I gave my mare Progesterone (or Regumate™), but it didn't work!

By Jos Mottershead

Progesterone or the synthetic progestin analogue altrenogest (Regumate[1]) is commonly used in the mare to cause her to enter estrus (come in to "heat") at an appropriate time. It does this by suppressing estrus long enough to allow natural regression of the Corpus Luteum (CL). In the case of the shorter duration of treatment, the CL (if it remains) is destroyed with a dose of prostaglandin F2α. About 3-5 days after the end of either treatment period, if all goes well, the mare enters estrus (comes into "heat").

The most commonly used treatment protocols are 8, 10 or 14 daily doses of the progestin. With the 8 or 10-day treatment period a luteolytic dose of prostaglandin F2α is given on the 9th or 10th day respectively[2]. The idea is that the prostaglandin F2α will cause the destruction of any CL remaining from an ovulation occurring on a previous cycle. It is supposed with the 14-day treatment that any such CL will have regressed naturally, and will no longer be secreting progesterone that would interfere with a timely return to estrus.

Unfortunately, mares have the ability to develop follicles, and indeed ovulate follicles, in the face of elevated progestin levels - i.e. during diestrus (the time in between "heat") or pregnancy[3]. This is perfectly normal, and although not seen in all mares, can lead to a failure of timely onset of estrus following progestin therapy.

In the case of the 10-day treatment protocol (coupled with prostaglandin F2α on day 10), the mare may have ovulated within the last 5 days of treatment. This means that even though a luteolytic dose of prostaglandin is given, there is no functional CL for it to act upon (see "Why prostaglandin may not cause estrus in mares" for more details). Consequently, the mare will not enter estrus in the anticipated 3-5 days after the last treatment.

With a mare that continues follicular development during the treatment period but does not ovulate, we are faced with a situation where the mare may actually ovulate very rapidly after the last day of treatment - even the same day, the next day or a day or two later! This rapid onset of cyclicity and ovulation situation can be increased by the use of prostaglandin F2α on the tenth day, as that hormone may actually accelerate the follicular growth and ovulation.

If one wishes to more accurately pinpoint estrus and ovulation, then a more reliable method involves the addition of estrogen to the hormonal treatment. This is most commonly achieved with the use of "P and E", which can accurately pinpoint ovulation to the day in up to 80% of cycling mares when coupled with a suitable ovulation-inducing agent[4].

There is evidence that the use of progestins during transitional phase can encourage the more rapid onset of regular cyclicity[2,5,6]. While the mare "ovulating through" the progestin is still a possibility, the establishment of regularity is probably of greater concern at that time of year. Even if the mare does ovulate in an untimely manner, once ovulation has occurred (and therefore transitional phase ended) prostaglandin F2α may be used to "short cycle" her back into estrus if an earlier breeding is desired. There has been some suggestion that the use of combined progesterone and estradiol during transitional phase may result in down-regulation of the ovarian activity and prolonged anestrus or transitional phase. This is associated with the estrogenic portion of the combination, and while it may not occur in all cases, could be a considerable problem if it does occur in your mare. For this reason, we are now reluctant to use P and E before the first ovulation of the year is detected.

Another possible situation impacting the suitable use of progestins in an attempt to induce estrus is that the uterine immune function is suppressed by the presence of progestins. This is a naturally occurring suppression, essential for pregnancy maintenance. If it occurs as a result of artificially elevated progestin levels (following progestin treatment) and an undetected uterine pathogen is present, it may result in the onset of a significant uterine infection[7]. This is generally more of an issue in mares that are being treated with long-term progestins to suppress estrus[8] (such as for competition enhancement), but can certainly also occur in mares that are being bred that have not had any uterine pathogenic diagnostics performed, or have had only a uterine swab culture performed, rather than a culture and cytology. It is unfortunately not uncommon for older mares being retired from competition and entering the breeding shed to be found with poor uterine condition (biopsy) because of this prolonged progestin treatment in the presence of a pathogen causing significant damage to the endometrium (lining) of the uterus.

Lastly of course, that well-known (to Internet users!) concern - the possibility of oral progestin therapy resulting in a

disturbance of the human menstrual cycle. This is most certainly a possibility, but can be easily circumvented by care and the use of suitable gloves at the time of treatment. Note that latex gloves are not suitable, as they are not impervious to the penetration of the hormone, and in fact can create a "patch-like" situation, as once the hormone has passed through the latex and is in contact with the skin, it will more easily pass through the skin and into the human system rather than back through the latex. It should also be noted that human health concerns should not be limited to the female, but all humans handling progestins should be aware of the possibility of an increased threat of thrombophlebitis or thromboembolic disorders and cancers if inappropriately handled[9].

Summary:

- For successful induction of estrus, the mare cannot be in a state of anestrus (winter or otherwise);
- For progestins to induce estrus, there must be a degree of cyclicity;
    - progestin therapy may be beneficial in assisting in stabilization of estrus during later transitional phase, and encouraging ovulation, but it will not cause the onset of cyclicity in the anestrous mare.
- For timely onset of estrus, there cannot have been a recent ovulation during the last 5 days of treatment with the progestin;
- Follicular growth will not necessarily be controlled, so a large follicle may be present at the end of the treatment period, resulting in a rapid onset of estrus and ovulation;
- Mares to be treated with progestins should not have uterine pathogenic issues (repeated uterine infections), and should have been checked to ensure an absence of uterine pathogens.

References:

1: Regumate is a registered trade mark of Intervet International

2: Squires EL, Stevens WB, McGlothlin DE, Pickett BW. (1979) Effect of oral progestin on the estrous cycle and fertility of mares. J Anim. Sci. 49: 729-735

3: Loy RG, Pemstein R, O'Canna D, Douglas RH. (1981) Control of ovulation in cycling mares with ovarian steroids and prostaglandin. Theriogenology, 15:191-200

4: Taylor TB, Pemstein R, Loy RG. (1982) Control of ovulation in mares in the early breeding season with ovarian steroids and prostaglandin. J Reprod. Fertil. Suppl., 32:219-224

5: Webel SK, Squires EL. (1982) Control of the oestrus cyclein mares with altrenogest. J. Reprod. Fertil. Suppl., 32:193-198

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7: Alexander SL, Irvine CHG. (1991) Control of onset of breeding season in the mare and its artificial regulation by progesterone treatment. J. Reprod. Fertil. Suppl., 44:307-319

8: Squires EL, Schideler RK, Voss JL Weber SK. (1983) Clinical applications of progestin in mares. Compend. Contin, Educ. Practicing Vet. 5:516-522

9: Regumate™ package insert
