Prolonging Function of the Corpus Luteum to Suppress Estrus in Mares

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The orally active synthetic progestin altrenogest is widely considered to be the “gold-standard” method of inhibiting estrous behavior in mares. However, its expense, need for long-term daily administration, safety concerns for personnel during handling, and increased public scrutiny regarding the use of exogenous steroids in performance horses have collectively prompted interest in the development of practical methods of prolonging corpus luteum (CL) function, which allows continued secretion of endogenous progesterone to keep mares out of heat naturally. Placement of an intra-uterine glass ball has been the most widely used method of prolonging CL function, but variable efficacy and the potential for deleterious consequences associated with them (if not eventually removed), have stimulated interest in alternative methods of prolonging CL function. Currently, oxytocin treatment appears to be the most practical and efficacious alternative method of prolonging CL function. Additional methods include inducing a late-diestrus ovulation, intrauterine infusion of plant oils, and establishment of pregnancy followed by manual reduction of the conceptus after day 16 of gestation. Author’s address: Department of Animal, Dairy and Veterinary Sciences, School of Veterinary Medicine, Utah State University, Logan, UT 84322; e-mail: dirk.vanderwall@usu.edu. © 2013 AAEP.

1. Introduction
A common complaint of horse owners, trainers, and veterinarians is variable performance of mares that is related to the estrous cycle. In a survey of more than 750 veterinarians, approximately 90% had the clinical impression that the estrous cycle affected the performance of mares, and the most frequently reported clinical sign associated with an effect of the reproductive cycle on performance was attitude change, whereas other signs included tail-swishing, difficulty to train, squealing, “horsing,” excess urination, kicking, and a decrease in performance. As the preceding list of objectionable behaviors suggests, not all problematic behaviors are necessarily associated with estrus. In addition, it is important to note that some behaviors displayed by mares that are thought to be associated with estrus are in fact not estrous behaviors. They are instead signs of 1) submissive behavior, 2) urogenital discomfort, or 3) stallion-like behavior. Of these, submissive behavior may be most easily confused with estrous behavior. Submissive behavior includes leaning away from perceived threats, swishing/ringing the tail, and actively squirting urine, which collectively can give the impression of estrus, whereas true estrous behavior is manifested by leaning toward the stallion (or other stimulus), a relaxed, lifting motion of the tail, stationary/squat-
ting stance, and passive urination (full stream or small amounts in dribbles). Urogenital discomfort may be the result of cystitis or renal disease, whereas stallion-like behavior may be associated with neoplasia of the ovaries or administration of exogenous anabolic steroids.

Because numerous factors (both reproductive and nonreproductive) can adversely affect performance, when evaluating an owner/trainer complaint of an estrous cycle-related behavior/performance problem in a mare, the first step is to determine if the problematic behavior is or is not related to a specific phase of the estrous cycle. To thoroughly evaluate the mare, additional expertise may be needed in the form of consultation with or referrals to behavior and/or reproduction experts, because a systematic team approach to evaluating and solving the problem may be most successful.

If problematic behavior is consistently associated with estrus, it is necessary to determine if the underlying cause is physical or behavioral. Some mares that exhibit performance problems during estrus may be having pain in the periovulatory period that can vary from sensitivity to weight and/or manipulation of the back (caused by tack and/or rider) to overt colic-like symptoms. Mares that have back pain and/or colic-like symptoms in the periovulatory period may benefit from the use of an ovulatory agent to reduce the time a large pre-ovulatory ovarian follicle is present or complete suppression of cyclical reproductive activity. In contrast to mares with an underlying physical cause of performance issues during estrus, some mares display such profound signs of estrus that the behavior itself impairs performance. For example, even under saddle, some mares may “break down” and show estrus in response to being around other horses and/or other stimuli. For these mares, suppression of estrus is clearly warranted. In other mares, the condition may be much more subtle, causing owners and trainers to report that the mare is less cooperative or attentive during estrus, causing owners and trainers to report that the mare is less cooperative or attentive during estrus, whereas stallion-like behavior may be associated with neoplasia of the ovaries or administration of exogenous anabolic steroids.

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It is also common to suppress estrus when the signs of estrous behavior are simply perceived to be associated with performance problems or to preemptively block the behavior to preclude the possibility of an adverse effect of estrus on performance. When suppression of estrous behavior is desired, the following general methods have been used in mares: 1) administration of exogenous progesterone or synthetic progestins, 2) extending the duration of corpus luteum (CL) function, 3) downregulating ovarian follicular activity, and 4) ovariectomy (for complete review, see Vanderwall and Nie).

When discussing methods of suppressing estrus, it is important to note that mares are unique among domestic animals, because in addition to ovarian-derived estrogen-induced signs of estrous behavior, many seasonally anovulatory and ovarioctomized mares exhibit paradoxical estrous behavior associated with hormone secretion from the adrenal cortex. The intensity of this type of “unseasonable” estrous behavior can be equivalent to the behavior intact cycling mares display during the initial and terminal days of estrus but is generally less intense than the behavior displayed near ovulation. It has been postulated that behavioral receptivity to a stallion outside the breeding/ovulatory season that is independent of ovarian estrogen secretion may have developed as a means of maintaining social bonds between a harem stallion and his mares. This phenomenon has important implications for the clinical management of estrous behavior in mares, since simply suppressing ovarian follicular activity or removing the ovaries may not ensure complete elimination of estrous behavior.

2. Exogenous Progesterone/Progestins

Historically, the use of exogenous progesterone/progestins has been the most widely used method of suppressing estrous behavior in mares. It was first demonstrated in the 1960s that daily intramuscular administration of 0.2 mg/kg progesterone in oil effectively suppressed signs of estrus in mares. Although progesterone in oil is available from compounding pharmacies, the need for daily administration and the potential for soreness at the site of injection are limitations to its use. An alternative to daily administration of progesterone in oil is a compounded long-acting injectable formulation of progesterone containing a total dose of 1.5 g progesterone that will maintain blood levels of progesterone above 1.0 ng/mL for approximately 10 days, which is a sufficient level of progesterone to block estrous behavior, however, the potential for soreness at the injection site is a limitation to its use in performance horses.

In contrast to native progesterone, the orally active synthetic progestin altrenogest is approved for suppressing estrus in mares and is widely considered the “gold-standard” method of inhibiting estrous behavior. Daily oral administration of altrenogest at a dose of 0.044 mg/kg is very efficacious for suppressing estrus in mares, however, its expense, need for long-term daily administration, and safety concerns for personnel during handling and administration are drawbacks to its use. As an alternative to oral administration, it was recently reported that intramuscular administration of a compounded preparation containing 225 mg or 450 mg of altrenogest in a sustained-release vehicle blocked estrous behavior for approximately 12 and 15 days, respectively, and administration of 500 mg altrenogest in microparticles suppressed estrous behavior for approximately 30 days. Veterinarians should use FDA approved products for this indication. Certain compounded products can vary significantly in potency and stability. Consequently results may vary substantially. There can also be legal and ethical issues with using a compounded product when there are FDA approved products.
available in the appropriate dosage form and for the appropriate indication.

Although there have been anecdotal reports on the use of synthetic progestins other than altrenogest for estrus suppression in mares, none have been found to be efficacious when rigorously tested. Because of the ineffectiveness of other synthetic progestins, altrenogest remains the primary exogenous hormone used for suppression of estrus; however, because it is a steroid hormone, it is facing increased scrutiny because of public concern about the use of steroids in performance horses. Therefore, finding effective alternatives to the use of exogenous steroid hormones is particularly prudent at this time.

3. Prolonging Function of the Corpus Luteum
An alternative method of suppressing estrus that does not require administration of exogenous progestrone/progestins is prolonging function of the CL, which allows continued secretion of endogenous progesterone to suppress estrus naturally. In nonpregnant mares, the CL secretes progesterone for approximately 2 weeks after ovulation (ie, the duration of diestrus) and then stops functioning when the endometrium secretes prostaglandin P2α (PGF2α) during luteolysis. As a result of luteolysis, progesterone levels fall below 1.0 ng/mL and the mare returns to estrus. Development of therapeutic strategies for prolonging function of the CL (ie, maintaining progesterone >1.0 ng/mL) as a means of long-term suppression of estrus has gained increasing interest because it obviates the need for administration of exogenous progesterone/progestins to mares. The remainder of this review will discuss various methods of prolonging CL function for suppression of estrus in mares.

4. Intrauterine Glass Ball
The most common method of prolonging CL function in mares has been intrauterine insertion of a glass ball (ie, marble). Nie et al 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 seven of 18 mares (39%) that retained the glass ball after insertion (six of 12 mares expelled the 25-mm glass ball soon after insertion). In mares with prolonged CL function after placement of the glass ball, CL function was maintained for approximately 90 days, during which time progesterone levels remained above 1.0 ng/mL and estrous behavior was not exhibited. In non-treated control mares, spontaneous prolongation of CL function occurred in four of 32 mares (13%). Although placement of a glass ball appeared to be an efficacious means of blocking estrous behavior for an extended period of time, it should be noted that in addition to the 11 mares that retained the glass ball and never developed extended CL function (ie., continued to cycle normally while the glass ball was in the uterine lumen), three of the seven mares that received a glass ball had one or two estrous cycles of normal duration after placement of the glass ball before CL function was prolonged. Therefore, on a “per-cycle” basis, the incidence of prolonged CL function was only 11% (7/62 cycles) in the mares that received a glass ball compared with 8% (4/50 cycles) in the nontreated control mares, which was not significantly different between groups.

More recently, Rivera del Alamo et al examined the effect of intrauterine placement of a 20-mm, water-filled polypropylene ball on the duration of CL function in mares with the specific objective of investigating two potential mechanisms by which CL function is extended: 1) the intrauterine device induces mild endometrial inflammation that completely blocks or markedly attenuates PGF2α secretion (ie, prevents high-magnitude luteolytic pulses) or 2) the physical presence of the device (movement and/or contact with the endometrium) directly mimics the inhibitory effect of a conceptus on PGF2α secretion. Corpus luteum function was extended in nine of 12 mares (75%) that received the intrauterine device with an average duration of 57 days compared with none of 12 control mares in which the average duration of CL function was 16 days. In six of the nine mares with extended CL function, small accumulations of intrauterine fluid (≤10 mm × 20 mm) were identified during the luteal phase, but no neutrophils or bacteria were recovered on uterine swabs when they were examined during the subsequent estrus. In addition, changes in uterine biopsy scores for inflammation and glandular dilation before and after treatment were similar for control and uterine device mares (with or without extended CL function); therefore, there was no evidence that the intrauterine device induced an inflammatory response in the uterus. On the basis of intensive blood sampling and measurement of PGF2α metabolite (PGFM) levels in the systemic circulation, on days 11 to 16 after ovulation in four control and eight uterine device mares, PGF2α secretion was attenuated in mares with prolonged CL function, with the exception of two mares; one mare showed a single PGFM peak and another showed two isolated PGFM peaks. Because there was no evidence of inflammatory changes caused by the intrauterine device, the author concluded the physical presence of the device in the uterine lumen somehow mimicked the effect of a conceptus by impairing endometrial secretion of PGF2α. In a subsequent brief report, the same group determined the “embryo-mimicking” effect of the intrauterine device prevents up-regulation of endometrial gene expression of cyclooxygenase-2 (COX-2) in mares that develop prolonged CL function, which is the key regulatory enzyme in PGF2α synthesis/secrition. In nonpregnant mares, endometrial COX-2 expression is upregulated on days 14 to 15, coincident with the onset of PGF2α secretion, whereas the expression of COX-2 remains at basal levels in pregnant mares.
Although placement of an intrauterine glass ball has been the most widely used method of prolonging CL function in mares, there have been reports of deleterious consequences associated with their use, such as spontaneous fragmentation of the glass ball in the uterine lumen.\textsuperscript{28} Although that specific complication can be avoided by the use of a device made of an alternative material such as plastic,\textsuperscript{23} it is important to note that regardless of the composition of the device, if it is not eventually removed (spontaneously or manually), some mares may retain the device for an extended period of time (ie, years), such that its presence in the uterine lumen may not be known to individuals working with the mare (Fig. 1). This has led to situations in which mares have been bred when an intrauterine device was present, and there are anecdotal reports of mares becoming pregnant despite the presence of an intrauterine device and subsequently aborting because the device compromised the pregnancy later in gestation. Because of potential complications such as these, there is a need for alternative methods of extending CL function that are practical, efficacious, and safe.

5. Oxytocin Treatment

In contrast to the use of an intrauterine glass ball, administration of exogenous oxytocin during diestrus is an alternative method of blocking luteolysis to prolong CL function. Endogenous oxytocin is involved in regulating PGF2\(\alpha\) secretion from the endometrium during spontaneous luteolysis in the mare,\textsuperscript{29,30} and, although administration of exogenous oxytocin to mares around the time of luteolysis (ie, days 11 to 15 after ovulation) stimulates an immediate onset of PGF2\(\alpha\) secretion,\textsuperscript{31–33} when oxytocin is administered starting in the mid-luteal phase prior to the expected time of luteolysis (ie, before day 10 after ovulation), it does not induce PGF2\(\alpha\) secretion and often paradoxically disrupts luteolysis causing prolonged CL function.\textsuperscript{32}

Experimentally, continuous infusion of oxytocin from day 8 to 20 after ovulation blocked luteolysis in four of five mares, whereas luteolysis occurred at the expected time in all four control mares that received saline infusion.\textsuperscript{34} Although it successfully induced prolonged CL function, continuous infusion of oxytocin would not be a practical method of long-term suppression of estrous behavior. As an alternative, in a "proof of principle" study, we showed that twice-daily intramuscular administration of 60 units (3 mL) of oxytocin on days 7 to 14 after ovulation was an efficacious method of disrupting luteolysis, because it caused prolonged CL function through day 30 after ovulation in six treated mares, whereas six saline-treated control mares underwent luteolysis by day 16 after ovulation.\textsuperscript{35} In a subsequent study, we compared the use of the same 60-unit dose of oxytocin given intramuscularly twice daily versus once daily on days 7 to 14 after ovulation and found that CL function was maintained for 50 days after ovulation in five of seven mares (71%) treated twice daily, five of eight mares (63%) treated once daily, and one of seven (14%) untreated control mares.\textsuperscript{36} There was no difference (\(P > 0.05\)) in the proportion of mares with extended CL function between once- and twice-daily administration of oxytocin, whereas collectively oxytocin treatment increased (\(P < 0.05\)) the proportion of mares with extended CL function. Therefore, the oxytocin treatment protocol can be simplified to once-daily administration on days 7 to 14.

In a third study, our objective was to monitor CL function and estrous behavior in mares for 90 days after administration of 60 units of oxytocin once daily on days 7 to 14 after ovulation.\textsuperscript{37} Two of nine control (22%) and six of nine oxytocin-treated (67%) mares had prolonged CL function (\(P = 0.08\)). The mean duration of CL function in the two control mares with prolonged CL function was 78 days and in the six oxytocin-treated mares was 69 days. In both of the control mares and one of the six oxytocin-treated mares with prolonged luteal function, estrus was not observed while progesterone remained above 1.0 ng/mL. For the remaining five oxytocin-treated mares with prolonged luteal function, weak estrus was occasionally observed during the period of elevated progesterone. Although oxytocin treatment effectively prolonged CL function for approximately 2 months in two thirds of the treated mares, enigmatically, weak estrus was occasionally observed in some mares during the period of prolonged CL function.

Other research groups have recently evaluated modifications to the oxytocin protocol for prolonging
CL function by altering the dose, route of administration, and/or duration of treatment. In 2012, Gee et al.\textsuperscript{38} reported that five of six mares (83%) treated with 10 units of oxytocin intravenously once daily on days 7 to 14 had prolonged CL function compared with only one of six (17%) and two of six (33%) mares treated with 10 units oxytocin or saline intramuscularly, respectively. The apparent inability of 10 units of oxytocin administered intramuscularly to prolong CL function indicates the threshold intramuscular dose of oxytocin needed to disrupt luteolysis and prolong CL function is between 10 and 60 units. In all of the oxytocin-treated mares that developed prolonged CL function, estrous behavior was inhibited throughout the period of extended CL function, demonstrating the clinical efficacy of oxytocin treatment for estrus suppression. In a 2013 study, Keith et al.\textsuperscript{39} initiated intramuscular treatment with 60 units of oxytocin on day 8 and compared three different durations of treatment (2, 4, or 6 days). Administration of oxytocin on days 8 to 10, 8 to 12, and 8 to 14 induced prolonged CL function in three of seven (43%), four of seven (57%) and six of seven (86%) mares, respectively, compared with none of seven (0%) control mares. The proportion of mares with prolonged CL function increased ($P < 0.01$) as the number of days of oxytocin administration increased, confirming the need to continue oxytocin treatment until the expected time of luteolysis (ie, day 14) for maximum effectiveness. Also in 2013, Bare et al.\textsuperscript{40} compared the estrous cycle characteristics of mares treated with oxytocin or the synthetic oxytocin analog carbetocin on days 7 to 14 after ovulation. Carbetocin has a circulating half-life after intravenous administration 2.5 times longer than oxytocin (17.2 minutes versus 6.8 minutes, respectively).\textsuperscript{41} Oxytocin-treated mares received 60 units of oxytocin intramuscularly once daily, whereas carbetocin-treated mares received 1.19 mg carbetocin intramuscularly, which, on the basis of its pharmacokinetics, is equivalent to 60 units of oxytocin. Compared with nontreated control cycles, administration of oxytocin increased the inter-estrous and inter-ovulatory intervals ($P < 0.01$), whereas carbetocin shortened the inter-estrus and inter-ovulatory intervals ($P < 0.01$), essentially “short-cycling” the mares. Therefore, with the use of this dose and treatment schedule, carbetocin was not efficacious for prolonging CL function.

In nonpregnant mares, the ability of the endometrium to secrete PGF2α in response to oxytocin (endogenous or exogenous) increases markedly between days 10 and 15 after ovulation concomitantly with an increase in the concentration of oxytocin receptors\textsuperscript{53,42} and PGF2α synthetic enzymes\textsuperscript{55} in the endometrial cells. In contrast, before day 10, the concentration of endometrial oxytocin receptors\textsuperscript{53,42} and PGF2α synthetic enzymes\textsuperscript{55} are low, which effectively blocks the ability of oxytocin to stimulate PGF2α secretion. We hypothesized that when oxytocin treatment is initiated before day 10 after ovulation, it prevents luteolysis by inhibiting the rise in endometrial oxytocin receptor concentration that would otherwise permit endogenous oxytocin-induced PGF2α secretion at the time of luteolysis; however, there was no difference in endometrial oxytocin receptor concentrations between salinetreated control mares and oxytocin-treated mares on day 15, which does not support that hypothesis.\textsuperscript{36}

More recently, it was demonstrated that oxytocin treatment suppresses PGF2α secretion by preventing upregulation of endometrial gene expression of COX-2\textsuperscript{35} which, as noted previously, appears to be the mechanism by which intrauterine placement of a polypropylene ball inhibits luteolysis and prolongs CL function.\textsuperscript{24} Also, it seems clear from the results of Bare et al.\textsuperscript{40} that carbetocin (with use of the dose and treatment schedule in their study) does not have the same effect.

Collectively, the studies described above provide convincing evidence that administration of exogenous oxytocin on days 7 (or 8) to 14 after ovulation is an effective method of disrupting luteolysis to prolong CL function that can be used as a means of suppressing estrous behavior in mares. An advantage of using oxytocin treatment to prolong CL function is that it can be readily reversed by simply administering a luteolytic dose of PGF2α to initiate resumption of cyclical reproductive activity, in contrast to the need to physically remove an intrauterine glass ball. Disadvantages of the oxytocin protocol include the need to determine the exact day of ovulation before initiating treatment and potential difficulties associated with its use in mares with a needle aversion (ie, “needle-shy”). Although the dose of oxytocin is fairly high (60 units), no difference in body temperature, heart rate, or respiratory rate was noted before and after treatment; however, mild sweating, urticaria around the injection site, and mild diarrhea were noted in some mares.\textsuperscript{40}

Notably, there was no evidence of abdominal cramping and/or transient signs of colic, which suggests the myometrium is much less responsive to oxytocin during mid- to late-diestrus than it is during other physiologic states (eg, immediately post-partum).

6. Inducing a Late-Diestrus Ovulation

In 2006, Hedberg et al.\textsuperscript{45} described the results of a preliminary study in which their objective was to prolong the luteal phase in mares with the use of human chorionic gonadotropin (hCG) to induce a late-diestrus ovulation to produce a new CL that would be too immature to respond to the luteolytic effects of endogenous PGF2α secretion at the end of diestrus (ie, day 14 to 15 after the initial “primary” ovulation). Mares were randomly assigned to control ($n = 4$) and experimental groups ($n = 5$), and, beginning on approximately day 8 after ovulation (or last signs of estrous in 3 mares), their ovaries were examined with transrectal ultrasonography every other day to determine the size(s) of their diestrous follicles. When a diestrous follicle $\geq 30$ mm was de-
ected, control mares were treated with saline and experimental mares were treated with 3000 IU hCG intramuscularly. After treatment, the mares were monitored with transrectal ultrasonography for up to 72 hours or until ovulation was detected, and then once weekly for 3 weeks. If a mare did not have a diestrous follicle ≥30 mm during the first diestrous period, she was monitored for a second, and if necessary, a third diestrous period.

Three of the nine mares had development of a follicle ≥30 mm during the first diestrous period, four mares during the second diestrous period, and one mare in the third diestrus period. One mare never had a diestrous follicle that was ≥30 mm during three diestrus periods and therefore could not be treated with hCG. Overall, three of the four mares (75%) treated with hCG ovulated within 72 hours after treatment with hCG, which resulted in luteal phases that lasted for 58 to 82 days after treatment. None of the control mares ovulated during the luteal phase; however, one control mare had a spontaneously prolonged luteal phase during both a non-oestrus; however, they also demonstrated that estradiol was not needed to induce prolonged CL function, because infusion of 1 mL fractionated coconut oil or peanut oil (neither containing estradiol) on day 10 induced prolonged CL function in 92% of the treated mares in both groups. In contrast to infusion of plant oils, infusion of mineral oil on day 10 did not reliably prolong CL function, whether it was administered alone or in combination with estradiol (17% and 25% prolonged CL function, respectively). The authors postulated that the fatty acid milieu in both plant oils modulated/attenuated synthesis and/or secretion of PGF2α at the expected time of luteolysis, resulting in prolonged function of the CL. Given the high proportion of mares in which prolonged CL function occurred when fractionated coconut oil or peanut oil was infused on day 10 (92% in both groups), infusion of plant oil appears to be a plausible method of prolonging CL function for estrus suppression, although additional work will be needed to fully develop a practical protocol for that purpose and to ensure there is no detrimental effect on subsequent fertility.

8. Pregnancy

Pregnancy is another means of suspending cyclicity by taking advantage of the natural ability of the conceptus to block luteolysis and maintain CL function/progesterone secretion. Although efficacious, this method has obvious disadvantages that may make it undesirable for many horse owners. In addition to the time and expense necessary to establish pregnancy is the need to eventually terminate a normally developing pregnancy (unless an offspring is ultimately desired). Lefranc and Allen reported that manual transrectal rupture of the conceptus between days 16 and 22 of gestation in 11 mares resulted in continued CL function for at least 60 days in all of the mares, during which time they did not display estrous behavior. Although efficacious, as noted above, terminating a normal, healthy pregnancy may be untenable to many horse owners.

9. Conclusions

Because of drawbacks and concerns associated with the use of alprogest for suppression of estrus in mares, there is increasing interest in the development of practical methods of prolonging CL function, which allows continued secretion of endogenous progesterone to keep mares out of heat naturally. Although placement of an intrauterine glass ball has been the most widely utilized method of prolonging CL function, their variable efficacy and potential for deleterious consequences (if not eventually removed), has prompted interest in the development of additional methods of prolonging CL function. Of the current alternatives to an intrauterine glass ball, oxytocin treatment appears to be the most practical and efficacious method of prolonging CL function. Administration of 60 units of oxytocin intramuscularly once daily on days 7 (or 8) to 14 after ovulation induces prolonged CL function in 60% to 70% of treated mares, which can suppress estrous behavior for approximately 2 months. Ad-
ditional methods of prolonging CL function in mares include inducing a late-diestrus ovulation, intrauterine infusion of plant oils, and establishment of pregnancy followed by manual reduction of the conceptus after day 16 of gestation.

References and Footnotes

42. Sharp DC, Thatcher MJ, Salute ME, et al. Relationship between endometrial oxytocin receptors and oxytocin-induced prostaglandin F2a release during the oestrous cycle


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