

Non-ovulatory follicles: characteristics, causes, and solutions?

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Ovulatory failure during the breeding season is a frustrating development. Non-ovulatory follicles have been called hemorrhagic anovulatory follicles (HAF), anovulatory hemorrhagic follicles, hemorrhagic follicles or persistent anovulatory follicles. Although most workers agree that anovulatory follicles are more common early or late in the season, they do sometimes occur during the normal breeding season, especially in older mares.¹ One investigator examined 737 cycles in 47 mares that were treated repeatedly with cloprostenol (CLO) and human chorionic gonadotropin (hCG) over a three year period.² The failure of ovulation was more common in the autumn (September/October 22%, November 59%), and approximately 50% of the mares developed an anovulatory follicle during at least one cycle, and 26% experienced them during at least two cycles. A tendency for an anovulatory follicle to recur in a mare from one breeding season to the next was noted. Others have reported no effect of season³ or the highest incidence from May to August,⁴ but again found a tendency for some mares to have repeated ovulation failure.

While the occurrence of these anovulatory follicles is well recognized, the ability to predict their occurrence has eluded us. Using grey-scale B-mode ultrasonography, there are no premonitory signs that can be used to predict that a follicle will fail to ovulate. Typically, a HAF is recognized by the sudden appearance of hyperechoic floating specks in the antrum of the follicle. Over the next few days, hyperechoic strands are observed to develop in the antrum and the wall of the follicle thickens as apparent luteal tissue develops. Using Doppler ultrasound, comparing follicles the day before ovulation with those at a similar stage of development that would fail to ovulate; increased vascularity in the apical area of the follicle (site of impending ovulation) was noted in follicles destined to fail to ovulate. This difference was attributed to minimal hemorrhage during ovulation vs. considerable hemorrhage during HAF formation.¹

Differentiating a HAF from a corpus hemorrhagicum (CH) can be difficult if an examination is not performed shortly after formation. If examined daily, early after formation a HAF will have a thinner luteal border, usually less than 3 mm, while a CH will have a border > 5 mm.⁵ In addition, the HAF will have the same or greater diameter than the pre-ovulatory follicle, while the CH will be smaller than the preovulatory follicle diameter.⁵ With less frequent examinations, as the contents of the structures clot and become organized, the same criteria can be used; however there is overlap. The luteal border of the HAF is usually, but not always, thinner than the border of the CH, and the diameter in relation to the maximum preovulatory follicle diameter is usually, but not always, greater in the HAF than the CH.⁵

The progesterone profile after observation of the formation of an HAF has been described, and in most cases (88%) when an HAF was observed, progesterone was increased. In one report, progesterone rose slowly and progressively to >8 ng/mL in 51% of the cases, while in 13% it rose rapidly to >10 ng/mL. In 25% of the HAFs, progesterone reached a plateau of 1 to 4 ng/mL, and in 11% it did not rise above 1 ng/mL.² Others have reported no significant difference in the concentrations of progesterone or luteinizing hormone (LH) between mares that developed an HAF and control mares that ovulated, and only a slightly greater concentration of estrogen in the mares with an HAF was observed three days before formation.¹ Other studies have similarly found that concentrations of progesterone in mares with an HAF are elevated to >1 ng/mL.^{6,7} However in mares which formed a HAF in response to flunixin meglumine administration, the concentration of progesterone on days 5 and 9 after HAF formation was lower than in control mares on corresponding days after ovulation.⁷ Consequently, most mares with an HAF will respond to a luteolytic dose of prostaglandin (PG) administered at the appropriate interval after formation of the HAF, with a return to estrus and normal ovulation.² However, as discussed below, treating an HAF with a luteolytic dose of CLO may in some cases not be the best course of action, especially in mares prone to forming HAFs.

Similar to the inability to reliably predict the occurrence of an HAF, the etiology remains elusive. Persistent endometrial cups can lead to HAF formation,⁸⁻¹⁰ and may repeat in the same mare.⁹ The presence of even low levels of equine chorionic gonadotropin (eCG), with its LH-like activity, can disrupt the normal ovulatory process resulting in non-ovulatory luteinized follicles. Recent work has revealed a relative lack of angiogenic activity in HAFs compared to corpora lutea formed after ovulation.⁶ Other reports have linked the use of CLO to induce luteolysis and a return to estrus with an increased risk of formation of HAFs.^{2-4,11} In one study, the histories of two mares that both had an unusually high incidence of HAFs were examined.¹¹ In these two mares, the use of CLO to induce estrus was associated with a high incidence of ovulation failure. Other studies, by the same authors (and including the same mares), examined 207 and 7 mares, respectively, over longer periods of time, with a variable number of estrous cycles included for each mare.^{3,4} These authors hypothesized that the administration of CLO results in a rapid drop in progesterone, which allows LH to rise. If this rise in LH occurs during the development of an immature follicle, before follicular deviation, it could interfere with the intrafollicular metabolism of substances necessary for ovulation and follicular collapse. Similarly, in a model using follicle ablation to induce follicular waves and estrus, the mares had an earlier rise in LH and the incidence of HAFs was increased.¹² Another report suggested that the use of hCG, when used in combination with other drugs, could contribute to an increased incidence of HAFs.³ Alternatively, administration of a prostaglandin inhibitor such as flunixin meglumine can interrupt the ovulatory process, resulting in an increased incidence of HAFs. This approach has been used to induce HAF formation for experimental purposes.^{2,13-15} In an attempt to reverse the effect of flunixin, CLO was administered around the time that the follicle produces PG during the ovulatory process.¹² In the same report, CLO was administered to mares after they began to show signs of HAF formation to determine if it might be an effective treatment once the initial signs were recognized.¹⁵ Neither approach was successful. It would appear that once the ovulatory process is disrupted, that it is difficult to get it back on track.

Certain mares appear to be prone to repeated occurrences of HAFs and some researchers feel that conditions such as laminitis may contribute to the occurrence of an HAF,^{1,3,11} which is plausible given the reports linking the use of CLO to HAF formation. From a retrospective study of breeding records, it has been proposed that the dose of CLO affects the chance of HAF development, with higher doses more likely to result in HAF formation.⁴ A factor which may play a role but was not described in these reports linking CLO usage and HAF formation is what stage of follicular development was present at the time of CLO administration. The status of follicular activity at the time of CLO administration affects the interval to onset of the subsequent estrus and interval to ovulation. It is possible that follicular status at the time of CLO administration may also have a role in the formation of an HAF. In a mare that is prone to HAF development, or when CLO administration to a mare with an HAF is deemed necessary, it may be prudent to use the lowest effective dose possible. Alternatively, it may be wise to forego administration of PG and allow the mare to return to estrus on her own, without hormonal intervention. In some cases, waiting a few days longer for a natural estrus may actually result in getting a mare in foal sooner than with hormonal intervention.

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