# Progesterone Levels in the Cycling Mare and the Luteolytic Effect of Prostaglandins

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There has always been a great deal of interest in efficient reproductive practices in equine breeding. Proper breeding time is best determined by assessing hormonal levels in the mare but as these are not readily measureable in most equine breeding operations the outward signs of estrus are utilized as practical substitutes. It is therefore necessary to understand the hormonal levels which characterize estrus if one desires to increase breeding efficiency by altering the mare's reproductive cycle. In this paper we will be concerned with the normal cycling levels of one of these hormones, progesterone, and its synchronization with estrus. We will also examine recent research on the effect of prostaglandins on progesterone and their possible role in more efficient equine breeding.

The mare is usually considered a seasonally polyestrus animal, that is, in the majority of cases she cycles from spring through fall (March to October) but is usually in a state of anestrus during the winter months (October to February). The estrous cycle is dependent upon many factors in-

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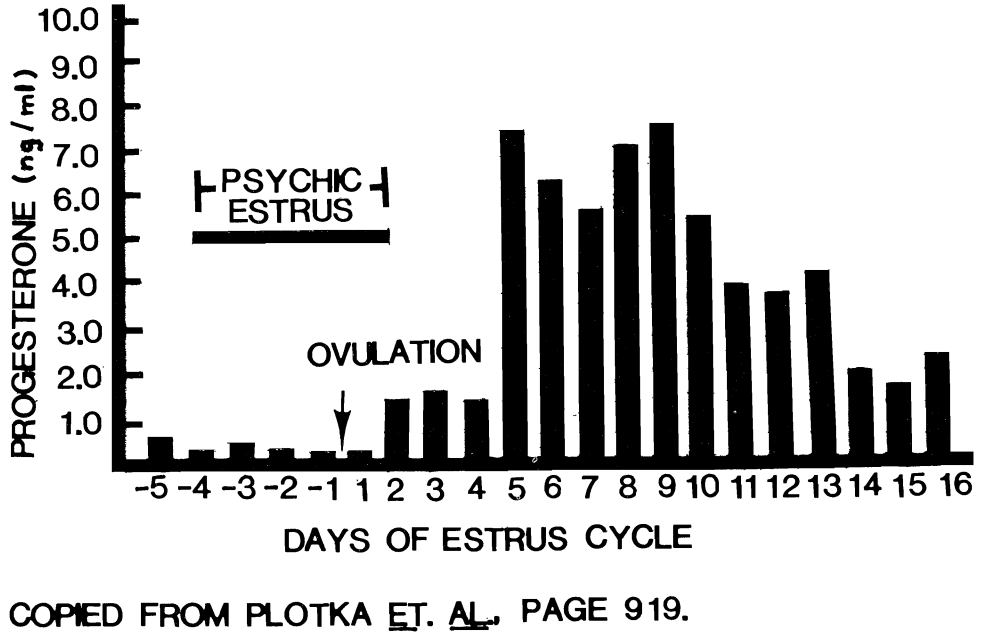


**Figure 1: Progesterone Concentration in Peripheral Blood Plasma***

cluding light, temperature and nutrition as well as individual differences. In the cycling mare the estrous cycle averages approximately twenty-one days (range 13–34 days), although there is considerable individual variation especially in the duration of diestrus. Proestrus usually lasts two to three days, estrus four to seven days, metestrus three to five days and diestrus eleven to fifteen days with ovulation ocurring twenty-four to forty-eight hours before the end of estrus.[16] If we consider day one to be the day of ovulation (i.e. day three to five after onset of estrus) we see a peripheral progesterone level throughout the estrous cycle as depicted in Figure 1.

Peripheral serum progesterone levels are very low two days before through one to two days after ovulation (0.9 ng/ml[10]; 0.22 ng/ml[13]). Approximately thrity-six hours after ovulation there is a marked rise in the progesterone level which remains elevated through approximately day thirteen after which it slowly falls to preovulatory levels. At its peak (days five to thirteen) progesterone values are $7.7 \pm 3.8$ ng/ml[14] to $10.9 \pm 1.4$ ng/ml.[13] We can correlate these progesterone levels with the establishment of a corpus luteum and its active secretion of progesterone. By approximately thirty-six hours post ovulation the corpus luteum is functional and continues to be active until just prior to day thirteen after which it regresses causing lowered plasma progesterone levels. External signs of heat or psychic estrus also correlate well with these progesterone levels. Both Plotka and Sharp report the onset of psychic estrus soon after the decrease in serum progesterone concentration, stating that estrus is not seen until peripheral progesterone levels drop to 1 ng/ml or lower. Psychic estrus is also seen to cease two to three days after ovulation when progesterone levels are again rising and approaching 1 ng/ml. Thus it appears that measurement of the plasma progesterone levels may indicate luteal function and these levels may be outwardly reflected by signs of psychic estrus.

In the normally cycling mare breeding is not usually a problem providing both mare and stallion are fertile. However, it is sometimes desirable to shorten the estrus cycle of a mare, to induce estrus in a mare which is not cycling properly or to bring a mare into estrus earlier in the year than she would normally begin to cycle. To accomplish this a great many treatments have been investigated. One of the new and promising treatments is the use of prostaglandins, especially Prostaglandin$_{2\alpha}$ ($PGF_{2\alpha}$) or its analogues. It has been shown in several species that there is a luteolytic substance in the uterus which determines the duration of the corpus luteum.[6] It has been proposed that this substance may be a prostaglandin, and considerable research has been done on the possible luteolytic effect of $PGF_{2\alpha}$ and its role on the level of progesterone in the peripheral plasma.

Working in the cow Rowson *et al* have shown that $PGF_{2\alpha}$ (0.5 mg/dy) administered into the uterus on two successive days between days five and sixteen of the cycle produced a psychic fertile estrus three days later. This was not, however, effective if administered before day five. It was also found to be necessary to use $PGF_{2\alpha}$ in the uterine horn ipsilateral to the ovary with the active corpus luteum rather than the contralateral horn. This indicates that the substance causing corpus luteal regression must pass directly by a local means rather than via a general systemic route from the uterine horn to the ovary. Moor and Rowson have shown that there is also a uterine luteolysin in sheep much like that in the cow. Removal of the uterine horn contralateral to the active corpus luteum produced no untoward effects on the life span of that corpus luteum, however removal of the uterine horn ipsilateral to the active corpus luteum resulted in a lengthened estrus cycle and increased life-span of the corpus luteum. Thus it would appear that in sheep also the luteolytic substance is locally rather than systemically transferred to the ovary. Several authors propose that the local means of transfer of this luteolytic substance is by means of the close anastamosis of the ovarian artery and uterine vein in the cow and sheep. However, this has been partially disputed by Restall *et al* who have shown that close apposition of the uterine vein and ovarian artery is not necessary for $PGF_{2\alpha}$ to act as a luteo-

lysin in the ewe. Injection of $PGF_{2\alpha}$ (80 mg/hr for 6 hours) into the uterine vein ipsilateral to the ovary with the active corpus luteum caused a drop in peripheral progesterone levels to less than 0.5 ng/ml and induced estrus whether or not the utero-ovarian vein was surgically separated from the ovarian artery. He also shows that $PGF_{2\alpha}$ given in the jugular vein has no effect, and he hypothesizes that the effect of $PGF_{2\alpha}$ may be mediated through the sympathetic nervous system.

There is also considerable evidence that prostaglandins are luteolytic in the mare. This hypothesis is based primarily on peripheral progesterone levels and induction of psychic estrus after administration of prostaglandins. Mares given $PGF_{2\alpha}$ either by intrauterine infusion (10 mg) or subcutaneously (15 mg) seven to nine days after ovulation exhibit a normal estrus within two days which lasts seven to eight days. Ovulation occurs on day six, and progesterone levels drop to 0.9 ng/ml within forty-eight hours after $PGF_{2\alpha}$ administration.[9] Douglas and Ginther have been able to shorten the length of a mare's normal estrous cycle to 8.3 days and return the mare to estrus within two to three days by giving 10 mg $PGF_{2\alpha}$ subcutaneously on the eighth day after estrus. They have also determined the minimum effective dose of $PGF_{2\alpha}$ to be 1.25 mg. and note that this dose will also cause abortion in approximately 50% of their mares between forty and one hundred twenty days of gestation. It is noteworthy that during this time interval progesterone levels are due to luteal activity in the ovary (original corpus luteum or accessory corpus lutea). After five months the placenta and membranes are established in the mare and produce the progesterone necessary to maintain the pregnancy rather than the ovaries. It would be interesting to know if prostaglandins at that time would still cause abortion although this would seem doubtful from present evidence. Indirect evidence for the activity of $PGF_{2\alpha}$ is advanced by Noden *et al.* Upon administration of $PGF_{2\alpha}$ an increased LH serum level is observed from near the onset of estrus to about eighteen hours after ovulation. This is similar to the LH changes which occur normally near estrus and support the conclusion that $PGF_{2\alpha}$ is indeed luteolytic and estrus inducing.

In the mare the uterus does indeed have an effect on regression of the corpus luteum as total hysterectomy in the mare will cause the active corpus luteum to be maintained. However, unlike the ewe and cow, it appears that the uterine luteolysin reaches the ovaries by means of the systemic circulation rather than by a local pathway. Unilateral hysterectomy of either the ipsilateral or contralateral horn causes the corpus luteum to be maintained approximately the same lending additional support to systemic transfer of luteolysin.[3] Ginther has subsequently shown that in the mare the ovarian artery and the common vein draining much of the uterus and ovary are not in anastamosis as they are in the ewe.[4] This makes local transfer even less likely.

On the basis of the above evidence it would appear that prostaglandins could be a valuable tool for controlling and shortening the length of the estrous cycle in mares. Although $PGF_{2\alpha}$ has been most extensively investigated, analogues such as ICI-79939 may be as effective or even more so. For example ICI-79939 given by either intrauterine infusion or intramuscularly between day four and thirteen of diestrus is highly luteolytic in the mare producing estrus three to four days after administration.[1] It is reported by Allen and Rowson to be two hundred times as potent as natural $PGF_{2\alpha}$.

In summary we note that progesterone levels in the mare reflect the luteal activity of the ovaries and that estrus is preceded by a drop in peripheral progesterone levels to a level of 1 ng/ml or lower. It would appear therefore that estrus could be induced by causing a decline in progesterone, that is by some substance which is luteolytic. Uterine luteolysin appears to be the factor controlling the life span of the corpus luteum naturally both in cows and sheep where the control is by local pathways and in the mare where the control appears to be by means of the general circulation. This luteolysin may be a prostaglandin and studies involving $PGF_{2\alpha}$ and its analogues show these substances to

be luteolytic and to produce a psychic estrus with accompanying peripheral progesterone levels below 1 ng/ml.

Although additional work needs to be done it seems that prostaglandins may have a use in horse breeding especially in breeds such as the Thoroughbred and Standardbred where breeding seasons are restricted by the registration associations. In breeds allowing A.I. they may be useful in estrus synchronization (as they have shown to be with cattle)[15] or conversely in breeds where A.I. is not allowed in preventing synchronization of breeding times to avoid overwork of a valuable stallion.

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