

THE DIAGNOSIS AND MANAGEMENT OF PREMATURE LABOR  
IN THE BITCH AND QUEEN  
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Late term gestational loss attributed to preterm or premature labor is a controversial topic in small animal reproduction. Both hypoluteoidism and inappropriate uterine activity accompanied by cervical changes have been implicated in the pathophysiology of preterm birth in veterinary medicine, but the syndrome is not well understood or even researched. While the human literature is abundant on the topic, publications on the topic are few in veterinary medicine.

Premature labor is defined here as uterine activity and cervical changes leading to the loss of pregnancy via resorption or abortion before term, for which no metabolic, infectious, congenital, traumatic or toxic cause is identified. Premature labor is associated with progesterone levels that are  $<2$  ng/ml. Premature labor is often a retrospective diagnosis, achieved after thorough evaluation of the dam and fetuses has been performed because of loss of pregnancy. This evaluation should include metabolic screening of the dam for systemic disease, infectious disease evaluation, histopathology of expelled fetuses and placentae, and review of kennel/cattery husbandry including nutrition, medications and environmental factors. All results are normal or negative. Dams experiencing premature myometrial activity in one pregnancy may or may not exhibit it during subsequent pregnancies, but the syndrome can be a chronic cause of failure to reproduce.

In human medicine, preterm birth complicates 10-12% of human pregnancies, but it accounts for 80% of fetal morbidity and mortality. The diagnosis of preterm labor placing the fetus at risk of premature delivery is dependent upon evaluation of uterine contractility by tocodynamometry, and fetal fibronectin and transvaginal cervical length measurement determined via ultrasonography, which together have high negative predictive value. Amniocentesis is also advocated as a method of evaluating fetal lung maturation and microbial invasion of the amniotic cavity. The presence of contractions alone does not warrant intervention. Tocodynamometry identifies labor onset earlier than subjective maternal perceptions, and home uterine monitoring is advocated in high risk groups as an initial screening test. Multifetal gestations (i.e. litters) are associated with exaggerated physiologic changes which promote premature labor and complicate tocolytic therapy. Women with histories of preterm deliveries do appear to be at risk for such in subsequent pregnancies.

If intervention is indicated, tocolytics agents have been commonly advocated. Antibiotics, bed and pelvic rest and hydration do not appear to have benefit. Contraindications to tocolytics therapy include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilation, and evidence of fetal compromise or placental insufficiency. Tocolytic agents inhibit myometrial contractions, and include beta mimetics (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers and prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac). Contraindications to beta mimetics include maternal cardiac arrhythmias, poorly controlled diabetes mellitus and hyperthyroidism; fetal and maternal tachycardia and myocardial ischemia, maternal pulmonary edema and hypotension and fetal myocardial hypertrophy, hyperglycemia and hyperinsulinemia are

potential side effects. A contraindication to magnesium sulfate is maternal myasthenia gravis; side effects include maternal lethargy, muscle weakness, headache, pulmonary edema and cardiac arrest, and fetal respiratory depression, hypotonia, lethargy and demineralization. Contraindications to calcium channel blockers include maternal cardiac disease, renal disease and hypotension; side effects include maternal nausea, hypotension and headache. Contraindications to prostaglandin synthetase inhibitors include maternal renal or hepatic impairment; side effects include maternal nausea and gastroesophageal reflux disease, and fetal constriction of the ductus arteriosus, pulmonary hypertension, reversible renal impairment, intraventricular hemorrhage, hyperbilirubinemia and necrotizing enterocolitis. Physicians hope to intervene in the future with anticytokine (interleukin-10) and antiprostaglandin therapy to more completely suppress the pathogenic process at multiple sites along the pathway rather than just treating the processes at the end of preterm labor.

Small human trials based on prophylactic treatment with progestational compounds have been reported. Not all reported positive results with meta analysis; the prevention of preterm delivery or the prevention of recurrent miscarriage appears to be based on the use of only the natural metabolite of progesterone, 17 alpha-hydroxyprogesterone caproate (17P). In one study, no increase in the rate of congenital anomalies in the progesterone group was noted over the control group. The benefit of 17P in preventing preterm delivery appears to be best in a cohort of women at very high risk, and the cohort still exhibited a high rate of preterm delivery (36%) despite significant reduction as compared to untreated control (54%), indicating that other causes of preterm delivery were at play. Tocolytic therapy was added in 17% of the treated group and 16% of the untreated control group. Interestingly, serum progesterone levels were not reported.

The maintenance of canine and feline pregnancy requires serum progesterone levels of >1-2 ng/ml. Serum progesterone levels during pregnancy normally range from 15 to 90 ng/ml, declining gradually during the latter half of gestation, and falling abruptly at term (usually the day before or the day of parturition). Progesterone promotes the development of endometrial glandular tissue, inhibits myometrial contractility (causes relaxation of myometrial smooth muscle), blocks the action of oxytocin, inhibits the formation of gap junctions and inhibits leukocyte function in the uterus. In several species, local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua or fetal membranes is important in the initiation of labor. Progesterone antagonists administered at term can result in an increased rate of spontaneous abortion. In the bitch, the corpora lutea are the sole source of progesterone, while in the queen, placental progesterone production occurs in the latter half of gestation. Canine luteal function is autonomous early in pregnancy but supported by luteotrophic hormones (LH and prolactin) after the second week of gestation.

Hypoluteiodism, primary luteal failure occurring before term gestation, is a potential but not yet documented cause of late term abortion in otherwise normal bitches. It has been documented that the induction of abortion in a normal but undesired pregnancy requires a reduction of plasma progesterone levels to <2 ng/ml. The diagnosis of gestational loss caused by premature luteolysis is difficult, requiring documentation of inadequate plasma progesterone levels prior to abortion for which no other cause is found. Measurement of precise progesterone levels, especially in the critical 1-3 ng/ml range, is not accurate using currently available rapid in-house Elisa kits, necessitating the use of commercial laboratories in most practice situations. A few

academic and human private laboratories provide more rapid (< 8h) turnaround, facilitating the diagnosis.

Progesterone levels diminish in response to fetal death, thus documentation of a low progesterone level after an abortion does not establish the diagnosis of hypoluteiodism as the primary cause for reproductive failure. Administration of progesterone to maintain pregnancy in dams with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of excessive progesterone to maintain pregnancy in a dam not actually requiring therapy can delay parturition and impact lactation, endangering the life of the bitch and her fetuses, and can masculinize female fetuses.

Dams with documented low progesterone levels and historical late term loss of pregnancy with no apparent pathology can also be evaluated for premature myometrial activity mid gestation, using uterine monitoring. Elaboration of prostaglandins from the endometrium and placenta associated with premature myometrial activity can secondarily result in luteolysis. Premature uterine activity endangering fetal survival can be identified before significant luteolysis occurs, and intervention indicated if the pregnancy is normal otherwise. Pharmacologic intervention to decrease myometrial activity is indicated, using progestational compounds and tocolytic agents alone or in combination.

Therapeutic intervention in primary hypoluteoidism can be accomplished with the administration of injectable natural progesterone or oral synthetic progestagens. Total serum levels of progesterone can be monitored only when supplemented with the natural product. Progesterone in oil is given intramuscularly at 2 mg/kg q 72h. Altrenogest (Regumate, Hoechst-Roussel), a synthetic progestagen manufactured for use in the mare, is dosed orally at 0.088 mg/kg q 24h. Both forms of supplementation must be discontinued in a timely fashion so as not to interfere with normal parturition, within 24h of the due date with the oral synthetic product, and within 72 h with the natural, injectable depot form. This requires accurate identification of gestational length via prior ovulation timing (parturition expected to occur 64-66 days from the LH surge or initial rise in progesterone, or 56-58 days from the first day of cytologic diestrus). Less accurate identification of gestational length can be made from breeding dates (58-72 days from the first breeding), radiography, or ultrasound.

Terbutaline (Brethine, Ciba Geigy, 0.03 mg/kg PO q 8h) has been used to suppress uterine contractility in bitches and queens with historical loss of otherwise normal pregnancies preterm. The dose is ideally titrated to effect using tocodynamometry. Therapy is discontinued 24h before term.

Further work evaluating the pathophysiology of premature labor and preterm delivery in the bitch and queen is needed, including evaluation of the ovary, placenta, myometrium and fetus for contributing factors. Multicenter studies including identification of the criteria for diagnosis of significant premature labor, specific therapy, outcome and follow up (dam and neonatal health, subsequent pregnancies) is encouraged.

## Selected References

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