Early intervention in a troubled pregnancy may allow for the birth of a vigorous foal with athletic potential. In a Thoroughbred production setting, where these principles can be maximally tested, the profit from birth of a healthy foal in contrast to a weak, small, septic foal pays for the cost of examinations.

Bosh et al (2009) described reproductive performance measures among 1,011 Thoroughbred mares in central Kentucky during the 2004 mating and 2005 foaling seasons. This study demonstrated a 12.9% pregnancy loss between day 40 of gestation and foaling.

<table>
<thead>
<tr>
<th>Mare age</th>
<th>2-8 years</th>
<th>9-13 years</th>
<th>14-18 years</th>
<th>&gt;18 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pregnancies lost days 15-40</td>
<td>4.6%</td>
<td>10.1%</td>
<td>16.7%</td>
<td>23.1%</td>
<td>8.9%</td>
</tr>
<tr>
<td>% pregnancies lost day 40-foaling</td>
<td>12.1%</td>
<td>11.2%</td>
<td>16.8%</td>
<td>20.0%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

Bosh et al 2009

This is similar to fetal loss rates between 3 and 10 months gestation published in other studies. In comparison, the human rate of preterm births in US in 12.5%.

In a review of 3,527 aborted fetuses and placentas, stillborn foals or foals that died <24 hours after birth, losses were due to:

- Feto-placental infection or placitis of unidentified etiology--34%. Of these, 17.8% were associated with bacterial infection.
- Complications during birth--19%
- Congenital anomalies including contracted foals--10%
- No diagnosis--17%
- Other causes included placental edema, premature placental separation, twins, umbilical cord anomalies, placental villous atrophy, body pregnancy, fetal diarrhea, and neoplasia.

Thus, management of inflammation and infection targets approximately one-third of the problem.
The vast majority of pregnancies will require no intervention. Pregnancy monitoring programs tend to be offered to anxious clients or mares at higher risk for problematic pregnancy. Mares are selected based on:

- History of previous and/or potentially repeatable problems during pregnancy
- Signs of premature parturition including premature mammary development, premature relaxation of ligaments around the tail head, premature vulvar elongation, vulvar discharge, urine staining beneath the vulva, or discharge found on the ventral aspect of the tail
- Any ongoing systemic compromise including infectious disease, metabolic disease, laminitis, colic
- Abnormalities detected during evaluation prior to the pregnancy such as cervical lacerations, vesicovaginal urine reflux, poor endometrial biopsy grade, metabolic or other systemic disease
- Abnormalities found during pregnancy monitoring. Monitoring can include physical examination, body condition score assessment, regular ultrasonographic assessment of the combined thickness of the uterus and placenta (CTUP), trans abdominal ultrasonographic assessment of the fetus and placenta, hormonal measurements

It is presumed that placentitis observed near the cervical start is due to pathogen ascent from the caudal reproductive tract and through the cervix. In women, inflammatory diseases of the genital tract are among the most frequent diseases during pregnancy and are thought to account for 25 to 40% of preterm births, with the most frequent and serious ascending from the lower genital tract. In horses, routine transrectal ultrasonographic monitoring of this region can be helpful to achieve diagnosis of placentitis sufficiently early to make a difference. Renaudin et al (1997) described evaluation of the combined thickness of the uterus and the placenta (CTUP) of 9 normal mares throughout gestation. Subsequently, evaluation of the CTUP has been incorporated into routine pregnancy monitoring programs.

<table>
<thead>
<tr>
<th>Month of Gestation</th>
<th>Mean CTUP (mm)</th>
<th>95% Confidence Interval (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3.98</td>
<td>3.81-4.47</td>
</tr>
<tr>
<td>5</td>
<td>3.58</td>
<td>3.50-3.81</td>
</tr>
<tr>
<td>6</td>
<td>3.84</td>
<td>3.78-4.04</td>
</tr>
<tr>
<td>7</td>
<td>3.91</td>
<td>3.86-4.07</td>
</tr>
<tr>
<td>8</td>
<td>4.33</td>
<td>4.21-4.69</td>
</tr>
<tr>
<td>9</td>
<td>4.38</td>
<td>4.28-4.66</td>
</tr>
<tr>
<td>10</td>
<td>5.84</td>
<td>5.53-6.77</td>
</tr>
<tr>
<td>11</td>
<td>7.35</td>
<td>6.93-8.54</td>
</tr>
<tr>
<td>12</td>
<td>9.52</td>
<td>8.51-11.77</td>
</tr>
</tbody>
</table>
In a field application of transrectal ultrasonographic assessment of the CTUP in 477 Thoroughbred mares on one farm in Central Kentucky, placentitis was diagnosed in 3.1% of the mares. The abortion rate among mares with placentitis was 15.8%, with pregnancy loss occurring at an average of 62 days (range 7 to 90 days) after detection and treatment onset. Of the non-aborting placentitis cases, 87% produced live foals with a mean gestational length of $327 \pm 2.23$ days. The mean birth weight of live foals from affected mares (48.8 $\pm$ 1.56 kg) was not significantly different from foals born from unaffected mares (53.9 $\pm$ 0.28 kg). Foals that were born dead or died shortly after birth (not counted among live foals) were significantly smaller than surviving foals.

Bucca (2011) has described the normal cervical dimensions of the pregnant mare as assessed with transrectal ultrasonography. In humans, ultrasonographic cervical measurement has proven to be useful to detect patients at risk for preterm delivery regardless of parity or obstetric history. Though accuracy of using cervical dimensions for placentitis monitoring needs to be determined, assessment of the cervix while performing CTUP assessment is important.

Transabdominal ultrasonography is also used to monitor fetal health. Parameters included to form a biophysical profile are fetal heart rate, fetal aortic diameter, fetal activity, fetal breathing movements, orbit diameter, tracheal diameter, stomach dimensions, kidney dimensions, gonadal dimensions, fetal fluid depth, uteroplacental thickness, uteroplacental contact and fetal presentation.

Maternal plasma total progestagen concentrations are used to monitor fetoplacental health. The true concentrations of total progestagens being measured can vary substantially depending on the assay and antibody cross reactivity. Progestagen production involves the fetal adrenal, thus progestagens can reflect fetal adrenocortical activity and stress. Rapid progestagen decline suggests severe fetal compromise. Progestagens higher than normal are normally seen before spontaneous parturition at term and can also be seen in cases of placentitis or poor placental function. Progestagen levels that fail to normally rise prior to parturition may suggest ergot alkaloid toxicity. In general, mares with high total progestagen concentrations are more likely to deliver live foals than those with low concentrations.

Estrogen concentrations seem less useful when used alone than progestagens for predicting fetal health. Of the estrogens, estrone sulfate is the most frequently measured. High estrone sulfate levels (>100 ng/mL) indicate a viable fetus. Low estrone sulfate levels (<10 ng/mL) indicate fetal loss or a non-pregnant mare. Estrone sulfate may be transiently decreased with compromised pregnancy.

The placenta is the sole source of circulating relaxin in the mare. As such, systemic relaxin concentrations could be used as a biochemical marker of placental function, fetal health, and a predictor of pregnancy outcome. Relaxin concentrations appear to be variable in
individual mares and with pregnancy maintenance treatment. A commercially available relaxin assay, if one becomes available, may prove to be useful to assess loss in placental function.

Serum amyloid A (SAA) is a major acute phase protein that rises with inflammation. Coutinho da Silva et al (2013) evaluated SAA levels in normal mares and mares with experimentally induced ascending placentitis. In normal mares SAA is low in late gestation, with an increase 36 hours post-partum and returning to normal levels 60 hours post-partum. In a placentitis model, SAA increased within 96 hours of inoculation of bacteria through the cervix of pregnant mares. Treatment of placentitis was initiated after inoculation. Six of 9 treated mares had no increase in SAA. One of 3 treated mares with elevated SAA after inoculation aborted. In this study, they found no association between SAA and other clinical parameters used to monitor placentitis or abortion.

Practitioners’ opinions vary with regards to obtaining cervical or uterine cultures from pregnant mares, due to the concern of disrupting or inflaming the vulvar, vestibulovaginal and cervical seals. If the procedure involves minimal disruption, for instance with the presence of discharge, microbial growth and antimicrobial sensitivity assessment can be helpful in constructing an antimicrobial treatment plan.

If pregnancy maintenance is deemed questionable, excellent client communication is necessary to manage everyone’s expectations regarding the outcome. Important information to obtain from the client is:

- Who takes medical priority in the event a choice needs to be made—mare or foal?
- What is the client’s expectation for the mare’s future reproductive soundness?
- Is the foal required to be an athlete?
- What is the budget?
- Is aggressive pursuit of pregnancy maintenance the best option?

Altrenogest or exogenous progesterone

In early gestation, progestins can stand in for ovarian progesterone and prevent endotoxin or prostaglandin induced abortion. In a study performed during the first trimester, altrenogest prevented abortion in 8/8 mares treated with cloprostenol, when control mares and 3/8 mares receiving progesterone aborted. In later gestation, experimental models suggest that progestagen supplementation improves the odds of maintaining a placentitis-compromised pregnancy to term. In two similar induced placentitis models where mares were treated with trimethoprim sulfa (30 mg/kg PO BID) and pentoxifylline (8.5 mg/kg PO TID) with and without altrenogest (0.088 mg/kg PO SID), twice as many mares delivered live foals with altrenogest treatment versus without altrenogest treatment. Once the pregnancy appears stable, many clinicians reduce the altrenogest dose to 0.044 mg/kg. Some clinicians prefer to use injectable progesterone (300 mg IM SID) or long acting formulations. Monitoring fetal health and viability periodically during
Progestagen treatment is recommended. The argument has been made that since progestagen concentrations can be elevated in mares with compromised pregnancy, it is questionable whether progestagen administration should be recommended in all cases. Clinicians’ opinions vary about discontinuing altrenogest prior to foaling (around 320 days gestation). In the placentitis model cited above, altrenogest treatment continued until parturition. In a study administering altrenogest (0.088 mg/kg PO SID) to 6 normal mares from 280 until parturition, with 7 mares serving as controls, stage II parturition was prolonged in altrenogest treated mares, with signs of decreased neonatal viability including lower respiratory rate.

Anti-inflammatory agents

Pentoxifylline is a theobromine derivative, non-selective phosphodiesterase inhibitor. Phosphodiesterase inhibitors can decrease uterine activity by increasing intracellular c-AMP concentrations and thus lowering Ca++ concentration. Pentoxifylline down regulates pro-inflammatory cytokines such as TNF-alpha, IL-6 and interferon-gamma, increases erythrocyte flexibility, fibrinolytic and tissue plasminogen activator activity and inhibits platelet adhesion. In mares, pentoxifylline has been shown to reach the allantoic fluid in normal pregnancy and in experimental placentitis models. A combination of altrenogest, antimicrobials and pentoxifylline (8.5 mg/kg PO BID) resulted in increased numbers of live foals in an induced placentitis study. In a study of women with imminent preterm labor, administration of pentoxifylline improved feto-placental blood flow parameters and led to a significantly lower risk of neonatal complications.

Non-steroidal anti-inflammatory agents such as flunixin meglumine (1.1 mg/kg) are commonly used as part of pregnancy maintenance therapy. Flunixin meglumine was not effective at preventing cloprostenol-induced abortion between 80 and 150 days gestation. Little additional research is available regarding is use for pregnancy maintenance.

Dexamethasone has been evaluated for induction of precocious fetal maturation. In a recent study in healthy Thoroughbred mares (n=10), mares received dexamethasone (100 mg IM SID) at 315, 316, and 317 days gestation. Dexamethasone treated mares experienced a significantly reduced gestation length. Foals were clinically mature with comparable body weights to controls, though with reduced crown-rump length. This treatment strategy can be useful in situations when parturition must be induced in late gestation in order to preserve the mare’s health (e.g. body wall hernia, prepubic tendon compromise, severe orthopedic compromise).

Antimicrobials
As mentioned previously, 34% of equine abortions or stillbirths were associated with feto-placental infection. Of these, 17.8% had an identified bacterial etiology. Antimicrobials that have evidence of reaching allantoic fluid include penicillin G (22,000 units/kg IM BID), gentamicin (6.6 mg/kg IV SID) and trimethoprim sulfamethoxazole (15-30 mg/kg PO BID). Other antimicrobials are anecdotally used with effect.

In an experimental ascending placentitis model with beta-Streptococcus, the introduced organism was able to be cultured from the uterus post-foaling in both treated and untreated controls. The treated ponies received antimicrobials (trimethoprim sulfamethoxazole 30 mg/kg PO BID) continuously until parturition. This information suggests that antimicrobial therapy in pregnant mares with placentitis may need to be prolonged and weighed against side effects of long-term antimicrobial therapy. Some clinicians and some farms routinely treat all mares with antimicrobials intermittently throughout gestation, presumably as a placentitis preventative. In a human parallel, in a survey of 38,151 newborn infants, 2,698 (7.1%) had mothers with vulvovaginitis-bacterial vaginosis diagnosed and treated in early pregnancy. The rate of preterm births was 7.5% among these patients. In contrast, the rate of preterm births was 9.3% in babies born to mothers without recognized genital infections. The rate of preterm births was lower in babies born to mothers without recorded vulvovaginitis-bacterial vaginosis yet treated with antimicrobials (7.2–7.8%).

Antimicrobial treatment alone has been contrasted with antimicrobial treatment in conjunction with an anti-inflammatory (either dexamethasone or acetylsalicylic acid) in an induced placentitis model. In this study, 4 of 6 (67%) mares treated with trimethoprim sulfamethoxazole (30 mg/kg PO BID) alone delivered viable foals while 8 out of 11 (73%) mares treated with trimethoprim sulfamethoxazole and either dexamethasone (40 to 25 mg IV SID) or acetylsalicylic acid (50 mg/kg PO BID). Acetylsalicylic acid has the additional function of improving uterine and ovarian perfusion.

Tocolytics

Various tocolytics are used to suppress uterine contractility in women in preterm labor. In the mare, the tocolytic that has received the most attention is clenbuterol, a beta-sympathomimetic agent. In one study evaluating the efficacy of tocolysis (based on trans rectal palpation of the uterus) of intravenous clenbuterol (300 micrograms) at various times through gestation in 4 mares found perceptible uterine relaxation lasting for up to two hours. Another study evaluated variable doses (0.6 mg IV, 1 mg IV, 1.5 mg IV) administered from 320 days to parturition and found no effect of treatment on outcome.

Oxygen
Oxygen therapy (10 -15 L/min nasal insufflation) can be utilized in pregnant mares with compromised placental function to improve oxygen delivery to the fetus. This is remarkably easy to institute in a farm setting.

Acupuncture

Acupuncture is a useful tool in equine reproduction. There are numerous studies supporting the use of acupuncture in achieving pregnancy. There are anecdotal reports regarding the efficacy of acupuncture for pregnancy maintenance, however there are few controlled studies. Many studies focus on observation of tocolysis, though acupuncture treatment encompasses other less measurable components. In one study in rats, acupuncture at LI-4, an important point for uterine quiescence, was found to suppress myometrial contractility in the face of oxytocin infusion. Another study demonstrated decreased expression of COX-2 in the myometrium of pregnant rats receiving acupuncture. In a small review evaluating acupuncture for inhibition of labor, 11 of 12 cases of preterm labor in women successfully carried to term.

Cervical cerclage

Cervical cerclage involves placement of a suture within the musculature of the cervix that is tightened to obliterate the cervical lumen. Method of suture placement and efficacy of this procedure is more critically reviewed in humans than in mares. This procedure is typically used in cases of cervical incompetence that jeopardizes the pregnancy and is not sufficiently improved with progestagen therapy. Cervical cerclage has been used to prevent pre-term births in women with a history indicating a risk of classical cervical insufficiency (e.g. previous painless mid-trimester miscarriages or cervical surgery) or with mid-trimester dilatation of the internal os. Cerclage may worsen the outcome in patients with cervical inflammation. Reports suggest that cerclage should only be offered to the 8% of women with a history of previous PTB and within this the subgroup of patients with a cervical length < 25 millimeters. Cervical cerclage is not commonly practiced in the mare. As cervical inflammation is present at the time of placentitis is diagnosed in advanced gestation, the optimum time for cerclage placement has passed. Also, if placed prophylactically prior to onset of placentitis, attentive monitoring for parturition is required in order to remove the suture prior to foaling.

References and Recommended Reading*


