-23 weeks in 10 of 16 vaccinated mares whereas the remaining 6 vaccinated mares did not return to

cyclicity for the remainder of the trial which was 14-18 weeks from the onset of initial injection.[45] A second retrospective study identified abnormal prolonged acyclicity for 1-3 stud seasons in retired Thoroughbred racing mares that all had an associated history of Equity® administration.[46]

Improvac® (Pfizer Laboratories Ltd; Sandton, South Africa) is another GnRH vaccine available and is labeled for immunocastration to control boar taint in meat. Improvac® may be used off-label to suppress cyclicity in mares with resumption of ovarian function and expression of estrus behavior being highly variable.[47] All mares in this study had suppressed cyclicity within 8 weeks of the first vaccination and cyclicity remained suppressed for a minimum of 23 weeks.[47] Improvac® is not labeled for use in animals intended for breeding due to the potential for extended ovarian suppression.

Vaccination against GnRH is successful and effective at suppressing ovarian function and may or may not be effective at estrus behavior suppression. The duration of ovarian suppression and potential estrus behavior suppression is variable and unpredictable. Thus, due to the potential of ovarian suppression of unknown length it is not recommended for use in potential breeding mares. Injection site reactions have been reported with all GnRH vaccines with variably severity from slightly raised flat swelling at the site of injection to systemic pyrexia the day after injection.[44,45,47] Gonadotropin releasing hormone vaccines are not currently available in the United States.

Porcine zona pellucida vaccine

The porcine zona pellucida vaccine (PZP) vaccine is derived from porcine zona pellucida protein 3 (PZP3). This binding site on the zona pellucida is similar across domestic species. The PZP3 binding site also happens to be the same binding site for a spermatozoon, therefore, this vaccine was developed as a contraceptive to prevent sperm binding and subsequent acrosome reaction and fertilization. Recently, the effect of the vaccine on ovarian function and estrous cyclicity was discovered.[48] Five out of 6 immunized mares showed intermittent to sustained evidence of ovarian suppression for greater than 5 weeks following the second immunization. Ovarian volume, follicle counts, maximum follicle diameter, and pregnancy rate in treated mares were significantly lower than control mares.[48] This study highlights the suppressive effect of the PZP vaccine on a majority of mares is consistent with previous studies,[49] however, behavior was not evaluated. Although this may be a potential therapy for estrus suppression via ovarian suppression, future research is required to investigate resulting behaviors and potential adverse side effects of vaccination.[49]

Bilateral ovariectomy

Bilateral ovariectomy is the most effective therapy for behavioral modification in mares who exhibit adverse behavior during diestrus or mares that exhibit adverse behavior due to 'mittelschmerz' as bilateral ovariectomy will result in abolishment of luteal potential and abolishment of ovulation and its associated discomfort. Bilateral ovariectomy may also be effective in mares that show estrus behavior problems only during the ovulatory season and do not exhibit estrus behavior problems during anestrus. However, bilateral ovariectomy may not be effective in those mares that exhibit overt estrus behavior during the ovulatory season and also overt estrus behavior during anestrus as bilateral ovariectomy will result in the same endogenous hormonal environment as is present during anestrus or even times of ovarian suppression. Therefore, when considering ovariectomy as a treatment option for overt estrus behavior, it would be useful to observe response to therapy aimed at suppression of ovarian activity (see above) or anestrus behavior. In general, client satisfaction with bilateral ovariectomy is relatively high with 78% (18/23) of owners being satisfied or very satisfied with the procedure.[50] Veterinarians must keep in mind that an ovariectomy may be classified as successful by an owner even if a behavior was not reproductively related. The advantage of this treatment option is that potential long-term success. However, due to mare variability, bilateral ovariectomy may not be effective in eliminating unwanted behavior. Additionally, ovariectomy poses surgical risk as well as irreversible loss of breeding potential. Case selection is therefore extremely important in considering this option.

Alternative therapies

Auricular acupuncture

Acupuncture is a form of alternative medicine that is becoming more commonplace in the equine industry. Anecdotal reports suggest application of an ear staple as a method of suppressing estrus. The premise behind the ear staple is that it stimulates the auricular vagal branches which results in an increase in parasympathetic nervous system tone.[51] This results in pineal melatonin release and consequent decreased production of GnRH from the hypothalamus. The hypothalamic-adenohypophyseal-ovarian axis becomes quiescent, similar to anestrus. However, there is no empirical evidence supporting this theory; thus, it is not recommended as a valid treatment option for estrus suppression in the mare.

Herbal remedies

Mare Magic (Mare Magic; Shelton, WA) is an herbal supplement marketed "to help influence a quiet disposition in mares and geldings". Its active ingredient is dried raspberry leaf which has been implemented in treating morning sickness, preventing miscarriage, and shortening and easing labor in women.[52] Raspberry leaf tablets are touted as being safe for pregnant women and may be beneficial for women during parturition by causing spontaneous rupture of the membranes and shortening labor duration.[53] However, its effect in horses regarding pregnancy, parturition, or estrus suppression etc. has not been empirically assessed. There is little to no evidence supporting its application.

Conclusions

Several therapies for estrus suppression are available with variable efficacy and advantages and disadvantages. Any time a mare is presented for undesirable behavior related to the estrous cycle or reproductive cyclicity, it is important to ensure that the behavior problem(s) are not related to medical or training issues. Once a diagnosis is made, treatment selection should be based on the time of year the behavior occurs, specific behaviors observed, the duration of suppression needed, and the cost associated with each treatment implementation. By far, the most reliable way to suppress estrus behavior any time of the year is administration of progestogens—compounded natural progesterone or altrenogest. However, oxytocin injections during the ovulatory season are found to be effective, low cost, and an excellent alternative to administration of progestogens.

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