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Canine Pseudopregnancy: A Review (23-Aug-2001)

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Summary

This chapter reviews the most relevant features of the patho-physiology, clinical signs, diagnosis, treatment and prevention of overt, i.e. clinical, pseudopregnancy in dogs. Clinical pseudopregnancy is a syndrome observed in non-pregnant dogs and is characterized by clinical signs such as nesting, weight gain, mammary enlargement and lactation. It typically occurs in non-pregnant bitches about 6 to 12 weeks after estrus. Diagnosis is based on clinical signs. While prolactin has a central role in the symptomology of clinical pseudopregnancy, the precise etiology is not yet completely understood. Some studies suggest that at some point during diestrus (metestrus) the circulating prolactin concentrations rise to higher than normal levels in overtly pseudopregnant bitches compared to those in unaffected bitches in diestrus. It is also possible that individual differences in peripheral sensitivity to prolactin, or even the existence of molecular variants of canine prolactin with different bioactivities, are involved in the variation of the incidence and severity of pseudopregnancy within and among breeds. Exposure to progesterone and subsequent withdrawal of progesterone is apparently involved, based on effects of exogenous progesterone and on the frequent induction of pseudopregnancy by spaying (ovariectomy or ovariectomy) during the luteal phase, i.e., in the metestrus (diestrus) stage of the cycle. Considering that overt pseudopregnancy is usually a self-limiting and possibly a quasi-physiological state, mild cases usually are not presented for treatment or are determined to need no treatment. However, physical as well as behavioral changes can be so extensive as to be intolerable for owners, and treatment is typically sought late in the course of the syndrome. The reported relation between a history of overt pseudopregnancy and subsequent mammary tumor development suggests that treatment may be more important than previously assumed. Sex steroids and in particular progestins traditionally used to treat pseudopregnancy have side effects which outweigh any benefits, although androgens like mibolerone may be useful where available. Inhibition of prolactin release by administration of an ergot derivative such as bromocriptine, cabergoline or metergoline has proven to be highly effective for the treatment of canine pseudopregnancy, and more appropriate than the use of steroids. Although some of these ergot derivatives can present some untoward side effects, such effects are typically transient and can usually be tolerated or managed. Predisposed bitches not intended for breeding should be spayed because ovariectomy is the only permanent preventive measure.

Introduction and Terminology

In dogs, the clinical condition of overt pseudopregnancy is usually simply called "pseudopregnancy", although other terms have also been used or suggested, including pseudocyesis, false pregnancy and nervous lactation. Unfortunately, the single term "pseudopregnancy" does not distinguish the clinical condition from "covert pseudopregnancy", i.e., the "physiological pseudopregnancy" that occurs in every non-pregnant ovarian cycle in bitches. Because the normal luteal phase of progesterone secretion is so long during the canine estrus cycle, compared to other species, it has been compared to the abnormally prolonged luteal phases observed in pseudopregnant laboratory rodents. In fact, there is considerable mammary development associated with the luteal phase of every ovarian cycle in dogs. And, therefore, the luteal phase of the normal bitch has been termed a physiological or covert pseudopregnancy. The extent of normal mammary development during metestrus (diestrus) varies within and among bitches. Further, it has been suggested that the clinical condition of overt pseudopregnancy actually represents the extreme of the physiological changes that normally occur during diestrus (metestrus). However, when the changes result in extreme behavior or atypical mammary activity, or are presented as clinical problems involving changes similar to those seen in late pregnancy or the early post-partum period, the condition can best be termed "clinical pseudopregnancy" or "overt pseudopregnancy" [1-4]. Overt or clinical pseudopregnancy is not uncommon in dogs. It seems likely that it represents the retention in domestic dogs of a previously functional evolutionary adaptation developed when non-bred she-wolves of a primitive canine species nursed the litters of other females [4,5]. The exact

incidence of clinical pseudopregnancy or its distribution among breeds is not known, although it has been estimated to be as high as 50 - 75%, using a rather broad definition of the condition [6].

The pituitary hormone prolactin plays a central role in the pathophysiology of overt pseudopregnancy, but its exact role is not completely understood [7]. There is substantial albeit anecdotal and unpublished evidence that the incidence of clinical pseudopregnancy may be influenced by age, breed, parity and environmental factors. It has also been suggested that nutritional practices may also have an influence on the occurrence of pseudopregnancy [8]. The purpose of the present review is to examine the most relevant aspects of the physiology, clinical signs, diagnosis, treatment and prevention of clinical pseudopregnancy. The term "pseudopregnancy" is used only to refer to clinical or overt pseudopregnancy, unless noted otherwise.

Clinical Signs and Complications

All non-pregnant bitches in mid and late metestrus (i.e., diestrus), and between 6 to 20 weeks after estrus, have mammary development much greater than at any other stage of the cycle (Fig. 1) and peak mammary size is seen at about 14 weeks [9].

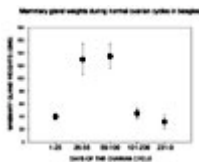


Figure 1. Weights of paired mammary chains obtained from normally cycling, asymptomatic beagle bitches at known days of the nonpregnant ovarian cycle. Adapted from Concannon, 1987 [9]. - To view this image in full size go to the IVIS website at www.ivis.org . -

While the extent of mammary development, and possibly other signs of prolactin action, are quite variable among bitches, bitches that show overly conspicuous signs are overtly and clinically pseudopregnant. The pseudopregnancy-syndrome (Table 1) usually begins with behavioral signs such as restlessness, decreased activity, nesting, aggression, licking of the abdomen and mothering inanimate objects. Later, pseudopregnant bitches show physical signs such as weight gain, mammary enlargement, even milk secretion and let-down, and sometimes abdominal contractions that mimic those of parturition [3-10].

Table 1. Clinical signs observed during overt pseudopregnancy in dogs
Common Signs
<ul style="list-style-type: none"> • Prepartum-like and maternal-like behaviors • Nesting, digging, over-affection, over-protectiveness, over-defensiveness, aggression, licking, mothering of inanimate objects • Mammary enlargement and distension • Lactation and milk release • Weight gain • Anorexia
Less Common Signs
<ul style="list-style-type: none"> • Emesis • Abdominal enlargement • Abdominal contractions • Diarrhea • Polyuria • Polydipsia • Polyphagia

In some cases the physical signs are noted before the behavioral signs. Mammary hypertrophy is usually more evident in the most caudal pair of glands (Fig. 2) although the entire mammary chain can be involved.



Figure 2. Enlarged caudal mammary glands in a bitch experiencing overt pseudopregnancy including behavioral signs. - To view this image in full size go to the IVIS website at www.ivis.org . -

Milk production during pseudopregnancy apparently results from the development of not only intra-acinar but also intracanalicular mammary secretion in predisposed bitches [11]. Lactation is often encouraged by self-nursing or by adoption of unrelated neonates [6]. Vomiting, anorexia, diarrhea, polyuria, polydipsia, and polyphagia have also been reported [6]. Bitches in which these behavioral or physical signs are so exacerbated as to become a clinical problem are, by definition, considered to present clinical pseudopregnancy and frequently require some kind of treatment.

Complications of pseudopregnancy, like mastitis and mammary dermatitis, are not common and, unless these complications appear, signs of pseudopregnancy normally cease after 2 to 4 weeks. Susceptible bitches have a high recurrence rate in successive estrous cycles [3,12]. Overt pseudopregnancy has also been observed to be induced under the following circumstances: during prolonged progestin treatment; after termination of progestin treatment; in response to antiprogestin treatments; and at 3 or 4 days after ovariectomy (spaying) during the luteal phase [6,12-14]. These instances of progesterone exposure and subsequent reduction or withdrawal of progesterone presumably have the same effects as occur in response to the decline in progesterone that normally occurs in pregnant bitches immediately before parturition.

Some studies suggest that there is a relationship between the occurrence of episodes of pseudopregnancy and later reproductive diseases [15] or fertility problems [6]. Whether prolactin plays a role in mammary tumor development is unclear. The number of prolactin receptors found in benign mammary tumors is no higher than that of normal tissue, and only 30% of malignant tumors have prolactin receptors [16]. Nevertheless, pseudopregnancy and prolactin have been implicated in the pathogenesis of mammary tumors [17,18]. An increased risk of mammary neoplasia associated with pseudopregnancy might be explained by a continuous mechanical distension of, and the accumulation of carcinogenic products within, the mammary acini caused by the formation and retention of milk [18,19].

Patho-physiology

Role of Progesterone - At one time, it was postulated that pseudopregnancy was caused either by an overproduction of progesterone or an abnormally long persistence of corpora lutea [20]. More recently it appears that the role of mammary exposure to progesterone is primarily permissive, in that an elevation in progesterone is required for mammary enlargement such as that observed in pseudopregnancy. Thus, pseudopregnancy appears to be related to and dependent on a previous prolonged, and in most cases a very recent, exposure to elevated levels of progesterone. Further, it has been suggested, based on indirect evidence, that pseudopregnancy may occur as a result of increased concentrations of prolactin or an increased sensitivity to prolactin induced by a more rapid than normal decline of progesterone levels in the late luteal phase [21-24]. In fact, spaying or ovariectomy during the luteal phase (i.e., during metestrus/diestrus) induces pseudopregnancy in some bitches (Table 2).

Table 2. Probable and proposed causes of clinical pseudopregnancy in female dogs

1. Idiopathic occurrence of a more extensive increase in prolactin than occurs in normal diestrus.
2. Idiopathic increase in sensitivity to the endocrine changes that normally occur in late diestrus, including the normal progressive decline in progesterone and modest elevation in prolactin.
3. Pseudo-luteal phase induced by administration of exogenous progestins
4. Progesterone withdrawal caused by:
 - a. ovariectomy during diestrus,
 - b. termination of long-term or short-term progestin therapy
 - c. idiopathic or prostaglandin-induced abrupt luteolysis
 - d. antiprogestin therapy
5. Idiopathic hyperprolactinemia potentially associated with pituitary microadenomas.
6. Psychogenic or reflexive hyper-prolactinemia occurring in response to stimulation by surrogate neonates or other visual, physical or social stimulation.

Likewise, the apparently successful treatment of pseudopregnancy by administration of a progestin often results in a full-blown recurrence of pseudopregnancy immediately following cessation of the progestin therapy. These induced bouts of

pseudopregnancy have also been noted to have some similarity to the events of normal parturition, where there is typically an abrupt increase in prolactin and the onset of lactation is precipitated by the normal prepartum decline in progesterone. In contrast, during non-symptomatic nonpregnant cycles, progesterone levels decline slowly and progressively because there is normally no abrupt luteolysis. Unfortunately, changes in progesterone during the genesis of spontaneous pseudopregnancy have not been reported. An abrupt decline in progesterone may be involved with some or even most cases of spontaneous pseudopregnancy. However, an abrupt decline in progesterone does not necessarily cause pseudopregnancy. In a study in which 11 diestrous bitches were ovariectomized to induce an abrupt decline in serum concentrations of progesterone levels, symptoms of pseudopregnancy developed only in the 4 animals that had a history of the syndrome [14]. Those results suggest that a fall in progesterone is not, *per se*, sufficient to induce pseudopregnancy in some bitches. Apparently, some bitches are more sensitive to the effects of progesterone withdrawal than others. Such differences might explain, in part, the variable incidence of pseudopregnancy among bitches and apparently among breeds.

Role of Prolactin - Evidence for a role of prolactin in pseudopregnancy is primarily provided by studies where the condition including all symptoms was successfully treated by administration of dopamine agonists, drugs which inhibit prolactin secretion [25-28]. Prolactin concentrations normally increase slightly above basal values between days 60 and 90 of the nonpregnant estrous cycle [29], with increases often seen as early as day 40. There is also an inverse relationship between progesterone and prolactin concentrations in the normal nonpregnant cycle between days 40 and 90 [30]. In some studies, bitches with pseudopregnancy had higher serum concentrations of prolactin than might otherwise be expected [31], whereas prolactin during pseudopregnancy was variable or not elevated in other studies [8,14,32,33]. In mammals, prolactin stimulates the mammary gland during all stages of gland development, from pubertal mammogenesis, throughout lactogenesis, and during lactation [34]. In most species, prolactin is required at all stages of mammary development, although there are species differences in prolactin requirements during lactation [35]. In the bitch, prolactin also seems to be involved in ensuring maternal behavior, including the preparation for delivery and care of the litter thereafter, behaviors which also happen during overt pseudopregnancy [29,36]. Although prolactin appears to be the most important endocrine factor in the development of the symptoms of pseudopregnancy, other hormones including estrogen might also play a role [34]. A positive correlation between prolactin and estrogens has been found in some bitches [37,38].

Prolactin secretion by the acidophil cells of the anterior pituitary is under a complex set of controlling factors (Table 3) and prolactin has metabolic effects in addition to those on mammary gland and behavior. Prolactin is also a required luteotrophin in the dog, and drugs that can cause prolactin suppression have been used to terminate pregnancy.

Table 3. Endocrine factors reported to directly or indirectly affect prolactin secretion by pituitary lactotrophs		
Locus and Mode of Action	Stimulatory Factors	Inhibitory Factors
<i>Central (Hypothalamic) Factors</i>		
Direct Actions	TRH VIP A-II GABA Oxytocin Bombesin	Dopamine Somatostatin GABA DKP GAP
Indirect Actions	Serotonin*	Opioids*
<i>Peripheral Factors</i>		
Direct Actions	Estrogen	Progesterone
Indirect Actions		Thyroxin**

* Serotonin inhibits dopamine release. Opioids stimulate dopamine release.

** Thyroxin is suggested to be inhibitory via a negative feedback effect on TRH release.

The expression of pseudopregnancy could theoretically result from increased serum prolactin concentrations, from increases in the number or sensitivity of receptors for prolactin, or from the presence of molecular prolactin variants with a particularly high bioactivity-to-immunoreactivity ratio. Several studies reported differences in prolactin levels between patients with overt pseudopregnancy and patients that were not pseudopregnant. In one study, about 55% of the prolactin values of

pseudopregnant bitches were included within the mean and standard deviation of the control bitches up to day 80, but prolactin levels were higher thereafter in the overtly pseudopregnant bitches [38]. In another study, overtly pseudopregnant bitches had higher prolactin than normal animals at day 60 of the estrous cycle [39]. In Afghan-hound bitches, prolactin concentrations were higher in pseudopregnant bitches when compared either with bitches in an earlier stage of the luteal phase or with non-symptomatic Beagle bitches at the same stage of the cycle [31]. However, another study found no significant differences in mean serum prolactin levels between pseudopregnant and non-pseudopregnant bitches during 13 out of 16 weeks in 28 Labrador Retrievers [8]. There was also no difference in prolactin between bitches with ovariectomy-induced pseudopregnancy and bitches that were not pseudopregnant [14,33]. An overlap of prolactin values was reported between bitches that were pseudopregnant and those that were asymptomatic following ovariectomy [40]. Two bitches that were pseudopregnant following ovariectomy were observed to have low prolactin [32]. Thus, high prolactin concentrations may be involved in the etiology of pseudopregnancy, but continuously high concentrations do not seem to be necessary for the maintenance of signs. Whether increased concentrations of circulating prolactin are always involved in the onset of pseudopregnancy, with concentrations being variable thereafter, or whether an increase in prolactin-sensitivity alone can be a sufficient stimulus, has yet to be determined. An increase in sensitivity to prolactin may be a response of some tissues to progesterone withdrawal. The potential causes of overt pseudopregnancy are outlined in Table 2. The role of growth hormone, which is deeply implicated in the process of mammogenesis in many mammalian species [34,41], is not clear in canine pseudopregnancy. However, no evidence of an association between overt pseudopregnancy and serum growth hormone serum levels has been observed [33].

Diagnosis

Diagnosis of pseudopregnancy is based on the presence and extent of the more commonly reported clinical signs (Table 1). Because unscheduled matings may be overlooked by owners, pregnancy should always be considered. In case of doubt, ultrasound or radiography should be used. Other conditions of the luteal phase, such as pyometra or recent pregnancy and abortion, should be ruled out by abdominal ultrasonography or radiography, a complete blood cell count and additional ancillary testing, including vulval and vaginal exams. It is also important to keep in mind that pseudopregnancy can coexist with other reproductive or non-reproductive clinical problems, sometimes making diagnosis more difficult. Other known causes of galactopoiesis associated with hyperprolactinemia, although not well characterized in the dog, should be considered, especially if lactation lasts longer than 3 or 4 weeks. Primary hypothyroidism, an endocrine disease of high prevalence in the dog, is associated with hyperprolactinemia in some women. Apparently, compensatory elevations of thyrotropin releasing hormone, or TRH, stimulates both thyrotropin and prolactin secretion [42]. Interestingly, a case of primary hypothyroidism associated with hyperprolactinemia in a cross-bred bitch has been reported [43]. Other frequent causes of hyperprolactinemia in other species, such as pituitary microadenomas, hepatic or renal failure, sex steroid administration and administration of psycho-active pharmaceuticals remain to be assessed in the bitch [42,44].

Treatment

Considering that pseudopregnancy is typically a self-limiting state, mild cases are usually considered to need no treatment other than discouraging maternal behavior. Sometimes placing Elizabethan collars to prevent licking of the mammary glands is recommended. Licking, milking, or use of compresses are potential stimuli for lactation and need to be avoided. Water removal overnight for 5 to 7 nights promotes fluid conservation and also helps to terminate lactation. However, normal renal function should be documented beforehand [3,10,45]. When behavioral signs are significant, light tranquilization with non-phenothiazine drugs can be useful. Conversely, phenothiazines are not recommended in pseudopregnant bitches because they stimulate prolactin secretion [46]. Nevertheless, it may be advisable to pharmacologically treat even mild cases of pseudopregnancy in bitches with repeated episodes considering the possible relationship between pseudopregnancy and subsequent development of mammary tumors recently reported [18].

Pharmacological approaches to the treatment of moderate to severe pseudopregnancy have historically included steroids, including estrogens, progestins and androgens. More recently the preferred method of treatment is the use of prolactin-suppressing drugs, especially dopamine agonists, where available. Recently proposed therapeutic agents are summarized in Table 4.

Sex Steroid Therapy

Sex steroids have been traditionally used to treat pseudopregnancy but the side effects usually outweigh any benefits of these medications. Although sex steroids are necessary for mammary development, high doses appear to exert a negative effect, either by suppressing pituitary prolactin or decreasing sensitivity to prolactin [1,6]. The most frequently used sex steroids in the past were veterinary preparations of estrogens, progestins and androgens.

Table 4. Approved and extra-label drug use reported for the treatment of clinical pseudopregnancy in dogs			
Drug	Name	Action	Note
<i>Contraceptive Androgens</i>			
Mibolerone	Cheque Drops®	Not known	Contraceptive. Extra-label use
<i>Dopamine Receptor Agonists</i>			
Bromocriptine	Parlodel®	Reduces prolactin	Human drug. Extra-label use
Cabergoline	Galastop®	Reduces prolactin	Veterinary drug marketed in Europe but not North America
<i>Serotonin Antagonists</i>			
Metergoline	Contralac®	Reduces prolactin	Veterinary drug marketed in Europe and some South American countries

Estrogens - Estrogens such as diethylstilbestrol, estradiol benzoate or estradiol cypionate have been used. They may cause signs of proestrus or estrus, uterine disease such as pyometra, and bone marrow depression resulting in anemia. The use of estrogen is not recommended.

Androgens - Androgens including testosterone and synthetic androgens can suppress lactation. Side effects can include clitoral hypertrophy, other forms of virilization, and epiphora. The synthetic androgen mibolerone has been shown to reduce the duration of pseudopregnancy. Mibolerone has been previously marketed as an oral contraceptive for dogs, administered daily as liquid added to the feed (Cheque Drops®). However, this product is no longer readily available.

Progestins - Progestins such as megestrol acetate and medroxyprogesterone acetate, administered orally, have been used to suppress the symptoms of overt pseudopregnancy. The mechanism is not known, but likely involves suppression of prolactin secretion or reduction of tissue sensitivity to prolactin. There is very often a rebound in symptoms including lactation when treatments are discontinued, with the progestin withdrawal mimicking the normal endocrine changes at parturition. Progestins can cause cystic endometrial hyperplasia-pyometra complex and insulin resistance, as well as mammary gland nodules, mammary tumors, and acromegaly [3]. Administration of progestins is therefore not recommended.

Prolactin-Suppression Therapy

Dopamine Agonists - Inhibition of prolactin secretion by ergot alkaloid drugs has produced a revolution in the treatment of canine pseudopregnancy. Prolactin secretion in mammals is under a complex set of stimulatory and inhibitory factors and hormones originating both peripherally and centrally (Table 3). Secretion of prolactin by the pituitary is mainly under tonic inhibitory control of the hypothalamus, mediated by a direct action of dopamine, the major prolactin inhibiting factor (PIF). This inhibition can be modulated indirectly by serotonin, which suppresses dopamine release and increases prolactin [47]. In addition, the hypothalamic tri-peptide, thyrotropin releasing hormone (TRH), causes release of prolactin as well as release of thyroid stimulating hormone (TSH).

The most common ergot compounds used clinically to inhibit prolactin secretion are the dopamine agonists bromocriptine and cabergoline which have a direct action on D2-dopamine receptors of the lactotroph cells of the anterior pituitary gland. Metergoline, another ergot alkaloid, is a serotonin antagonist, and thus has a dopaminergic effect and thus reduces prolactin secretion when administered at high doses [26,27,48]. Selected pharmacological attributes of bromocriptine, metergoline and cabergoline are summarized in (Table 5) and in the text below.

Bromocriptine - Bromocriptine (Parlodel®) is marketed as a drug for human use in Europe, North America and Latin America, but is not marketed with any indication for use in animals. However, it has been used extra-label and experimentally in veterinary medicine since 1980. A large number of therapeutic protocols have been proposed, using oral doses of bromocriptine ranging from 10 to 100 µg/kg/day for 10 to 14 days [18,26,28,49]. It has a short half-life (± 4 - 6 h) and should be administered at least twice a day for greatest efficacy. Bromocriptine also has activity on GABA, serotonergic and adrenergic receptors and therefore is less specific than cabergoline (see below). Unlike cabergoline, bromocriptine also crosses the blood-brain barrier and can stimulate other brain centers in addition to the hypothalamus. Emetic effects result from stimulation of the hypothalamic vomiting center. The ED50 for emesis is near the commonly used therapeutic doses (13 µg/kg vs. 10 to 20 µg/kg) and digestive side effects are frequent and proportional to the dose [11]. Common side effects include vomiting, anorexia, depression, and other behavioral changes [18,50]. Side effects tend to

decrease during the course of treatment. To prevent or reduce the incidence of emesis, bromocriptine can be administered in low and then increasing doses, or administered with the food [10,28]. In addition, vomiting can be managed by administration of anticholinergic drugs such as atropine. Care should be taken, when trying to prevent emesis, not to use central dopamine blockers of synaptic transmission whose action would oppose that of bromocriptine.

Bromocriptine is formulated in 2.5 mg tablets for use in humans, and fractionation of the tablets is necessary to achieve dosages of 10 to 30 $\mu\text{g}/\text{kg}$ typically administered to pseudopregnant bitches [5,18,45,51]. This makes it difficult to administer exact doses, and may have caused an overestimation of the drug's side effects. Preparation of exact dosages is important. In a study in which 10 pseudopregnant bitches were precisely administered 15 $\mu\text{g}/\text{kg}/\text{day}$ for 15 days, mild side-effects that did not lead to the termination of the therapy appeared in only 30% of the animals, and occurred only during the first week of the treatment [14]. Administration of the 10 to 30 $\mu\text{g}/\text{kg}$ dose twice or even 3 times a day is preferable to once a day administration.

Cabergoline - Cabergoline has greater bioactivity, superior D2-receptor specificity, and a longer duration of action compared to bromocriptine. The biopotency is greater than some anti-prolactin dopamine agonists used in human medicine (tergulide and lisuride) and is about equivalent to that of pergolide. It can be effectively administered once a day. Cabergoline crosses the blood brain barrier only slightly and consequently has much less central emetic effects than some other dopamine agonists [2,4,32,52]. The ED50 for emesis is 4 times the therapeutic dose and gastrointestinal signs are rare [11]. Cabergoline (Galastop®) is marketed as a veterinary drug in several European countries with an indication for use in pseudopregnant bitches at a dose of 5 $\mu\text{g}/\text{kg}/\text{day}$ for 5 to 10 days, given orally (Fig. 3).



Figure 3. Galastop®. A commercial preparation of the dopamine agonist cabergoline, marketed in Europe by Vetem for treatment of canine pseudopregnancy, is available as a suspension in liquid for oral administration. - To view this image in full size go to the IVIS website at www.ivis.org . -

In line with the prolonged duration of action, cabergoline remains bound to receptors of the pituitary and retains some efficacy for 2 or more days following termination of therapy. In North and South America, cabergoline is marketed only for human use (Dostinex®), and its use in animals is experimental and extra-label in these countries.

Metergoline - Metergoline is an anti-serotonergic veterinary drug (Fig. 4) marketed for the treatment of pseudopregnancy in bitches in Europe and in some Latin American countries (Contralac®). It has a short half-life so it has to be administered twice a day. The recommended dose is 0.1 mg/kg, orally, twice a day, for 8 to 10 days. Anxiety, aggressiveness, hyper excitation and whining are the most frequent side effects of metergoline, which are due to its central anti-serotonergic effect [11,48,53,54].



Figure 4. Contralac™, a commercial preparation of metergoline, marketed as 0.5 and 2.0 mg tablets in Europe and South America by Virbac Laboratories (France and Brazil) for treatment of canine pseudopregnancy. - To view this image in full size go to the IVIS website at www.ivis.org . -

When the changes in prolactin concentrations in dogs following single oral administrations of bromocriptine, metergoline and cabergoline, each at 3 different dose, were studied, the results demonstrated a greater and more prolonged efficacy of cabergoline (Fig. 5).

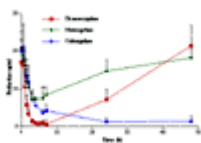


Figure 5. Serum prolactin concentrations in dogs administered single oral doses of bromocriptine (25 $\mu\text{g}/\text{kg}$), metergoline (200 $\mu\text{g}/\text{kg}$) or cabergoline 5 $\mu\text{g}/\text{kg}$). From [58]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Table 5. Efficacy and activity of three anti-prolactinic agents that have been used for the treatment of canine pseudopregnancy.

	Bromocriptine (Parlodel [™] , by Sandoz)*	Metergoline (Contralac [™] , by Virbac)*	Cabergoline (Galastop [®] , by Vetem)*
Pharmacokinetics of Antiprolactinic Effects	Poor absorption (~30%) Max effect: 1.5 - 3h Half life: 3h	Max effect: 2 - 4 hours Half-life: 4h	Good absorption (> 80%) Max effect: 18 - 24 h Half life: 17 - 24h
Serotonergic Effects	Weak antagonist	Strong central and peripheral antagonist	Weak antagonist
Dopaminergic Receptor Effects	D2 Agonist D1 Antagonist Less emetic effect than ergotamine	Weak D2 Agonist D1 Antagonist Little or no emetic effect	Agonist D2 D1 Antagonist Less emetic effect than ergotamine
Alpha-Adrenergic Effects	Weak antagonist	Unknown	None
Ecboic Uterine Effect	Inactive	Weak or absent	Inactive

*These drugs are not available in all countries, or may only be marketed for human use. Parlodel[™] a brand of bromocriptine (2.5 mg) is marketed for human use only, in most countries. Metergoline is also formulated and marketed for human use as Liserdol[™] in some countries. Cabergoline is also marketed for human use as Dostinex[™].

Ovariectomy

Predisposed bitches not intended for breeding should be spayed. Ovariectomy is the only permanent preventive measure [6,27]. This should preferably be done during anestrus. Ovariectomy during lactation can lead to an extended pseudopregnancy [1,10]. In bitches with a history of overt pseudopregnancy, spaying during metestrus (diestrus) may provoke an episode of pseudopregnancy 3 to 7 days after surgery [14].

Conclusion and Discussion

Although "pseudopregnancy" is the most frequent term used to describe this clinical condition in bitches in both English and Spanish languages, the more precise and appropriate terminology includes "overt-pseudopregnancy" and "clinical-pseudopregnancy". The unmodified term "pseudopregnancy" in reproductive biology simply refers to the prolonged luteal phase of non-fertile induced ovulatory cycles [34]. Moreover, in the dog, the signs of clinical pseudopregnancy are comparable not so much to those of pregnancy but to those of the peripartum and postpartum periods and lactation [1]. Pseudopregnancy is easy to diagnose and easy to treat using dopamine agonists. Although some of the agonists have side effects, these are transient and can usually be managed. The patho-physiology of the condition is not fully understood but a central etiologic role for prolactin is widely accepted. A number of hypotheses have been proposed to explain why overtly pseudopregnancy occurs only in some bitches during non-fertile ovarian cycles. It may be due to particular features of the estrous cycle of certain breeds. A short luteal phase with an abrupt decline in progesterone, which would be expected to stimulate prolactin release, has been proposed as the cause of pseudopregnancy [21]. However, it may not be universally the case, since only predisposed bitches had a sharp increase in serum prolactin concentrations levels and became symptomatic following ovariectomy in diestrus [14].

If the absolute concentrations of circulating prolactin do not necessarily determine the appearance of pseudopregnancy, then the question of peripheral sensitivity to this hormone should be taken into account. Thus, it can be hypothesized that, for a given prolactinemia, those bitches with the highest sensitivity to prolactin will be more prone to developing overt signs than bitches with a lower sensitivity to prolactin [3,28]. For this reason, a universally applicable serum prolactin threshold for triggering an episode of overt pseudopregnancy in the bitch is unlikely to exist. This is in line with findings in some women where no correlation existed between typical signs of hyperprolactinemia and the serum prolactin concentrations [55,56]. Research has uncovered a surprising degree of molecular heterogeneity for prolactin, with different biopotencies associated with varying molecular forms of the hormone [57]. In dogs, the presence of molecular heterogeneity for prolactin was recently reported for samples obtained in metestrus (diestrus) [14]. Therefore, differences in the bioactivity and immunoreactivity of canine prolactin within some bitches could account, at least in part, for the lack of consistency between immunoassayable prolactin concentrations and the extent of pseudopregnancy observed. These unanswered questions open interesting avenues of clinical and molecular research to determine the molecular basis underlying the phenomenon of

pseudopregnancy in the bitch.

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