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CASE REPORT
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Juvenile Panhypopituitarism in a Dog - What are the Therapeutic Challenges?

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ABSTRACT

***Background*:** Juvenile panhypopituitarism is an endocrinopathy that affects young dogs and must be differentiated from other causes of height disorders, as one could have a deficiency of one or more adenohypophysis hormones, besides growth hormone. Diagnosis consists of excluding endocrine and non-endocrine causes. Treatment requires administration of heterologous porcine growth hormone or progestins, as well as supplementing other hormones that are deficient in the circulation. The prognosis for these patients tends to be unfavorable and they have a shorter life expectancy. The present case aimed to report the therapeutic challenges in a dog diagnosed with juvenile panhypopituitarism.

***Case*:** This study presents the case of a 6-month-old crossbred Labrador/Brazilian Fila dog, not neutered, 6.7 kg of body weight (body condition score 5/9), with a growth disorder and persistence of the puppy coat, when compared to other members of the same litter. During inspection, it was possible to observe an undersized dog and soft puppy coat, besides no bone irregularities or joint tenderness was noted. The other physical examination parameters were within the normal range for the species. No changes in complete blood count and only increases in urea, cholesterol and alkaline phosphatase activity were observed. Thyroid and abdominal ultrasound (US) examination did not reveal any remarkable changes. After serum dosage of insulin-like growth factor, thyroxine, thyrostimulating hormone, and cortisol, the patient was diagnosed with juvenile panhypopituitarism and underwent therapy with medroxyprogesterone and thyroid hormone supplementation. Monitoring was instituted at intervals of 3, 6, and 12 weeks, and currently every 3 or 4 months and the IGF-1 values normalized after 6 months with. After 8 months of therapy, the patient had good body growth and bone mineralization compared to the time of diagnosis. However, skeletal development was completed only 12 months after hormone replacement, accompanied by the presence of vertebral osteophytes and coxofemoral osteoarticular alterations. Considering chronic use of progestins, ovariosalpingohysterectomy (OSH) was recommended, but for personal reasons, the owners chose to do not submit her to surgery. After 18 months of treatment, the dog starts to exhibit prostration, selective appetite, and increased abdominal volume. After imaging exam, she was forwarded for OSH, due to consistent findings of pyometra. Subsequently, even the supervision of possible comorbidities involved in the chronic use of progestins was maintained at half-yearly intervals, the bitch returned to the service with skin thickening, increased limb volume, and macroglossia after 60 months of therapy. At this point IGF-1 values were higher when compared to the previous measurements and the application of medroxyprogesterone was suspended. Its supplementation was reintroduced only after 8 months when IGF-1 was significantly reduced. To date, the patient is close to 6 years of age and with a good quality of life.

***Discussion*:** The greatest therapeutic challenge for these patients involves dealing with the adverse effects of progestins, mainly related to reproductive disorders and alopecia at the application site, as well as maintaining adequate hormone replacement in order to avoid hypersomatotropism. Although longevity is lower in these individuals, the patient in this report has achieved 6 years of age and has had an excellent quality of life so far.

Keywords: adenohypophysis, growth hormone, pituitary dwarfism, thyrostimulating hormone.

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INTRODUCTION

Pituitary dwarfism (PD) is a congenital endocrine disorder defined by stature retardation secondary to growth hormone (GH) deficiency [16]. When it involves the absence of other adenohypophysis hormones, such as thyrostimulating hormone (TSH), follicle stimulating hormone, luteinizing hormone, prolactin, and/or adrenocorticotropic hormone (ACTH), it is classified as juvenile panhypopituitarism (JPH) [9,18].

In the first months of age, dogs with JPH physically resemble the rest of the litter. However, when they reach adulthood, a lot of deficiencies begins to appear involving dermatological, bone, reproductive, digestive [6,10,18,24], neurological and urinary [12,14,19] tracts, which makes the life expectancy of these patients lower when compared to dogs of the same breed [2,11,12,21].

Treatment involves supplementing deficient hormones. GH replacement in dogs is achieved using the commercial heterologous molecule, however, its cost is restrictive, and it is not exempt from adverse effects such as insulin resistance and reproductive disorders, including pyometra and breast cancer [1,11,25]. Progestins can be an alternative, and although more financially accessible, can also bring some risks such as pyoderma, musculoskeletal malformations, cystic endometrial hyperplasia, pyometra, insulin resistance, and breast cancer [16,17].

The present case aimed to report the therapeutic challenges in a dog diagnosed with juvenile panhypopituitarism treated with medroxyprogesterone and levothyroxine, which after controlling some reproductive and morphological complications, had longevity greater than described in the literature, and so far, follows with a good quality of life.

CASE

A 6-month-old crossbred Labrador/Brazilian Fila, not neutered female, weighing 6.7 kg (body condition score 5/9), was referred to Endocrinovet® clinic (São Paulo, SP, Brazil) due to growth retardation since the 3rd month of life. Persistence of the puppy coat was also mentioned. During inspection, it was possible to observe an undersized dog and soft puppy coat (Figure 1). No bone irregularities or joint tenderness was noted. The other physical examination parameters were within the normal range for the species. No changes in complete blood count (CBC) and blood biochemistry were observed, except for an increase in urea, alkaline phosphatase, and cholesterol (Table 1).

Limb and chest radiographs were performed and revealed the absence of mineralization in the proximal and distal epiphyses of the long bones, and the same findings in the cranial and caudal extremities of the thoracic and lumbar vertebral bodies (Figure 2 A & D), similar to puppies of 2-3 months old. Thyroid and abdominal ultrasound (US) examination did not reveal any remarkable changes.

The adrenal function test was performed from stimulation with ACTH, showing the basal and post-ACTH cortisol in the reference values for the species [3]. The assessment of thyroid activity revealed reduced TSH and radioimmunoassay free thyroxine values. Even if the patient's IGF-1 dosage was in the normal range, it was significantly lower when compared to the siblings. The values obtained from the laboratory analyses mentioned above are outlined in Table 1.

All these findings allowed establishment of a diagnosis of JPH. Therefore, medroxyprogesterone was prescribed [Depo Provera[1] - 3 mg/kg, SC, with intervals of 3 to 6 weeks (induction and maintenance phase, respectively)] [2]. Levothyroxine was also supplemented [Tyrox[2] - starting with 10 mcg/kg, PO, SID, requiring gradual readjustments and reaching 22 mcg/kg, PO, BID]. Based on the occurrence of alopecia at the sites where the progestins were applied, it was decided to perform them in the abdominal region.

The patient assessment interval, collection of routine and hormonal tests (IGF-1 and thyroid hormones) varied from 4 to 12 weeks initially, until the results were more stable. The doses of the aforementioned drugs were adjusted according to the hormone replacement values obtained in the respective exams. The IGF-1 values normalized after 6 months with medroxyprogesterone, and this was continued in 6-week intervals, as recommended by other authors [2,19]. After 8 months of therapy, the patient had good body growth and bone mineralization compared to the time of diagnosis. However, skeletal development was completed only 12 months after hormone replacement (Figure 2 C & F), accompanied by the presence of vertebral osteophytes (Figure 2 B & E) and coxofemoral osteoarticular alterations.

Ovariosalpingohysterectomy (OSH) was recommended, as the chronic use of progestins may predispose to reproductive tract infections. For personal reasons, the owners chose to wait for the bitch's body development, before submitting her to any procedure. Even emphasizing the risks, we opted for follow-up with periodic abdominal US. After completing 18 months of treatment, the dog returned to the service earlier than expected, with prostration, selective appetite, and increased abdominal volume. After performing an imaging exam, she was forwarded for OSH, due to consistent findings of pyometra.

Subsequently, the supervision of possible comorbidities involved in the chronic use of progestins was maintained at half-yearly intervals. After 60 months of therapy, the bitch returned to the service with skin thickening, increased limb volume, and macroglossia (Figure 3), suggesting acromegaly. During this period, the levels of thyroid hormones remained within the reference range for the species, without dose adjustments being made.

Regarding morphological changes, the IGF-1 values were higher when compared to the previous measurements (Figure 4), therefore, it was decided to suspend the application of medroxyprogesterone. Its supplementation was reintroduced only after 8 months (when IGF-1 was significantly reduced). No evidence of hyperinsulinemia or hyperglycemia has been observed since then (fasting insulin 22.14 μIU/mL ref. 6-32; and blood glucose 103 mg/dL).

To date, the patient is close to 6 years of age and with a good quality of life. After these sequences of episodes, it started to be followed up with shorter intervals (3 to 4 months), which aimed to maintain the levels of thyroid hormones and IGF-1 within the normal range, through exogenous supplementation of levothyroxine and sex steroids. One of the biggest challenges of this treatment continues to be the adverse effects of the chronic use of medroxyprogesterone, which include alopecia at the site of application of the hormone, as well as the possibility of developing breast cancer and/or iatrogenic acromegaly.

DISCUSSION

The clinical recognition of a dwarf is something relatively simple to be done by the owner or veterinarian. However, several differential diagnoses must be considered to determine the underlying cause. Among them there are endocrinopathies, malnutrition, metabolic alterations, malformations (portosystemic shunt, congenital heart, and nephropathies), pancreatic insufficiency, and genetic abnormalities [11,18].

The GH congenital deficiency is known as PD, however, it is essential that the production of thyroid, adrenal, and other hormones also be investigated, as they may be reduced in JPH [15,22]. Differentiating these 2 diagnoses interferes directly in the therapeutic

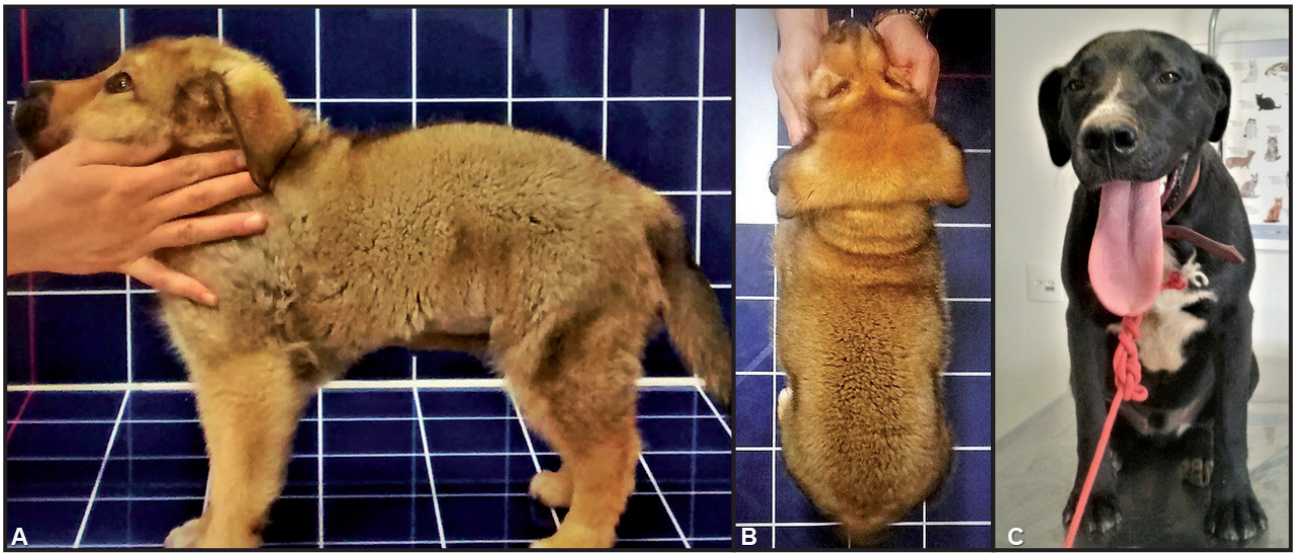

Figure 1. Female dog with juvenile panhypopituitarism and her brother at 6 months old, at the time of diagnosis. A- Side view, in which it is possible to see the short stature and puppy coat incompatible with the size of the sibling and the patient's age. B- The dorsal view allows visualization of the thoracic and waist silhouette, apparently without musculoskeletal irregularities. C- Crossbred Labrador/Brazilian Fila, sibling of the bitch diagnosed with JPH. Note the discrepancy in size, coat appearance, and body development of this animal compared to its sister. [Courtesy of Dr. Alessandra Martins Vargas and Dr. André Luís Soares dos Santos].

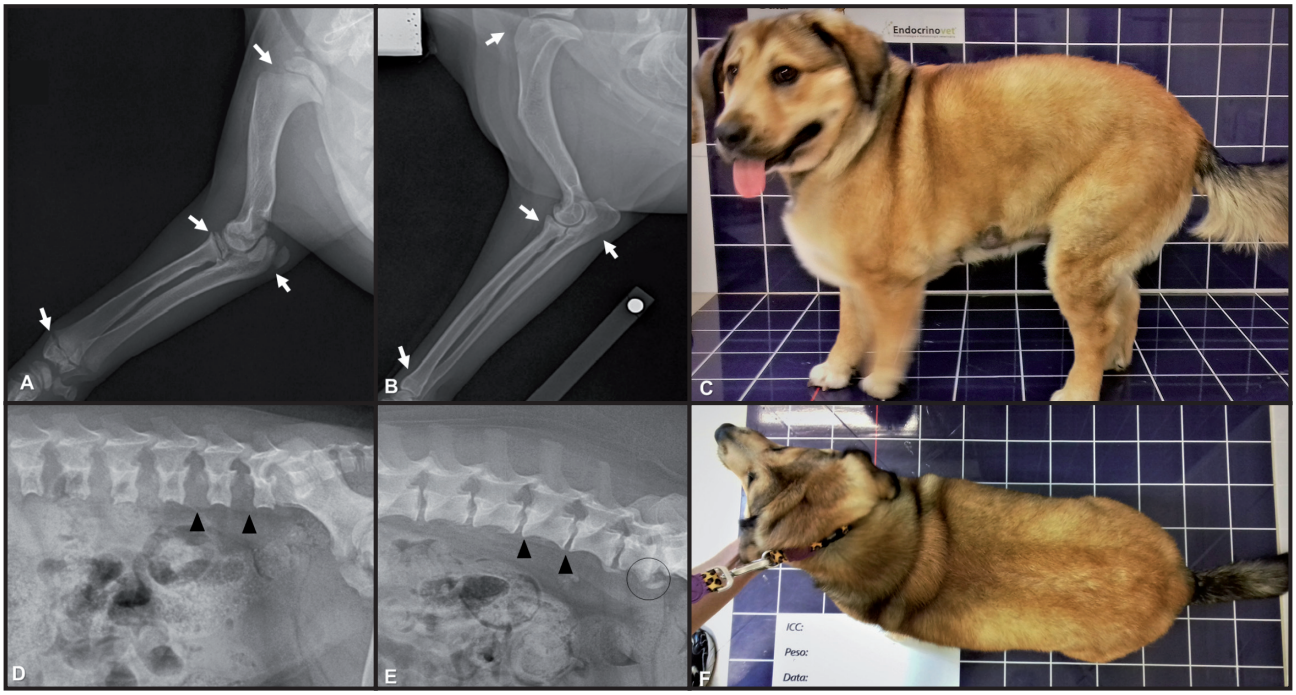

Figure 2. Radiographic image of the dog with juvenile panhypopituitarism at diagnosis and after 12 months of treatment. A- Mediolateral projection of the right thoracic limb at diagnosis. The arrows show the absence of mineralization of the proximal and distal epiphyses of the radius and proximal of the humerus and ulna. B- Mediolateral projection of the right thoracic limb during disease monitoring. Arrows show complete closure of the bony epiphyses. C- Patient with JPH after hormone replacement, complete development of the adult skin (side view). D- Right thoracic laterolateral projection. The arrowheads show the absence of mineralization of the cranial and caudal ends of the thoracic and lumbar vertebral bodies, compatible with individuals aged 2-3 months. E- Right thoracic laterolateral projection. Presence of mineralization of vertebral bodies (arrowheads) and osteophytes (circle). F- Dorsal view of canine patient post-treatment of JPH. [Courtesy of Dr. Alessandra Martins Vargas, Dr. André Luís Soares dos Santos and Provet, Veterinary Medicine Diagnosis, São Paulo, SP, Brazil].

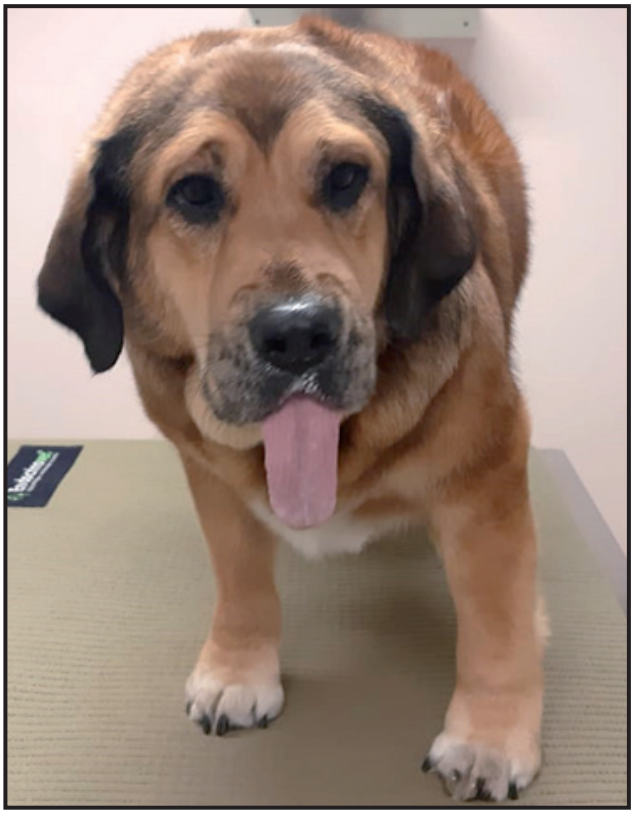

Figure 3. Appearance of the dog with JPH after 5 and a half years of hormonal supplementation. It is possible to notice increased volume of the thoracic limbs and macroglossia. [Courtesy of Dr. Alessandra Martins Vargas and Dr. André Luís Soares dos Santos].

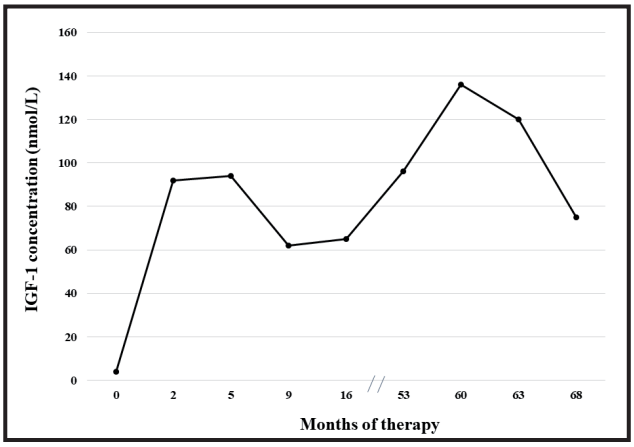

Figure 4. Graphic representation of IGF-1 values according to time of therapy at diagnosis, first 16 months, and during manifestations of acromegaly (identified at 60 months). Note that after stopping medroxyprogesterone, IGF-1 values reduced and normalized only after 8 months.

decision established for the patient and may compromise their life quality and expectancy.

In screening tests of animals with JPH, relevant alterations are usually not observed, except when there is disturbance in the development of the kidneys. In these cases, azotemia and hypercalcemia are mainly observed due to reduced renal clearance [7,12,18], which become even more evident when there is concomitant hypothyroidism. This condition

Table 1. Hematological parameters, renal and hepatic biochemical profile, lipid profile, blood glucose, insulin, electrolytes, and assessment of adrenal, thyroid, and somatotropic function at the time of diagnosis and control (after 5 months of therapy) of JPH*.

Parameters	Diagnosis	Control of JPH	Reference value
Complete blood count			
Erythrocytes	5.53	5.66	5.5-8.5 10^6/mm^3
Hematocrit	38.7	38.4	37-55%
Leukocytes	14.5	11.8	6-17 10^3/mm^3
Platelets	355	291	200-500 10^3/mm^3
Biochemical tests			
Urea	69.2	53.5	10-60 mg/dL
Creatinine	1.11	0.89	0.5-1.6 mg/dL
Alanine aminotransferase	38	79	7-92 UI/L
Alkaline phosphatase	450	109	10-160 UI/L
Cholesterol	336	304	116-300 mg/dL
Triglycerides	90.8	41.8	32-125 mg/dL
Blood glucose	92	90.9	60-118 mg/dL
Phosphorus	5.73	6.65	2.2-7.9 mg/dL
Total calcium	NA	11.1	9.7-12.2 mg/dL
Ionized calcium	NA	1.26	1.12-1.4 mmol/L
Sodium	NA	142	139-150 mmol/L
Potassium	NA	4.10	3.5-5.4 mmol/L
Chloride	NA	114.6	108-120 mmol/L
Adrenal function test			
Pre-ACTH cortisol	1.18	NA	1.8-4 µg/dL
Cortisol 60 min post-ACTH	5.33	NA	4-16 µg/dL
Thyroid function test			
TSH	0.04	0.05	0.1-0.5 ng/mL
Radioimmunoassay free thyroxine	0.37	1.19	0.82-3.65 ng/dL
Basal total thyroxine	NA	1.84	1.25-3.9 µg/dL
Total thyroxine pos-pill (levothyroxine)	NA	3.92	2.5-5.0 µg/dL
Somatotropic function test			
IGF-1 (patient)	4	94	4-95 nmol/L
IGF-1 (sibling)	92	NA	

NA= not applicable. *Provet, Veterinary Medicine Diagnosis, São Paulo, SP, Brazil.

can also compromise the nervous system, leading to neurological deficits ranging from mild to severe. When added to the other changes, they contribute to a lower life expectancy [4,11].

Although rare, alkaline phosphatase can be elevated in dwarf dogs in the presence of marked bone remodeling [4,23]. In this report, even though no structural anomaly was evident at the time of diagnosis, it was possible to observe disturbances in mineralization and a delay in closing of the bone epiphyses associated with hyperphosphatasemia. We emphasize that in patients with JPH, especially when associated with hypothyroidism, dyslipidemia, anemia, and/or hypoglycemia may also be observed [11]. Despite ionized calcium not being measured at diagnosis, it is important that it be considered in the list of laboratory tests, since

it can be elevated in hypothyroid dogs because of the reduced clearance of this electrolyte and increased enteric reabsorption [12].

Humans as well as mice with hyposomatotropism can develop hypercholesterolemia. This may be involved in the suppressive effect that IGF-1 exerts on hepatic cholesterol deposition [5,8]. Added to the effect of thyroid hormones on the degradation of serum lipids [4], such findings clarify the presence of mild hypercholesterolemia at the time of JPH diagnosis in the reported case.

Even though IGF-1 measured in the diagnosis of JPH could be interpreted as appropriate by the reference ranges provided by the laboratory, physical development characteristics and the patient's IGF-1 values were clearly lower than her sibling at 6 months old. Therefore, it is necessary to clarify that the normality limits of this hormone are standardized for different breeds and sizes of dogs [13], so it is essential that this finding be correlated with one or more members of its litter, to avoid misdiagnosis.

Progestins can be an alternative to heterologous GH supplementation, as they act on the expression of genes that lead to the production of this hormone from the breast tissue [2,20]. Additionally, even if they are financially viable, adverse effects must be expected and monitored, as seen in this case in which pyometra occurred at 18 months of therapy and during its maintenance phase. Although insulin resistance and breast cancer are commonly described in the literature [17], these were routinely evaluated and were not evident in the patient in this report.

Medroxyprogesterone is recommended for routine administration in those patients with a GH deficit. The interval between applications begins at 3 weeks and usually reaches 6 weeks [3]. However, this period can vary according to physical and laboratory changes, with the best way to monitor GH levels in humans and animals being through the measurement of IGF-1 [19]. Therefore, it is important to emphasize that even with IGF-1 being stable for years, it was possible to notice an imbalance in its levels, accompanied by unwanted clinical repercussions, when evaluated at 6-month intervals [16]. Currently, the intervals have been reduced to 3 to 4 months in order to avoid these issues.

Although the literature reinforces the importance of performing OSH in females undergoing hormone replacement with progestins [16,19], the patient in this report was vetoed from the elective surgical procedure for personal reasons of the owners, even after becoming aware of the risks, which later became unavoidable. These and other obstacles to the treatment of JPH in dogs still make it a challenge for veterinary medicine and studies involving different therapeutic approaches are essential.

Juvenile panhypopituitarism is a complex endocrine disorder that can cause serious damage to the affected animal, even under hormone replacement therapy. The biggest challenge of this disease includes maintaining hormonal control of patients, in addition to avoiding the appearance of side effects. Continuous monitoring can help to reduce such unwanted issues, but it does not exempt the animal from presenting with secondary problems.

MANUFACTURERS

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