Premature Mammary Development in the Pregnant Mare

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Introduction
Mammary development prior to day 300 of gestation is a common clinical sign in mares that are at risk of aborting\textsuperscript{1-3}. Many papers have reviewed the causes of abortion in mares\textsuperscript{1,4-12}. Premature induction of lactation in mares reflects a change in circulating steroid hormone concentrations. The predominant steroid hormones in the serum of late pregnant mares are 5α-pregnanes and estrone sulfate\textsuperscript{13}. The normal mare has no progesterone in her serum during the last few months of gestation. Sex steroids are produced in the placenta, using precursors that are produced in the fetus (gonad for estrogens and adrenal for progestagens). No definitive role has been assigned to the very high concentrations of estrogens found in pregnant mares (pregnancies are maintained even when the fetus is gonadectomized)\textsuperscript{13,14}. Progestagens are, however, essential for the maintenance of pregnancy. No commercial assay is available for 5α-pregnane and most diagnostic laboratories exploit the cross-reactivity between progesterone and 5α-pregnane in the readily available progesterone assay to indirectly measure 5α-pregnane concentrations\textsuperscript{14}. During the last few weeks of gestation (when most mares develop a functional udder) maternal progestagen concentrations rise very significantly, presumably as a result of increased production of their precursors by the maturing fetal adrenal. A few hours or days prior to the actual birth of a normal foal, maternal progestagen concentrations decline sharply. The trigger for this decline is presumed to be the increased secretion of fetal cortisol\textsuperscript{13}.

Fetal and/or placental disease (or even death) will result in the disruption of the synthesis of steroid hormones. Mares with placentitis have higher concentrations of progesterone and lower concentrations of estrone sulfate than healthy mares\textsuperscript{3,13,15,16}. It is not known whether either steroid hormone’s change in concentration is directly linked to the induction of abortion. In one report, the administration of estradiol cypionate or estradiol-17β was claimed to have prevented abortion in the majority of mares with signs of impending abortion, while mares not treated with estrogens aborted in large numbers\textsuperscript{15}. Most clinicians, however, agree with Macpherson in that they administer progesterone or altrenogest to mares with premature mammary development in order to prevent abortion\textsuperscript{2}.

Types of placental disease
The most common cause of placental failure today is ascending placentitis\textsuperscript{5,7,10,12}. The relative surface area of the placenta that is directly affected by the infection is usually small and is relatively insignificant in terms of the nutritional impact on the developing fetus. The resulting abortion is thus likely to be caused by the spread of the pathogen to the fetus, causing fetal disease and death. As only a relatively small portion of the placenta is affected by the disease, its successful treatment may very well result in the term delivery of a relatively normal, well developed foal. A second form of placental disease results when the placenta becomes diseased as part of a fetal bacteremia or viremia, e.g. equine herpes virus. In this case the pathogen multiplies in the fetus and then spreads back to all parts of the placenta as part of a fetal infection. If the fetus does not die as a result of the organ disease it is likely to die as a result of extensive placental disease. If treatment were to be successful, the fetus must be expected to suffer significant intra-uterine growth retardation, because much of its placenta will
have suffered permanent damage. The third form of placental disease results when portions of the placenta die abruptly, while others remain virtually healthy. The best example of this pattern occurs when one fetus of a set of twins dies during the second half of gestation. In these cases the amounts of placental steroid hormones are radically reduced in a precipitous manner, but the relative proportions may remain normal. The abortion of the entire pregnancy (both fetuses) is probably triggered by the sudden decrease in 5α-pregnane output, frequently resulting in the expulsion of one live fetus and one dead fetus. If the delivery process can be halted, the remaining fetus is likely to be born small and compromised as it will have had a much smaller placenta than a singleton would have had.

All forms of placental dysfunction have in common that they result in the induction of lactation and labor, presumably through similar endocrine pathways as prevail at the time of parturition. While they present with similar clinical signs it may prove useful to identify the exact cause of the impending abortion in each case. This will aid the clinician in selecting the appropriate treatment for each case, as well as formulate a prognosis for the outcome of the pregnancy.

Clinical examination
The mare should be examined for the presence of any vaginal discharge that may be indicative of an ascending placentitis. If present, samples for culture and cytology should be collected from the exudate. The author discourages any vaginal speculum or manual cervical examinations as they may predispose mares to the development of an ascending infection. In mares with ascending placentitis transrectal ultrasonography will usually reveal the accumulation of an exudate between the endometrium and the chorion, partial separation of the placenta and/or the thickening of the utero-placental unit in this area. Ultrasonography of the pregnant uterus should follow next. If the fetus is already dead, no efforts should be made to preserve the pregnancy. If a live fetus can be identified, the uterus should be examined for a twin fetus that may already have died. If a singleton live fetus can be identified, as much of the placenta as possible should be examined for possible focal lesions, such as fluid pockets between the endometrium and chorion (ascending placentitis and nocardioform placentitis) or areas of placental detachment. Including various measurements and variables that are correlated with fetal well-being, growth and development may be useful in an effort to assess fetal distress (heart rate, fetal activity) and possible intra-uterine growth retardation (aortic diameter, ocular diameter, fetal fluid depth and echogenicity), but such findings have, in the author’s experience, little impact on subsequent decision making.

Therapeutic approaches
An excellent review on the rational use of a variety of drugs in mares with placentitis was recently published. Flunixin meglumine controls the release and effects of inflammatory mediators circulating in the dam’s and/or fetus’ blood. Initial doses may be high (1 mg/kg, IV, twice daily), but may be reduced to the anti-endotoxic level (0.25 mg/kg, intravenously, 3x per day) once the initial insult has been overcome. Pentoxifylline also has anti-inflammatory properties and is routinely administered to mares with suspected placentitis (7.5 mg/kg, orally, 3x per day). The best antimicrobial drug for use in placentitis cases is trimethoprim sulfamethoxazole, because it covers an acceptable spectrum and is very well distributed to the uterus and across the placenta to the fetus. Due to its relatively low toxicity it is well suited for long periods of therapy. The usual dose is 25-30 mg/kg (combined amount of trimethoprim and sulfadiazine), given orally, twice per day. The combination of gentamicin and penicillin also provides a broad spectrum of coverage, but the former drug is too toxic for use over extended
periods of time and should thus only be used when specifically indicated (i.e. resistance to trimethoprim sulfa). To the author's knowledge nothing is known about the efficacy or possible toxicity of antifungal agents for use in cases of fungal or yeast placentitis. When the initial clinical examination clearly reveals that the placental failure is not due to any bacterial or fungal agent, the antimicrobial and anti-inflammatory therapy described above obviously need not be applied.

**Progesterone and altrenogest** are the only progestagens available that actually bind to the appropriate receptors in the horse. The dilemma caused by finding elevated progesterone concentrations in mares with placentitis has been raised in the introduction. It is important to remember that elevated progesterone concentrations can at best be associated with placental disease (and fetal distress). The trigger for actual labor is associated with a sharp fall in progesterone concentrations. The author speculates that the rising concentrations of progestagens in cases of placentitis simulate the endocrine conditions that usually prevail during the last few weeks of gestation in normal mares (rising progestagens and falling estrogens; udder development). The rise in progestagens is then usually followed by a sharp decline in progestagen concentrations hours or a few days prior to delivery. Suppression of this final trigger for delivery with very high doses of progestagens may allow sufficient time for the feto-placental unit to regain its ability to secrete normal amounts of progestagens and the pregnancy to stabilize sufficiently to reach a stage at which the fetus could induce its own maturation and be born relatively mature and viable. Based on experience with several different cases of imminent abortion very high doses of progestagen are required to achieve cessation of lactation, reduction in udder size and prevention of abortion. The author will administer as much as 88 mg altrenogest twice daily or 500 mg progesterone IM twice daily. If the udder has not become smaller 24 h after the initial treatment and the fetus is still alive, the same high doses are administered 3 times daily. If the udder becomes smaller, the dose of progestagen can be reduced by increments of 10% every other day. While reducing the dose, the mare's udder is monitored and as soon as it starts increasing in size, the dose is adjusted upwards again. Some mares only need treatment for a few weeks after a threatened twin abortion and are completely weaned off all exogenous progestagen therapy well before 300 days of gestation. Others remain on variable doses of progestagens until at least 300 days of gestation at which time the dose is decreased by 10% every other day. Regular examinations of the fetus are necessary in order to confirm that it is still alive. The frequency of such examinations is adjusted to what is affordable to each client.

Whenever treatment for a threatened abortion is initiated, the owner is alerted to the possibility that the mare might still abort despite the treatment or, if she carried to term, deliver a small and/or dysmature foal.

**References**