Progestins as a treatment for subinvolution of placental sites in the bitch.

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Progestins as a treatment for subinvolution of placental sites in the bitch.

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Abstract

Eight postpartum bitches diagnosed with subinvolution of placental sites (SIPS) were followed in this retrospective study to investigate the efficacy of treatment with low oral doses of progestins in stopping bloody vulvar discharge. Two other bitches diagnosed with SIPS were included in this study not receiving treatment.
A progestin derivate was administered orally once a day in low dose for two weeks, with half the daily dose reduced the second week. Cessation of vulvar discharge was seen in all eight treated dogs within this two week treatment period. The untreated dogs persisted with the problem respectively until a few weeks before and till onset of the next proestrus. No adverse effects on future heat, fertility, gestation and parturition was found in both the treated and untreated dogs. The results of this study indicate that oral low dose progestin therapy is effective and probably safe in treatment of SIPS.

Key words: SIPS, megestrolacetate, medroxyprogestroneacetate, trophoblast cells, progestins

Introduction

Persistent sanguineous postpartum vulvar discharge in female dogs can be due to numerous causes, including trauma, genital tract neoplasia, endometritis, brucellosis, coagulopathy and subinvolution of placental sites (SIPS) [1].

SIPS occurs when there is a delay in or failure of normal uterine involution after whelping. Johnston (2001) reports a normal postpartum hemorrhagic discharge lasts up to 3 weeks. In SIPS the animal loses a scant amount of blood daily (a few drops) in the absence of other clinical symptoms. The incidence of SIPS is not exactly known. Al-Bassam (1981) observed 20 cases of SIPS out of 95 reproductive tracts from postpartum bitches, based on the history, gross and histologic findings. SIPS in dogs is a benign process and spontaneous resolution is usual [2,3]. Duration is variable, lasting a few weeks in some cases but persisting to the next proestrus in many others. Although there is no compelling indication for treatment, dog owners often consult veterinarians seeking treatment for the bloody discharge.

The pathology of SIPS is not well-understood. Complete involution of the placental sites requires 4-6 weeks [4]. Uterine involution in dogs is normally completed by twelve weeks postpartum [5].

It has been suggested that a continuous invasion of trophoblast-like cells into the endometrium and myometrium could be involved in SIPS, preventing normal thrombus formation in endometrial blood vessels [1,6]. This could be reason for the prolonged duration of vulvar discharge. It is assumed that these trophoblast-like cells would normally be only present during the first two weeks postpartum [5].
Besides the occurrence of SIPS in the dog and humans[7] one study shows pathologic findings in a capybara consistent with placental subinvolution[8]. Arbeiter (1975) describes a persistent uterine hemorrhage in postpartum cows.

SIPS most commonly occurs in the setting of a normal delivery and litter size, with healthy pups. An ultrasound of the uterus to exclude other causes of hemorrhage supports the diagnosis of SIPS.
Bleeding due to SIPS may at times be erroneously attributed to primary postpartum endometritis, resulting in ovariohysterectomy after failure of antibiotic[2,9] or other therapies [4].
Evidence to support the use, ergot alkaloids [3], antibiotics [2,9] or oxytocin [10] in the treatment of SIPS is weak and often conflicting. Subcutaneous progestins have been used with success [11,12]. However high dose progestins can cause pyometra [1] and mammary tumors and therefore not recommended.

The objective of this retrospective study was to investigate the efficacy of treatment with low oral doses of progestins in stopping bloody vulvar discharge in dogs with SIPS. Furthermore we wanted to inquire if the animals, after treatment, had a normal estrus, conception if mated, gestation and parturition and if the development of SIPS was a recurred problem.

Animals and Methods

Selection criteria

The computer database system (Vetware) including all medical records of dogs examined between 2003 and 2011 at the Reproduction Service of the University Clinic Companion Animals, Utrecht University, was searched for cases with prolonged vulvar discharge after parturition.
Ten clinically healthy dogs, with presentations meeting criteria for SIPS from 48 to 85 days postpartum (Tab. 1), were identified for inclusion in this study. Five of the ten animals had measurement of hematocrit, leucocytes and differential. All results were within the normal values. Three animals had an ultrasound of the uterus to exclude other causes of hemorrhage.

Animals and Treatment

The breeds in this study comprised one Polski Owczarek Nizinny, one West Highland white Terriër, one Golden Retriever, one Labrador retriever, one Beagle, one Welsh Corgi Cardigan, one Cairn Terriër, one Rhodesian Ridgeback, one White Swiss Shepherd and one German shepherd.
Mean age was 2 years and 9 months, ranging from one year and 10 months to 6 years and 7 months (Tab. 1).

Except for the Cairn Terriër which was administered medroxyprogesterone acetate, the other seven dogs were given megestrolacetate. A difference in administration of progesterone derivate in this one bitch was due to the fact that megestrolacetate was not available at the moment of treatment.
The therapy period was two weeks. During the first week the dose was 0,1 mg megestrolacetate per kg bodyweight once a day, the second week the daily dose was halved to 0,05 mg/kg megestrolacetate. The bitch that was administered medroxyprogesterone acetate was treated with 0,2 mg medroxyprogestrone acetate/kg daily during the first week, this was halved to 0,1 mg/kg daily the second week.

Data collection
Information about the breed, age, body weight, aspect and duration of vulvar discharge, parity, mode of parturition and litter size, treatment advice, prescription medication, dose and parity was collected from the Vetware database of the selected animals.
A master veterinary student conducted telephone interviews with owners of the ten included dogs. The questionnaire included the following questions:
1- Confirmation of data found in Vetware concerning owner, birth date and breed of the dog.
2- Confirmation if the administration of medication was given as prescribed?
3- The duration of the vulvar discharge and the date the discharge was not noted anymore
4- If the owner had returned to his/her veterinarian concerning this problem and the results of this visit?
5- Information regarding the parity, the mode of the parturition and the litter size before the onset of the persistent sanguineous vulvar discharge post-partum.
6- Information about the next heat: if the bitch had come into heat as normally expected by the owners referring to her normal cycle length.
7- If she was mated again after the treatment and if so, if she had become pregnant; the litter size and parturition process in case of the next parturition.
8- If SIPS recurred.

The interviewer was not blinded to the treatment advice of the dog.

Results

Duration of vulvar discharge postpartum to start of SIPS treatment
No data could be traced from the German shepherd regarding the duration in days of vulvar discharge postpartum to the start of treatment for SIPS. The data collected from the remaining seven dogs showed an averaged start of treatment from 62 to 85 days postpartum with a median of 66 days. The two dogs not medically treated visited the clinic respectively 48 and 73 days postpartum for consultation (Tab. 1).

Administered medication
Eight of the ten dogs diagnosed with SIPS had a progesterone derivate orally administrated (Tab. 1). Seven of these dogs were treated with megestrolacetate and one dog with medroxyprogesteroneacetate. In all eight dogs the drug was administered once a day for two weeks. Within the first week 1 to maximum 3 mg megestrolacetate was administered

orally per bitch depending their bodyweight. In the second week of treatment the dose was halved. Two dogs, did not receive any medication.

Duration of the vulvar discharge
Cessation of vulvar discharge was seen in all eight treated dogs within the two week treatment period (Tab. 1). The owners reported in all cases that symptoms resolved rapidly after the start of treatment, within the two week treatment period. Precise information concerning the time from the initiation of treatment to resolution of discharge was available for the Golden Retriever and the Labrador retriever, which both had complete resolution on the third day of treatment. No dogs returned to the veterinarian for persisting symptoms.

The two dogs that were not treated for SIPS persisted with the problem for a much longer period than the treated dogs (Tab. 1). The Welsh Corgi Cardigan remained symptomatic until the end of the next heat period. The Rhodesian ridgeback was free of symptoms approximately 6 weeks before start of her next follicular phase. She remained symptomatic for approximately 38 weeks in total.

Parity of development SIPS
Seven of the dogs developed SIPS after their first parity, two after their second parity and one after the fourth parity (Tab. 1). At the time of this study none of these dogs had developed SIPS in an earlier or later parturition.

Mode of parturition and litter size before SIPS
Nine dogs whelped naturally, except for the Rhodesian Rigdeback which gave birth by Caesarean section (Tab. 1). There were no abnormalities noted concerning the course of gestation and parturition. The litter sizes averaged between 5 to 11 puppies, with an average of 7,2 and median of 7,5 puppies.

Course of fertility
Seven of the eight dogs that were treated with progestins were mated again during a future heat cycle, with six of them impregnated (Tab. 1). It is unknown why one bitch did not conceive as no veterinary fertility counseling was done during heat and mating. Of the two dogs that were not treated with progestins, one was mated again and conceived. All subsequent gestations and parturitions, for treated and untreated animals, were normal and uncomplicated, without abnormalities reported in offspring.

Discussion

SIPS in humans suffering of postpartum hemorrhage would be caused by the subinvolution of the uteroplacental arteries in the human placental bed with perivascular and intravascular trophoblasts [7]. Subinvolution of the uteroplacental arteries may be the result of an abnormal interaction between maternal uterine cells and fetal trophoblast cells [13].
It is assumed that trophoblast like cells could also be related to the development of SIPS in dogs [1,5]. These cells would be present during the first 2 weeks postpartum but in the case of SIPS present for a longer period of time. This is used as one of the veterinary diagnostic tools to confirm SIPS[3]. A recent study however, shows that these cells remain present on the surface of the uterine epithelium, the placental tissues, as well as in smears of vulvar

discharge during the whole period of involution even up to 84 days postpartum in normal involution of the uterus in the bitch [14]. Unfortunately no further information could be found.

Treatment with different antibiotics have had no results in bitches with SIPS [2,9], although Arbeiter (1993) describes it as an obligate treatment in SIPS. A recent study treating a bitch diagnosed of SIPS consisting of a seven-day course with 8 µg/kg twice daily of methylergometrine hydrogen maleate orally resulted in no improvement in clinical signs [3]. Arbeiter (1993) suggests medical treatment with oxytocin or careful use of megestrolacetate however, but no further information on results with this treatment is given. Ovariohysterectomy is a therapy preceded by medical treatment with no desired results or for bitches diagnosed with SIPS that will not be used for breeding [1,4,9,10]. Progestins have generally not been recommended as treatment for SIPS because of perceived adverse effects [1,3] and conflicting evidence of efficacy.

In this study treatment with low dose oral progestins appeared effecting in eliminating vulvar discharge in case of SIPS. Prior studies [11,12] have used higher doses and parenteral routes of administration, and sometimes a single dose. Daily administration over two weeks may be superior to single-dose parenteral administration, although optimal duration of treatment has not been studied. In this small retrospective study oral low dose progestins did not appear to affect future reproductive success.

The mechanism by which progesterone may terminate sanguineous postpartum vulvar discharge is unknown. In a study treatment with megestrol acetate in a dose of 25-50 mg subcutaneous per bitch in combination with antibiotics intrauterine diminished the symptoms of vulvar discharge within 3-5 days [12]. Another study where bitches with persistent postpartum uterine hemorrhage were treated with a single subcutaneous dose medroxyprogesterone acetate suspension (2 mg/kg bodyweight) vulvar discharge disappeared on day three [11]. However there were unsuccessfully results if half of the dose of medroxypregesterone acetate was used. These negative results could be possible due to the fact that the dose progestins were given only once, whereas in our study the dogs were treated daily for two weeks. The symptoms disappeared within the end of treatment period, with two owners who could specify this to within three days after treatment.

The dogs that conceived after SIPS had a normal delivery and litter size, with no abnormalities in the pups or bitches, with three of them having produced two litters at the time of this study (Tab. 1). SIPS may have no impact on future reproduction, with or without treatment. It seems that progestins do not adversely affect the course of a possible gestation.
The untreated dog was covered after SIPS, became pregnant and went gestation and parturition completely normal. So not treating SIPS seems to have no adverse effects on future reproduction.

One bitch was administered medroxyprogesterone acetate in a higher dose as the megestrolacetate was prescript for the following reason. Both drugs have different kinetics, with megestrolacetate being a more potent drug. The prescript dose to prevent estrus in cats is 2 mg medroxypregestrone once a week (1 tablet). For medroxyprogesterone acetate

it is one tablet of 5 mg a week. Assuming this information the dose of medroxyprogesterone acetate was adjusted. The results of this dog were comparable to the other dogs which received megestrolacetate.

Spontaneous regression of the symptoms regarding SIPS usually occurs [2,3]. Therefore a medical or surgical intervention could be avoided in bitches.

Several articles write about a predisposition for SIPS in young and/or primiparous bitches [3,6]. The ten bitches included in this study were different of age, with a mean age of 2 years and 9 months (range 1-6 years). Seventy percent of these bitches were primiparous and the remainder developed SIPS after their second (n=2) and fourth (n=1) parturition.
While our study was not designed to characterize the epidemiology of SIPS in dogs, it does demonstrate that SIPS does not occur exclusively in primiparous or young dogs.

Conclusion

In conclusion the results of this study suggest that when therapy is warranted to stop prolonged postpartum vulvar discharge due to SIPS, oral low dose progestin therapy is effective and probably safe. While the study is too small to exclude the possibility of adverse effects on future reproduction, the therapy appeared to be benign.
Furthermore, this study shows that a good alternative in the case of SIPS could be to not medically or surgically interfere. Waiting for a spontaneous remission of the vulvar discharge doesn't seem to have any negative effects on a subsequent heat, fertility, gestation and parturition.

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Breed	Age/ Kg	Parity	The course of parturation (littersize)	Treatment time in days after parturation	Treated dose megestrolacetate mg/kg	Effect within treatment period	Mated again	Pregnant after mating	Gestation and parturation proces	Development of SIPS after parturition
Polski Owczarek Nizinny	1 y + 10 m/ 14,9	1	Na, (5)	77	wk 1: 0.101 wk 2: 0.067/ 0.034*	+	Yes	Yes	Na, 2 litters produced after SIPS (2-1***)	No
West Highland White Terriër	2 y + 0 m/ 7,5	1	Na, (5)	66	wk 1: 0.133 wk 2: 0.067	+	Yes	Yes	Na, 2 litters produced after SIPS (2-4***)	No
Golden Retriever	2 y + 2 m/ 32,8	1	Na, (10)	65	wk 1: 0.091 wk 2: 0.030	+	Yes	Yes	Na, 1 litter produced after SIPS (11***)	No
Labrador Retriever	2 y + 4 m/ 26	1	Na, (9)	85	wk 1: 0.115 wk 2: 0.058	+	Yes	Yes	Na, (unknown)	No
Beagle	2 y + 5 m/ 13,4	1	Na, (8)	63	wk 1: 0.112 wk 2: 0.037/ 0.075*	+	Yes	Yes	Na, 2 litters produced after SIPS (6-8***)	No
Cairn Terriër	3 y + 1 m/ 9,6	2	Na, (4)	79	wk 1: 0.260** wk 2: 0.130**	+	No	-	-	-
White Swiss Shephard	4 y + 1 m/ 29,5	2	Na, (5)	62	wk 1: 0.102 wk 2: 0.051	+	Yes	No	-	-
German Shepherd	6 y + 7 m/ 31	4	Na, (11)	-	wk 1: 0.048 wk 2: 0.016/ 0.032*	+	No	-	-	-
Welsh Corgi Cardigan	3 y + 1 m/ 18,5	1	Na, (8)	73	_	Vulvar discharge until next heat	Yes	Yes	Na, 1 litter produced after SIPS (8***)	No
Rhodesian Ridgeback	3 y + 8 m/ 31,7	1	Caesarean, (7)	48	_	Vulvar discharge until 8 weeks before next heat	No	-	-	-

Table 1 Results of the use of progestins in bitches in case of SIPS

Na= no abnormalities
* = wk 2: the doses was alternated one day with the nest with these two doses megestrolacetate mg/kg
** = administration of medroxyprogesterone acetate mg/kg
*** = the total quantity of puppies in the next litters

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