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Progesterone Therapy and Pregnancy Loss

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Introduction

Progesterone insufficiency and progesterone supplementation are recurrent themes in equine gynecology. This is likely a reflection of the frustration we as clinicians endure when facing mares that fail to conceive or to carry a pregnancy to term. It is certainly also a reflection of our lack of understanding of early pregnancy failure. Currently, the use of exogenous progestins in pregnant mares is widespread, and a rational method for selection of mares for progestin therapy is lacking. In many cases, progestin supplementation does not appear warranted and may even be counterproductive. However, there is a growing body of evidence that progestin supplementation may be useful under specific circumstances. Rational application of progestin therapy requires some consideration of mechanisms that might lead to pregnancy failure and the relationship of these mechanisms to progesterone.

When trying to make an informed decision as to whether or not implement progesterone supplementation we need to consider the role of progesterone during pregnancy, the source of progesterone during equine pregnancy, the choice of progestagen, route of administration and the measurement of endogenous progesterone levels. It is only when we fully understand these elements that we can come to an informed decision and make a well-founded recommendation to our clients.

Role of Progesterone

It has been demonstrated that progesterone is the only hormone that needs to be replaced to maintain pregnancy. Pregnant mares that are ovariectomized during the first 3 months of pregnancy or mares that have received a luteolytic dose of prostaglandin F2α remain pregnant if supplemented with progesterone. Similarly, ovariectomized and anoestrous mares remain pregnant after embryo transfer if they are supplemented with progesterone. However, this does not necessarily mean that progesterone is the only hormone that plays a role during early pregnancy. It has been demonstrated that the equine embryo produces measurable amounts of estrogens only days after conception. An interaction between locally secreted estrogens and progesterone (produced by the corpus luteum or administered) is very likely to play a role in the well-being of the early embryo.

During Pregnancy

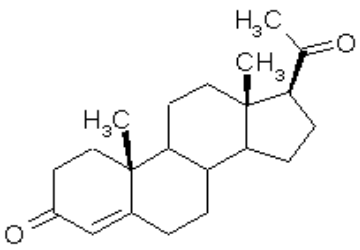
During the first 120 days of gestation, progesterone is produced by the primary corpus luteum (CL). After 40 days of gestation, progesterone production by the primary CL is supplemented with progesterone produced by secondary CLs. Luteal production of progesterone persists through approximately Day 100 to Day 210 of gestation. Beginning around Day 50 to 70 of gestation, there is a measurable production of progestogen by the placenta, and the placenta is the only source of progestogen during the second half of gestation in the mare. Placental progesterone is rapidly metabolized to 5α- pregnanes in the placenta. These 5α-metabolites cannot be measured by most conventional progesterone assays. Therefore, after mid-gestation

in the mare, the circulating progesterone concentration is low and does not accurately reflect progesterone production by the fetoplacental unit. In broad terms, one can consider that before 100 days of gestation the progesterone concentrations measured by the available assays reflect progesterone production by the maternal CL(s). After 150 days of gestation, progesterone concentrations represent only 1 to 5% of the total progestogens and are an unreliable parameter for assessment of placental progesterone production. Practically, at 100 days of gestation one can have a normal pregnant mare with essentially no measurable progesterone concentrations.

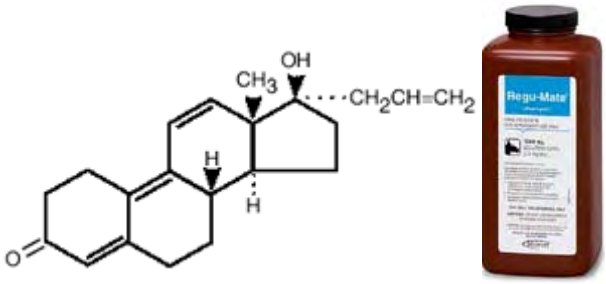
Products for Progesterone Supplementation

Like all steroid hormones, progesterone must bind to a specific progesterone receptor. The progesterone receptor across species has a specificity for progesterone (therefore it does not bind with oestrogen or testosterone) however within each species this receptor has characteristics that allow it to bind with some synthetic progestagens and not with others. In the horse, altrenogest (aka allyltrenbolone or ReguMate®) is the only progestagen with proven bio-activity.

There are number of other progestagens on the market that are used in cattle, swine and humans and are also used in horses. Proof of their bio-activity in the mare is always anecdotal and wherever their activity in the mare has been verified it has been shown not to be active. The following products have been shown not to be active in the mare: melgestrol acetate, norgestomet implants, hydroxyprogesterone caproate, acetoxyprogesterone, and medroxyprogesterone acetate.



Progesterone



Altrenogest

Currently, two preparations are available: injectable progesterone (typically in an oil vehicle such as sesame oil) and oral altrenogest. Altrenogest is typically used at a daily dosage of 22 mg per os and progesterone-in-oil is used at a daily dosage between 150 and 300 mg administered intramuscular. Lower dosages or less frequent administration does not maintain blood levels adequately between administrations.

Timing and Duration of Progestin Supplementation

In normal mares, progesterone supplementation can be started immediately after ovulation without adverse effects on conception rate and early embryonic development. However, in mares with post-insemination endometritis it may be preferable to wait a few days and thus avoid that the cervix closes prematurely. Sometimes progestin administration is recommended after a positive diagnosis of pregnancy at Day 14. This strategy seems best applied to mares which are notorious for losing their pregnancy after the first diagnosis but this seems late in

mares that have difficulty conceiving. Therefore, beginning progestin therapy early, on Day 3-4 after ovulation, may have the largest potential benefit.

Although it has been suggested that progestin therapy should be continued for most of gestation, many of the potential benefits of supplemental progestin are limited to the first 100 days of pregnancy. After 100 days, placental progesterone production is adequate to maintain pregnancy, villous placentation is reasonably well established and the conceptus is less dependent on secretion of uterine milk (histotroph) for its growth and development. Continuation of progestin therapy beyond 100 days probably has limited benefits. When supplemental progestin is stopped after 3 to 4 months of pregnancy, it is preferable to reduce the dosage by 50% for 1 or 2 weeks rather than a complete dose on alternate days. In our experience, altrenogest treatment can be stopped on Day 80 of gestation without transition in fertile pregnant mares that were ovariectomized or lutectomized on Day 18 without loss of pregnancy. This was applied on about 30 mares without any loss of pregnancy suggesting that at Day 80 the placenta is fully capable of producing the progestagen necessary for pregnancy.

It is very important to remember that in about 10% of altrenogest-treated mares luteal production ceases and progesterone concentrations drop to zero. In these mares, supplementation needs to continue until Day 80 as these mares are 100% dependent on daily treatment until the placenta has taken over progesterone production. Therefore, it is essential to measure endogenous progesterone levels when considering stopping supplementation before Day 80.

Adverse Effects of Progestin Supplementation

Casual use of progestin supplementation can have ill effects. Mares that are receiving exogenous progestin will not return to estrus if pregnancy loss is not detected and monitoring of pregnancy status during treatment is indicated. Progesterone suppresses phagocytosis by uterine neutrophils and clearance of material from the uterus. If a mare with a residual endometritis is treated with progestin, there is an increased risk of a prolonged and exacerbated endometritis during treatment with progestin. Administration of altrenogest (44 mg/day) from Day 20 to 325 to pregnant mares does not have significant effects on the reproductive activity of the offspring.

Progesterone Insufficiency

From reading the literature it appears that there is no consensus on what constitutes progesterone insufficiency in the mare. Neither is it clear if the presumed defect is inadequate blood progesterone levels (which can be measured) or a relative progesterone insufficiency (more progesterone required to obtain the same effect). There are many conflicting reports that either attempt to prove or disprove the thesis that progesterone sufficiency exists and very few are able to reach a data-based conclusion. It is important to distinguish between the absence of adequate progesterone secretion due to factors that affect the function of the corpus luteum and the inability of “normal” circulating progesterone levels in maintaining pregnancy. Examples of the first include inadvertent PGF2α administration, luteolysis subsequent to endotoxemia, and failure of maternal recognition. Examples of the second are mares that repeatedly loose their pregnancy in the presence of “normal” progesterone levels, placentitis and impending abortion due to stress in late gestation. Making the distinction between the two types is not always easy but recognizing its existence may help the debate.

It has been suggested that pregnancy failure may be related to low or reduced luteal progesterone production through a number of mechanisms: 1) primary luteal insufficiency, 2) luteolysis due to uterine inflammation (endometritis) and release of prostaglandin F2α, 3) failure of the embryo to prevent luteolysis and return to oestrus, 4) luteolysis due to systemic endotoxemia, and 5) stress. Our ability to relate detected pregnancy loss to one of these potential mechanisms is limited.

Although luteal insufficiency or inadequate production of progesterone by the CL has been proposed as a cause of early pregnancy failure, there is limited evidence to support primary luteal insufficiency as a cause of early pregnancy loss in mares. In other species, there remains considerable controversy concerning the importance of luteal insufficiency in early pregnancy loss. Ginther (1992) examined characteristics of embryonic losses in 21 mares. Embryonic losses that occurred prior to Day 20 appeared to be related to endometritis and premature luteolysis in most cases. Embryonic losses that occurred between Days 20 and 40 of pregnancy were associated with a decline in progesterone preceding embryonic death in 25% of cases, and it was suggested that these losses could have been due to luteal insufficiency. Irvine et. al., (1990) examined serum progesterone concentrations in 179 mares between 17 and 42 days of gestation and found only one mare in which detected embryonic loss was associated with a preceding decline in progesterone concentration.

Uterine-induced luteolysis is reasonably well documented as a cause of early pregnancy loss in mares. Uterine inflammation with subsequent release of prostaglandin F2α and a shortened diestrus interval appears to be a frequent cause of pregnancy loss. Many of the embryo losses resulting from endometritis appear to occur prior to Day 20 (Ginther, 1992). Frequently, embryonic losses associated with endometritis are preceded by the appearance of endometrial edema or intraluminal free fluid, and this finding may provide clinical evidence of the cause of such losses. When endometritis due to uterine infection is present, progestin supplementation is contraindicated as it may exacerbate the problem.

Pregnancy failure related to failure of maternal recognition of pregnancy is also relatively difficult to document in mares. Although maternal recognition of pregnancy can be disrupted experimentally and results in luteolysis and return to estrus, there is only one report to date to support spontaneous failure of maternal recognition of pregnancy as a cause for embryonic loss in mares. It is possible that conceptuses that are retarded in development might not adequately signal their presence in the uterus and therefore might not prevent luteolysis. Such small-for-age conceptuses do appear to be lost with higher frequency than normally sized conceptuses. Mechanical obstruction due to presence of large cysts in the uterine lumen may restrict the movement of the embryo and result in failure to recognize the pregnancy.

During the first two months of gestation, endotoxin-induced PGF-2α secretion results in pregnancy failure due to regression of the maternal CL(s), the main source of progesterone at this stage. Although other factors, such as bacteremia and fever, could also have detrimental effects on fetal survival, the experimental data suggests that progestin supplementation is very effective in the prevention of pregnancy loss in mares in which endotoxemia is suspected. Later in gestation, endotoxin-induced luteolysis is not the main reason for pregnancy failure since the feto-placental unit is capable of supporting pregnancy in the absence of the maternal ovaries. However, clinical experience suggests that endotoxemia and systemic illness is occasionally associated with pregnancy failure. It is possible that prolonged exposure of the gravid uterus to high levels of PGF-2α, as may be the case during endotoxemia, culminates in PGF-induced myometrial contractions and abortion. The potential detrimental effect of PGF-

2α on the gravid uterus can effectively be blocked by increasing progesterone levels. Exogenous progesterone (300 mg/day) or altrenogest (44 mg/day) administered to pregnant mares at four months of gestation reduces the incidence of abortion following 5 daily PGF-2α injections. These observations suggest that progesterone or altrenogest supplementation may be useful in the prevention of pregnancy failure in systemically ill mares. It is noteworthy that progestin supplementation was terminated after the last PGF-2α injection, and this did not appear to compromise pregnancy. Thus there appears to be no residual effect of PGF-2α on pregnancy, and treatment only needs to be applied while an acute risk is present. In contrast, pregnant mares exposed to endotoxin early in gestation need to be maintained on progestins until either a new CL has developed or the fetoplacental unit is capable of maintaining adequate progesterone levels.

Stress related to conditions such as transport, disease, climate, social separation or nutrition has long been proposed as a potential cause of pregnancy loss in mares. Anecdotal reports have indicated that stress may depress progesterone concentrations and result in pregnancy loss. However, in a controlled study, transport of pregnant mares (third or fifth week of gestation) for 9 hours resulted in elevated cortisol and transiently increased progesterone concentrations with no detectable effect on embryonic survival. Therefore, the relationship between stress and reduced progesterone concentrations remains unclear.