Abnormal Endocrine function, Diagnosis and Treatment

Dr Stuart Mason BVSc (Hons) MANZCVS DACT
Monash Veterinary Clinic
1662 Dandenong Road
Oakleigh East, Victoria, 3166

Introduction
This paper discusses three commonly purported endocrine disorders of the bitch, hypoluteoidism, hypothyroidism and ovarian cysts. The diagnosis and treatment implications of each are often poorly understood and managed.

Hypoluteoidism (luteal insufficiency)
Pregnancy in the bitch is maintained solely by progesterone secreted from the corpus luteum. From around day 25 (post LH surge) relaxin from the placenta is produced which directly stimulates an increase in prolactin which in turn through its luteotrophic effect increases progesterone production from luteal tissue, and extends the life of the corpus luteum. This results in increasing serum progesterone levels despite increased circulating volume and increased progesterone metabolism of pregnancy. From approximately day 25 of dioestrus progesterone levels will slowly wane with the rising prolactin levels having less effect on supporting the corpus luteum and more effect on mammary development and lactation induction.

Hypoluteoidism in the bitch is defined as a failure of the bitch to produce adequate progesterone to maintain pregnancy. The phenomenon is controversial as it is difficult to prove with the literature being full of case reports of successful pregnancy maintenance with progesterone supplementation and monitoring, however there always appears to be other probable underlying causes. Progesterone stimulates the secretion of uterine milk from the uterine glands, inhibits uterine contractions and maintains closure of the cervix. The corpus luteum of the bitch is supported by both LH and prolactin during early gestation and prolactin primarily in later gestation. A progesterone level of greater than 6 nmol/L is required to maintain pregnancy in the bitch. Parturition occurs as a result of a sudden drop in serum progesterone as a result of the induction of luteolysis; as a result of sustained cortisol release from the foetuses. Therefore, any infectious or non-infectious disease of the uterus, placenta or foetuses can result in cortisol release by the foetuses and premature luteolysis. The same can occur with any inflammatory response releasing prostaglandins into the systemic circulation. Bitches suspected of suffering from hypoluteoidism are often presented because of multiple failed attempts to get pregnant, early embryonic loss (resorption) or abortion.

In order to make a diagnosis of hypoluteoidism it is imperative to rule out infectious and non-infectious causes of abortion and pregnancy loss in the presented bitch. Uterine disease (CEH), endometritis, placentitis, spermatozoal abnormalities (DNA damage), foetal abnormalities, lethal genetic disorders must all be ruled out which is difficult. It is important to run a blood profile including thyroid profile and uterine ultrasound in anoestrus/dioestrus to assess for and rule out other diseases. Uterine culture in dioestrus/anoestrus is also useful to rule out other disease (endometritis). When there is no evidence of a primary disease causing a failed pregnancy, resorption or abortion, hypoluteoidism may be considered.

It is important to undertake good ovulation timing to stage the cycle of the bitch in question. Serial progesterone samples should be taken twice weekly through dioestrus with consistent and appropriate handling of the samples (collection into plain tube no gel, no refrigeration for 2 hours, serum centrifuged if not to be analysed within 4
hours of collection). If serum progesterone is approaching 6 nmol/L then progesterone supplementation may be started. Progesterone may be supplemented using natural progesterone or progesterone analogues (e.g. medroxyprogesterone acetate, altrenogest).

Natural progesterone supplementation is the preferred method as the total serum progesterone (naturally produced and that supplemented) are measured, whereas with progesterone analogues they are not measured by routine progesterone assay (although some practitioners prefer this so that they can actually monitor the corpus luteum function). Once progesterone supplementation has begun then the bitch must be monitored closely, at least twice weekly, via ultrasound to confirm presence of viable foetuses and through serum progesterone assays to make sure that the serum level is adequate. Should the foetuses die inside the uterus they will not be passed out due to the exogenous source of progesterone, which could impact the health of the bitch. If natural progesterone is to be used it can be compounded (micronized progesterone) and supplemented at 10 mg/kg twice daily orally with some oil to aid absorption. Serum levels should be maintained at 50-100 nmol/L.

Progesterone supplementation will increase the risk of development of diabetes, pyometra, placentitis, dystocia, prolonged gestation, agalactia and septicaemia. Long acting progesterone preparations and analogues will cause masculinisation of female foetuses, however natural progesterones will not have this effect due to their short half-life (~72 hours). It is probable that progesterone supplementation will provide negative feedback on the HPA axis and worsen the problem.

It is important to remember that low progesterone is a symptom of a disease and likely occurring as a result of other disease such as low relaxin and prolactin levels secondary to foetal or uterine disease. Diagnosis and treatment of hypoluteoidism should be treated with caution and the owners well counselled with respect to diagnosis, treatment, monitoring and possibility of underlying diseases.

**Hypothyroidism**

For some time hypothyroidism has been implicated as a cause of infertility in the bitch, yet it is unproven in this species. Thyroxine supports granulosa cell function in developing follicles and is also required for normal trophoblast function. TSH stimulates prolactin, so it would be expected that bitches with hypothyroidism would either suffer from persistent anoestrus or have increased inter-oestrus intervals. Other reported symptoms of hypothyroidism and fertility includes abortion, mummification, resorption, prolonged proestrus, increased duration of oestrus and galactorrhoea.

Normal thyroid function is necessary for follicular development and so low thyroid levels would result in reduced number and quality of follicles which would support resorption, mummification and abortion. TT4 levels rise through dioestrus with rises in prolactin levels. When assessing a bitch for hypothyroidism it is important to measure thyroid hormone in anoestrus, as during oestrus thyroid levels are usually low, whilst TT4 levels are higher in dioestrus and pregnancy. TT4 levels should always be assessed with TSH, as the specificity of these tests in conjunction is 98% (2% false positives; euthyroid dogs diagnosed as hypothyroid). Other changes of blood pathology to support hypothyroidism include a non-regenerative anaemia and hypercholestrerolaemia.

Treatment of bitches with hypothyroidism involves supplementation with thyroxine at 0.01-0.02 mg/kg twice daily, with peak serum TT4 levels assessed 4-6 weeks later, 4-6 hours post pill and the dose titrated appropriately. Once stable, TT4 levels are achieved serum levels should be monitored 6 monthly.

Whilst supplementation of hypothyroid bitches will return them to normal fertility, due to this being an inherited disease, it is not advisable to breed with affected animals.
Hyperthyroidism has been shown to cause infertility in women so diagnosis and treatment must be accurate; i.e., ensuring sick euthyroidism is absent.

**Silent heats**

Silent heats occur in bitches wherein there is normal ovarian activity but no overt signs of oestrus. Vulval swelling may be minimal and not noticed by the owners, and vaginal bleeding may be minimal to non-existent. In many cases this may be brought to the attention of the owner through interest shown by other females or males in the household of the bitch in question with no evidence of oestrus. Silent heats are often unnoticed in single bitch households. In order to rule in or our silent heats monthly serum progesterone assays with any results above 6 nmol/L indicating ovarian activity. Weekly vaginal smears looking for cornification will also indicate functional ovarian activity and help to identify likely timing of cyclicity.

**Ovarian disease – follicular cysts, luteal cysts**

There are 8 different types of cysts in the canine ovary, with only two of them being pathogenic via endocrine effects.

Follicular cysts are defined as thin walled cysts with a diameter of 8 mm or greater. They are caused by an abnormal HPA axis wherein there is an inability to produce or release LH, or an absence of LH receptors in the follicle. Follicular cysts produce oestrogen and clinically present as persistent oestrus. Treatment may be attempted with HCG to induce luteinisation or ovariectomy if unilateral, however the prognosis is poor and OVH is the treatment of choice. Follicular cysts may be iatrogenically induced through the use of deslorelin to induce oestrus; the initial intense LH and FSH release following deslorelin injection followed by immediate suppression will often lead to a failure of LH surge (and ovulation) and follicular cyst formation.

Luteal cysts (luteinised cysts) are luteinised or ovulated follicular cysts. They are thick walled ovarian cysts with a diameter of over 8 mm. Luteal cysts secrete low levels of progesterone and result in persistent anoestrus.

**References**

1. Johnson SD, Root Kustritz MV, Olson PNS. Canine and Feline Theriogenology. 2001 Saunders PA.