PARSEMUS FOUNDATION

Spay-neuter syndrome and hormone restoration for spayed and neutered dogs

Preface

Over the past two decades, a growing body of research has reported that gonadectomy (spay and neuter) in dogs has not been an innocuous procedure related only to sterilization. Instead, the loss of the sex organs results in a cascade of hormone changes leading to hormone imbalance and the possibility of increased health and behavior problems. Therefore, many veterinarians and pet parents are turning to alternative sterilization methods that preserve the gonads and the natural hormones they produce.

What can be done for spayed and neutered dogs who may have health issues due to the loss of hormone balance (or spay-neuter syndrome)? Canine hormone therapy or restoration is a new but promising treatment method.

As an organization at the forefront of advocacy and research on improved dog sterilization methods and hormone restoration, the Parsemus Foundation offers both veterinarians and pet parents educational resources to help them determine the best methods of care. We are not veterinarians, but we support research and work closely with key stakeholders and opinion leaders to provide the most up-to-date information.

This document includes three sections:

A primer on canine sterilization, written for the public: An overview of the impacts of traditional dog sterilization. This includes the basic concepts of sex hormone function after spaying or neutering, a brief overview of risks of the resulting hormone imbalance, and hormone-sparing alternative sterilization options.

Background research on hormone restoration, written for veterinarians: A review of our current knowledge on canine hormone restoration. This section includes an overview of research on various types of hormone supplementation with a focus on canine studies.

Hormone restoration protocols, written for veterinarians: We have included a working protocol for hormone restoration procedures. It is important to note that this protocol is based on current knowledge, which is limited but growing. Various methods currently used by clinicians are included.

We appreciate the input of many veterinarians and pet parents who contributed to this document and expect it to be updated as new research and experience become available.

The information in this document is not intended to be a substitute for professional veterinary advice, diagnosis, or treatment. Pet parents should consult a knowledgeable veterinarian to determine the best method of care and treatment for their individual dog.

Contents

For the public: A primer on canine sterilization

Gonads and hormones

The gonads (or sex organs) form part of an elegant system of checks and balances, keeping the reproductive processes, as well as many other functions across the body, working properly. The gonads, including the ovaries in females and the testes in males, produce gametes (eggs and sperm, respectively) as well as sex hormones (also called sex steroids or gonadal steroids).

The testes in males produce:

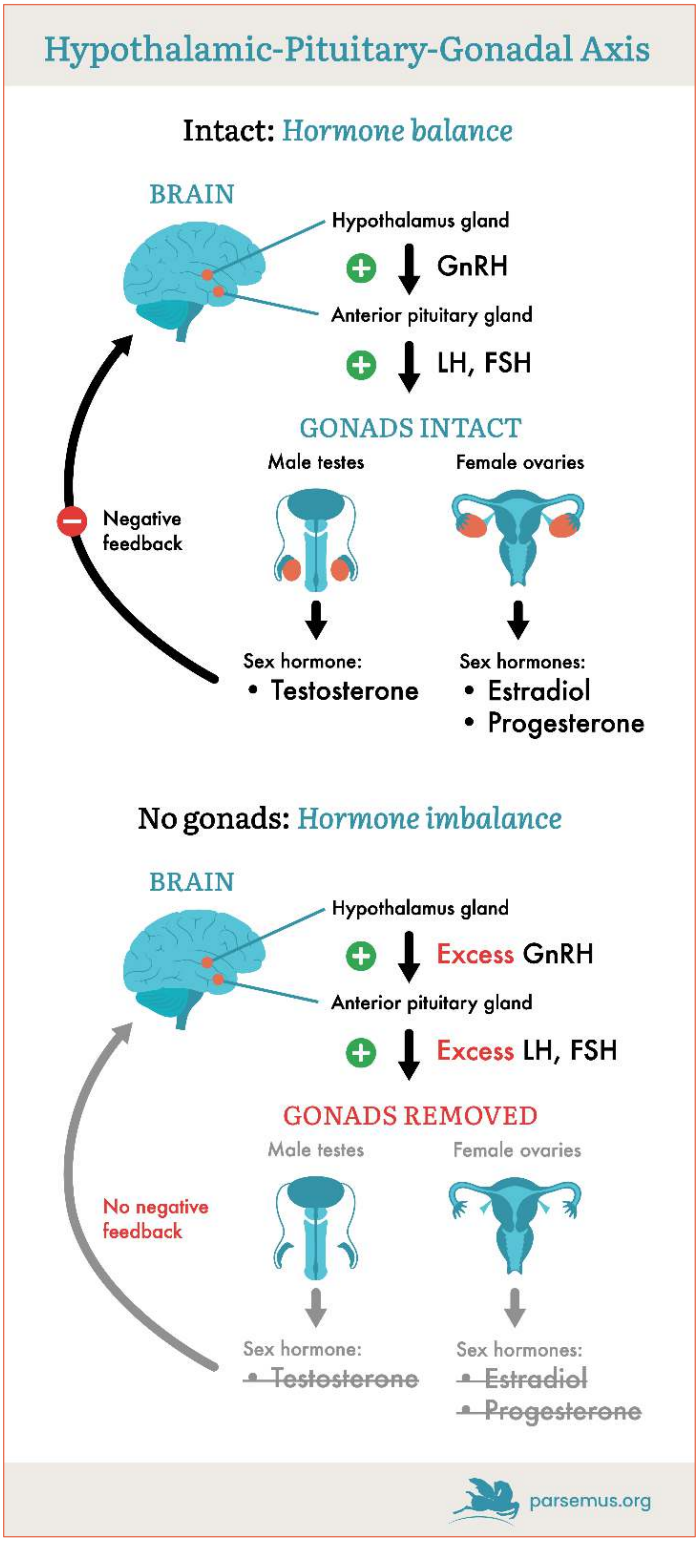
- **Testosterone:** An androgen produced by the Leydig cells of the testes that supports skeletal maturation, sperm development, development and maturation of the external genitalia (including the prepuce and penis), and male reproductive behaviors.

The ovaries in females produce:

- **Estrogens**: Necessary for skeletal maturation, final development and maturation of the external genitalia (including the vulva and vagina), and production of female pheromones when they are in heat.
    - **Estradiol (E_2)** is the main estrogen produced by the follicles in the ovary that drives the estrous cycle, which results in bloody discharge and swollen vulva when females are in heat.
    - **Estrone (E_1)** is a weaker form of estrogen.
    - **Estriol (E_3)** is also a weak estrogen used in veterinary medicine to treat urinary incontinence, as it has fewer side effects than estradiol.
- **Progesterone**: Produced by ovarian follicles before and after ovulation to produce female receptive behavior while in estrus, as well as prepare the uterus for pregnancy and the mammary glands for milk production or lactation.

All of these sex hormones communicate with the brain to regulate the release of luteinizing hormone (LH).

While sex hormones are most often related to reproductive functions and physical changes occurring at puberty, they are also important for many other bodily functions. Sex hormones influence thyroid, adrenal, and other endocrine functions, muscle mass, red blood cell production, and immune functions. Importantly, sex hormones are part of a cascade of hormones produced by different organs that function in harmony. It is called the **hypothalamic–pituitary–gonadal (HPG) axis**. The HPG axis functions in a feedback loop (see diagram below).



In the brain, the hypothalamus produces **gonadotropin-releasing hormone (GnRH)**. This stimulates the pituitary gland to release **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH).** These hormones stimulate the gonads to produce testosterone, estradiol, and progesterone.

When the sex hormone levels are low, the hypothalamus and pituitary produce more GnRH, LH, and FSH. When the level of sex hormones is high, the hypothalamus and pituitary produce less GnRH, LH, and FSH. This "negative feedback" system regulates sex hormone production.

What happens to the endocrine system when dogs are spayed or neutered

Spaying and neutering, also called gonadectomy, surgically remove the testes in males and the ovaries in females. When the organs are removed by spaying or neutering, dogs no longer produce sex hormones. Although spaying and neutering sterilize the dog, preventing reproduction, other sterilization methods are available that retain the sex hormones.

Many people think that removing the sex organs in dogs only influences one thing: reproduction. However, we now know that many other body systems change without sex hormones.

Besides sexual development and behavior, the hormones produced by the ovaries or testes are critical for normal:

- Growth and development
- Metabolism, energy, appetite, and body composition
- Immune system functioning
- Stress response
- Bone health and development
- Cognitive and mood regulation

Dog Sterilization Definitions

Gonadectomy: sterilization by removal of the sex organs or gonads

- Orchiectomy (neuter/castration): surgical removal of the testes in males
- Ovariohysterectomy (spay, common in the U.S.): surgical removal of the ovaries and some of the uterus in females
- Ovariectomy (spay, common in Europe): surgical removal of the ovaries

Hormone-sparing (or gonad-sparing) sterilization: sterilization without removing the sex organs or gonads

- Vasectomy: surgically cut and seal the tube that carries sperm (vas deferens) in males
- Hysterectomy (ovary-sparing spay): surgical removal of the uterus and cervix in females
- Tubal ligation: blocking or sealing the fallopian tubes that connect the ovaries to the uterus

The loss of gonads after spaying and neutering means that the body no longer has the sex hormones needed for normal functioning. In addition, this change throws the entire HPG axis out of balance. Without negative feedback from the sex organs, the hypothalamus continues to pump out GnRH, which tells the pituitary to make more LH and FSH, all in a futile effort to increase production of sex hormones from sex organs that are no longer there. What happens? The levels of LH and FSH in the body skyrocket!

Studies have shown that significant increases in basal LH and FSH occur in males and females following spaying and neutering (de Gier et al. 2012). A study of 10 ovariectomized beagles reported that in 12 months, mean FSH increased 17 times, and LH increased 8 times above the pre-spaying values (Reichler et al. 2004).

Any tissue influenced by the hormones of the HPG axis will be affected by the loss of sex hormones due to this imbalance. Dr. Michelle Kutzler has shown that many tissues express LH receptors, including skin and hair follicles, the anterior cruciate ligament, the thyroid and adrenal glands, immune cells, and cancers such as lymphoma and hemangiosarcoma. These tissues may become overstimulated when LH levels are too high in spayed and neutered dogs. This overstimulation may impact organ function and even result in cancer, immune problems, abnormal behaviors, and orthopedic disorders. (Kutzler 2023).

"... LH can block the normal function of the cell (e.g. to reduce the amount of thyroid hormone produced by thyrocytes); increase the function of the cell (e.g. to overproduce cortisol from the adrenal gland); stimulate nitric oxide release to induce smooth muscle and ligament relaxation (e.g., resulting in urinary incontinence or joint instability); stimulate cell proliferation (e.g. in the case of cancer)."

Michelle Kutzler, BVS, DVM, PhD, MBA, British Veterinary Association, 2023

As an example, spayed and neutered dogs have higher levels of hypothyroidism. Kutzler's research found that because LH receptors are located in the thyroid gland adjacent to thyroid-stimulating hormone (TSH) receptors, high LH levels can interfere with TSH functioning, resulting in thyroid disease. Activation of LH receptors found in lymphoma and hemangiosarcoma cells stimulated cancer cell growth and invasion (Kutzler et al. 2022). Increased LH- and GnRH-receptor mRNA expression related to bladder function may explain the high incidence of urinary incontinence in spayed or neutered dogs (Coit et al. 2009).

Does high FSH cause problems, too? FSH primarily functions on reproductive organs, so most receptors are located in the gonads. Research in humans shows that they also exist in bone, immune cells, and the brain, indicating broader roles in metabolism, immunity, and other systems. In dogs, FSH receptors have been found in the lower urinary tract (bladder, urethra), prostate, lymphocytes, and even certain tumors (e.g. Welle et al. 2006). We don't have much information on the impact of elevated FSH levels in gonadectomized dogs. A recent study found that spayed females had higher LH receptor levels in mammary tumors, whereas intact dogs showed higher FSH receptor levels. These differences in the tumor microenvironment may explain the finding that spayed dogs often have a lower incidence of mammary tumors, but more aggressive forms (Li et al. 2025). More studies like this can help us understand the impact of elevated FSH levels in gonadectomized dogs.

The recognition of spay-neuter syndrome

The removal of gonadal hormones has complex effects on canine physiology. Over the last two decades, research has shown both benefits and risks of spaying and neutering dogs beyond sterilization (Romagnoli 2025). Removing the sex organs means that we no longer have to worry about diseases associated with those organs (such as ovarian or testicular cancer, which is very rare in dogs) or diseases reliant on sex hormone stimulation (such as pyometra or mammary tumors). However, spaying and neutering have also been associated with increased risks of joint disorders, cancers, and metabolic diseases. These risk profiles depend on the dog's breed, age, size, sex, and environment (Hart et al. 2020a, 2020b; Moxon et al. 2024; Reichler 2009). Neutered males have shown increased risks for orthopedic disorders and certain cancers, while spayed females more frequently experience urinary incontinence and weight gain (Urfer and Kaeberlein 2019; Zink 2017).

The negative physical and behavioral effects of the loss of sex hormones are called **Spay-Neuter Syndrome**, in recognition of the diverse impacts on physical and psychological health that gonadectomy can have.

Dog Gonadectomy Risks

Lowers risk of:

Diseases of the sex organs or diseases influenced by sex hormones:

- Mammary, ovarian, and testicular cancers
- Pyometra — infection of the uterus
- Perineal and inguinal hernias
- Prostatitis, benign prostatic hyperplasia, prostatic cysts, and squamous metaplasia of the prostate

But raises risk of:

- Obesity
- Urinary incontinence and urinary calculi
- Immune-mediated diseases: atopic dermatitis, autoimmune hemolytic anemia, hypoadrenocorticism, diabetes mellitus, hypothyroidism, immune-mediated thrombocytopenia, inflammatory bowel disease
- Hip dysplasia and cranial cruciate ligament rupture
- Aggressive and fearful behavior, cognitive dysfunction syndrome
- Cancer: hemangiosarcoma, osteosarcoma, transitional cell carcinoma, prostate adenocarcinoma, lymphosarcoma

Given the importance of the sex hormones and the broad impact the HPG axis imbalance has on the body, it shouldn't be surprising that gonadectomy may result in concerning health conditions. However, acknowledgement of the impact of gonadectomy on dog health has been slow, likely due to: (a) the importance of sterilization for population control of cats and dogs and associated public campaigns urging spaying and neutering of pets as good for the health of dogs, and (b) difficulty recognizing gonadectomy-induced health conditions that are rare and often vary by breed, sex, size and other characteristics.

Many people still believe that there are only two options when it comes to decisions about sterilization: removing the gonads or leaving the dog intact. However, there are other options.

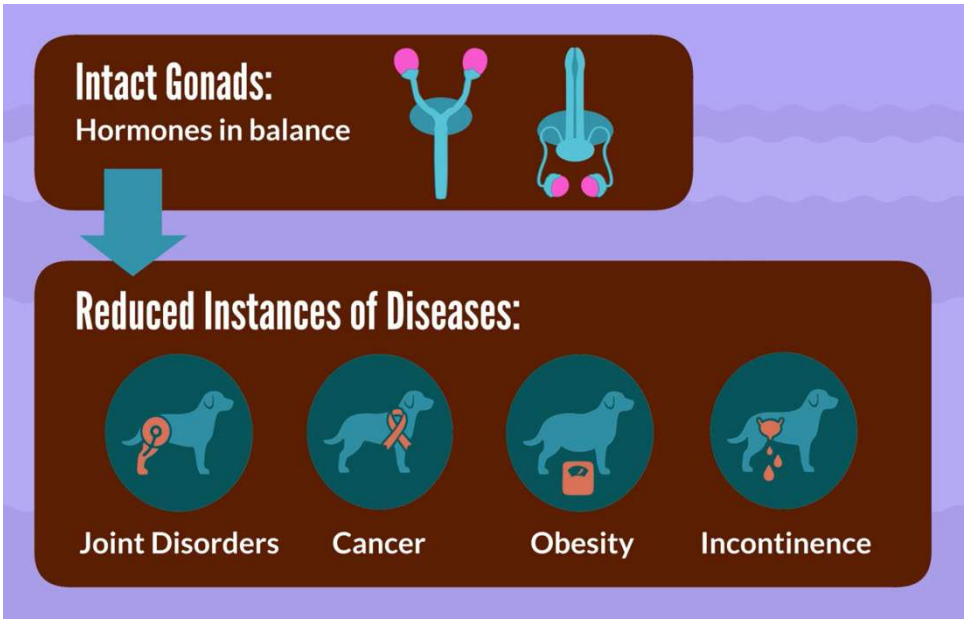
Preserving sex hormones: Hormone-sparing sterilization

As a result of the health problems that occur more frequently after gonadectomy, pet owners and veterinarians have sought alternatives. That is where hormone-sparing sterilization comes in. Hysterectomy (also called ovary-sparing spay) for females[1] and vasectomy for males are surgical methods that sterilize the pet while preserving the sex organs (ovaries and testes) that produce natural hormones. Hormone-sparing sterilization is increasingly practiced by veterinarians due to the

[1] Tubal ligation is also a hormone-sparing sterilization method, but is less common due to concerns for pyometra in a dog with a uterus.

growing demand from responsible pet parents. However, many veterinarians have not yet had training or experience with these alternative methods of sterilization.

Hormone-sparing options should be considered for dogs with a higher risk of health problems after spay/neuter. For example, Boxers have a higher chance of brain tumors (Rzechorzek et al. 2019), Rottweilers have shorter lifespans (Joonè and Konovalov 2023), and Golden Retrievers have higher chances of orthopedic conditions and cancer after hormone loss (Torres De La Riva et al. 2013). Large-breed dogs take longer to mature and are more prone to orthopedic problems, such as cranial cruciate ligament tears, if spayed or neutered before puberty. This is because natural hormone surges during puberty help to stop growth at the right time. Dogs that are spayed or neutered too early lack these signals and continue growing, often leading to misaligned or weaker joints that predispose them to joint disorders. Thus, decision-making about whether and how to sterilize a dog involves many factors (see the review by Romagnoli 2025).



Dogs that have undergone hormone-sparing sterilization will still produce natural hormones and usually behave the same as before the procedure. Although they cannot produce offspring, females will undergo dry heat cycles and may show interest in males. But there should be no bleeding if all the uterine tissue is removed. Males may be interested in females and be prone to roaming and marking. Diseases of the sex organs or those reliant on sex hormones (such as benign prostatic hyperplasia in males and mammary tumors in females) may still occur, requiring monitoring and treatment if necessary. It is thus important that pet parents are responsible for their pet's health and welfare by ensuring secure housing, providing routine veterinary care, and monitoring behavior.

For more information on hormone-sparing sterilization, how to decide if this procedure is appropriate for a particular dog, and details on performing the procedures, see our webpages on Hormone Sparing Sterilization. For a comprehensive review of sterilization methods and recommendations, see the WSAVA Guidelines for the Control of Reproduction in Cats and Dogs (Romagnoli et al. 2024).

For veterinarians: Background research for hormone restoration in dogs

The growing recognition of the potential negative health and behavior outcomes of traditional spaying and neutering has led veterinarians and pet parents to consider alternative methods of sterilization. This has resulted in greater demand for hormone-sparing sterilization alternatives like hysterectomy and vasectomy. But what if a dog has already been spayed and neutered, and is showing signs of spay-neuter syndrome? Can anything be done?

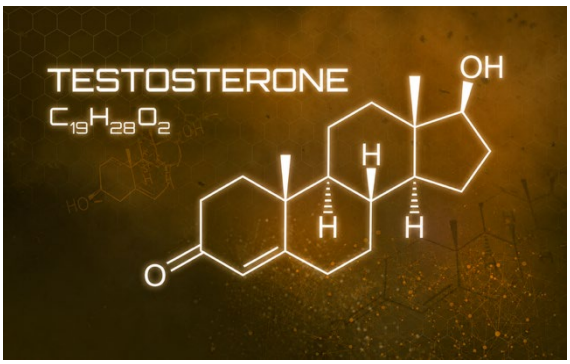
Bringing balance through hormone restoration

Spayed or neutered dogs have no gonads, so they have low levels of gonadal sex hormones (estrogen, progesterone, and testosterone), and the lack of negative feedback to the brain results in high levels of signaling hormones (GnRH, LH, and FSH). This imbalance in the hypothalamic-pituitary-gonadal (HPG) system has been linked to numerous health issues, from orthopedic disorders to obesity, urinary incontinence, and cancer. **The goal of hormone restoration is to bring the HPG axis into balance.** This is accomplished by restoring hormones to normal levels (those of intact dogs). The treatment usually involves two components: 1) Administration of appropriate sex hormones, and 2) Treatment with medication to decrease GnRH produced by the hypothalamus and LH and FSH produced by the pituitary glands in the brain.

Hormone restoration is a new therapy for dogs, with limited published information to guide treatment. This document provides a basic review of our current understanding of hormone restoration in dogs, with information from human studies to fill in gaps. *If you prefer to skip the science review, just scroll down to the protocols in the next section.*

Testosterone for neutered male dogs: Types, uses, side effects

Choosing the right testosterone



There are many formulations, dosages, and delivery methods for testosterone therapy. Testosterone is commonly available as an oral, transdermal, or injectable medication. Buccal, sublingual, nasal, and rectal methods have also been used less commonly in humans.

- Oral administration of C-17α alkylated testosterone (e.g., methyltestosterone, fluoxymesterone) is well known to cause liver damage in dogs and humans (Barbonetti et al. 2020; Heywood et al. 1977) and is not recommended for testosterone replacement. Testosterone undecanoate is available orally but also has shortcomings (see table below).
- Transdermal testosterone (gel, lotion, patch) is complicated by the potential for ingestion, transfer to humans, and few application sites in dogs.

- Injection of a testosterone ester is likely the most effective method for dogs. Testosterone cypionate is a common formulation, but other testosterone esters are available, with varying doses, half-lives, and impacts.
- Pellets may be an option for dogs for long-term use, although they involve variability in hormone levels.
- New testosterone preparations that avoid some of the downsides of current options are in development, so recommendations may change over time.

Comparison of Delivery Methods for Testosterone Therapy

From Brent et al. 2025

Method	Form	Pros	Cons
Oral **(Testosterone undecanoate)**	Capsule	• Ease of administration • T. undecanoate avoids hepatic metabolism • Fast reversal	• Poor availability requiring multiple daily doses in men • Short half-life • T. undecanoate requires high-fat meal and causes initial high dihydrotestosterone level
Transdermal	Gel, lotion	• Ease of administration • Fast reversal • More stable testosterone level	• Daily administration • Short half-life • Skin irritation • Transference to others • Lack of application sites in dogs • Possible ingestion in dogs
Injection **(Testosterone cypionate)**	Oil-based liquid	• Absorbed by tissue • Systemic action • No transference to others **Weekly subcutaneous injection:** • Less pain • Ease of administration • More stable testosterone level	• Possible erythrocytosis **2-6-week intramuscular injection**: • Difficult to administer • Inflammation and pain at injection site • Fluctuation in testosterone levels
Implant	Pellets	• Long-lasting • Absorbed by tissue • Systemic action • No transference to others	• Requires surgical implantation • Site infection or pellet extrusion • Longer half-life — peak then long decay • Difficult to remove if necessary • Replacement timing depends on multiple factors (BMI, # pellets) • Possible erythrocytosis

Testosterone levels in intact dogs are not static. Levels fluctuate greatly in adolescence and then stabilize in adulthood. Even then, levels vary daily and seasonally, often peaking in the morning (Fukuda et al. 1988). Daily testosterone application would most closely resemble the normal cycle in intact male dogs, but transdermal methods have drawbacks in dogs. Injectable testosterone with frequent subcutaneous dosing (e.g., weekly, twice weekly) provides more stable levels and is less painful than less frequent intramuscular bolus injection (e.g., monthly) or implants. Studies in men have shown that weekly or bi-weekly subcutaneous injections provide more stable levels of testosterone than injections of longer duration and produce less pain than the intramuscular route (Ahmad et al. 2022). Additionally, frequent application of testosterone reduces the common side effect of erythrocytosis (a high concentration of red blood cells) (Williamson et al. 2022).

Research on testosterone treatment in neutered dogs

Published information on hormone restoration in dogs is limited. A 1986 experiment induced benign prostatic hyperplasia in 7 months in neutered dogs using testosterone-filled implants delivering a dose of 0.25 mg/kg/day (Berry et al. 1986). A 2017 retrospective evaluation of testosterone therapy to treat incontinence in castrated male dogs found no side effects for monthly intramuscular injections of testosterone cypionate (median dose 1.5 mg/kg/month) (Palerme et al. 2017). The treatment resulted in mixed success but reported no adverse outcomes, including one dog on the therapy for 19 months.

A 2021 case study provided evidence for hormone restoration in a neutered mixed-breed dog suffering from diverse symptoms of spay-neuter syndrome. A **dose of 0.5 mg/kg/week of testosterone cypionate subcutaneously** greatly improved the orthopedic and behavioral symptoms without health side effects (Brent et al. 2021). Suprelorin, a GnRH agonist, was used to reduce excessively high LH levels. The dog has remained on this treatment for 5+ years.

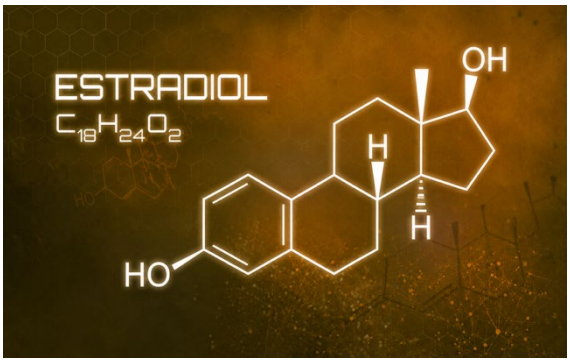
A controlled study on the safety and dosing of testosterone for dogs was published in 2025 (Brent et al. 2025). Twelve 0.9–6.3-year-old previously neutered dogs were divided into four equal groups, receiving 0 (controls), 1x, 3x, or 5x the standard weekly dose of subcutaneous testosterone cypionate (0.5 mg/kg) for 90 days. Testosterone levels increased in a dose-dependent manner, with those in the 3x and 5x groups being significantly higher than controls when measured 1 week after dosing. LH decreased after a month of treatment in most dogs, with significant drops in dogs receiving 5x the standard dose. Behavioral measures, Zambelli prostate health score, body condition scores, clinical evaluations, and routine blood hematology and chemistries showed minor variation over time or across groups. Side effects were low, although two seizures were documented in a group 3x dog with previous suspected idiopathic epilepsy.

The study also provides some information on the safety of testosterone replacement therapy for dogs neutered early. In the study described above, five study dogs were between 0.9-1.6 years at study initiation, and each was castrated at less than 6 months of age. No significant adverse events were found, but one dog in the 3x group showed transiently elevated estradiol levels at study conclusion. All dogs, including three dogs treated at 1x-5x the standard dose, completed the study without incident.

The human literature on testosterone therapy is much more expansive, and can be used to identify potential methods, outcomes, and issues until more research is conducted in dogs.

Estrogen for spayed female dogs: Types, uses, side effects

Choosing the right estrogen



Humans and dogs have the same types of estrogens: estradiol (E_2), estrone (E_1), and estriol (E_3), as well as the same estrogen receptors. However, estrogen potency and receptor sensitivity differ between species. Unlike the other estrogens, estriol is not produced in the ovaries. Instead, it is derived from estradiol and estrone in the liver.

Dogs are more sensitive to the effects of estrogens than humans and other animals. Administering excessive or repeated doses of some estrogens to dogs, including estradiol cypionate, estradiol benzoate, or diethylstilbestrol, has caused bone marrow damage (Sontas et al. 2009), although research on long-term use of conjugated estrogens did not (Veronesi et al. 2009). The weak estrogen **estriol is usually used for hormone treatment** in dogs, as it has not been associated with bone marrow depletion and remains bound to the estrogen receptors for a short duration (1-6 hours in women) (Kuhl 2005). Oral administration also results in reduced bioavailability due to rapid metabolism and excretion. In dogs, estriol may affect thyroid hormones.

Research on estrogen treatment in spayed dogs

Estriol was discovered in 1930 and has been used as a medical treatment for menopause symptoms in women and urinary incontinence in spayed and estrogen-deficient dogs (approved by the US FDA in 2011). It is available as an oral tablet under the brand name Incurin® (Merck Animal Health) for female dogs.

While there is no research specifically on the use of estrogens for hormone restoration in dogs with spay-neuter syndrome, estrogenic compounds have a history of use for treating incontinence. Urinary incontinence occurs in 3-20% of spayed female dogs. Urethral sphincter mechanism incompetence, or USMI, is the most common cause and is often related to hormone loss after spaying or neutering. It is usually treated with estrogens (such as estriol) or the alpha-agonist phenylpropanolamine (PPA) (Kendall et al. 2024).

Merck Animal Health states that there is no relationship between a dog's size and the required dose. An initial dose of 1 mg per day (1 oral tablet) is recommended for urinary incontinence; if effective for the first 1-2 weeks, it should be titrated down to ½ tablet or ½ tablet every other day. If the initial dose is ineffective, the dose can be increased after 1-2 weeks to 2 mg/day (maximum). Incurin is intended for once-daily oral administration and can be continued for life. For treatment of other conditions related to gonadectomy, veterinarians may consider starting at a lower dose for smaller dogs, and adjusting the dosage as needed.

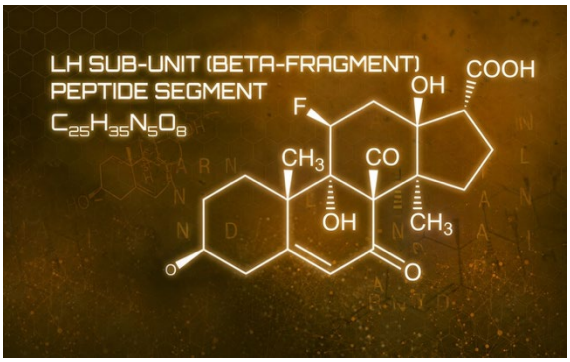
When used in ovariohysterectomized dogs, the most common side effects of Incurin treatment under field conditions included loss of appetite, vomiting, excessive water drinking, and swollen vulva (Incurin FOIA). Lethargy, mammary hyperplasia, estrous behavior, and sexual attractiveness have also been reported when using doses higher than 1.0 mg/dog. In pre-approval studies and post-approval surveillance, other adverse events have been reported (see detailed information on Incurin from Merck Animal Health), but are uncommon in practice.

Overall, estriol has a good safety profile. For example, a study of Incurin for urinary incontinence in 20 dogs reported no side effects at the minimum effective dose (Janszen et al 1997). Information on estriol treatment for female dogs less than 12 months of age is lacking (Incurin).

A concern for spayed dogs is the influence of estrogen on remnant uterine tissue, although the risk with estriol appears low. An early safety study was performed in 14 beagles given 2, 6 and 10 mg of estriol daily (higher than the normal daily dose). Histopathology did not report any signs of pyometra. A dose-dependent estrogenic effect on the uterus, ovaries, and mammary glands was found (Hendriks and Janszen 1998, as reported in Mandigers and Nell 2001). A case study reported vaginal purulent discharge with uterine stump inflammation attributed to estriol treatment (Schotanus et al. 2008). In a larger study of 14 dogs treated with estriol for urinary incontinence, enlarged vulva (7 dogs) and uterine stump enlargement (3 dogs) were found, but no serious conditions (Mathews et al. 2020). The risk of pyometra may be low for spayed dogs receiving estrogen treatment, as they have no progesterone, a hormone often related to the development of pyometra (Mandigers and Nell 2001).

The development of canine mammary tumors is estrogen-dependent. A study of 129 dogs treated with estriol for urinary incontinence reported that one dog had a 1 mm mammary tumor at the end of treatment (42 days), but that this small tumor may have been missed at the first examination (Mandigers and Nell 2001). In postmenopausal women, oral estriol was not associated with a risk of breast cancer (Lyytinen et al. 2006).

Deslorelin for spayed and neutered dogs: Uses and side effects



Gonadotropin-releasing hormone (GnRH) agonists or antagonists are often used to suppress sex hormones in humans. In dogs, they are used to control the estrous cycle, treat hormone-dependent diseases, and provide contraception for intact dogs (Gobello 2007). Stimulation from **GnRH agonists** initially increases sex hormone levels (flare period), but with continued stimulation, GnRH receptors are desensitized, and LH and FSH synthesis are inhibited, leading to a decline in estrogen and testosterone levels. **GnRH antagonists** act directly on LH and FSH synthesis without an initial surge ("Gonadotropin Releasing Hormone (GnRH) Analogues" 2012).

Reducing high LH and FSH levels in spayed and neutered dogs can be accomplished with GnRH agonists or antagonists. While several options have been studied and marketed for humans, only the GnRH agonist deslorelin acetate is commercially available for use in dogs. It is marketed as Suprelorin® for the temporary control of reproduction in male dogs and prepubertal females. In practice, deslorelin has been used off-label in both intact and gonadectomized dogs for various

purposes, including estrus induction, suppression of cyclicity in females, delaying puberty, treating benign prostatic hyperplasia, perianal adenomas, behavior disorders, and alopecia X and coat disorders (Driancourt and Briggs 2020; Romagnoli et al. 2023; Stempel and Goericke-Pesch 2020)

Suprelorin is an implant that is fully degraded at the end of its release period. Suprelorin has been available in Australia and New Zealand since 2007, the European Union (EU) since 2008, China and Mexico since 2019, and Canada since 2022. Two versions of the implant are available: a 6-month (4.7 mg) or 12-month (9.4 mg) implant. In the United States, only the 4.7 mg product is available and is limited to treating adrenal disease in ferrets[2].

Research on deslorelin for neutered dogs

Deslorelin has a good safety profile, with side effects uncommon and usually related to increased sex hormones in intact dogs during the flare period, activity changes, or coat changes (Driancourt and Briggs 2020). Most research has been conducted on intact dogs, and information for gonadectomized dogs is limited mainly to the treatment of urethral sphincter incompetence. Research has shown that reducing LH and FSH with GnRH agonists restored continence for prolonged periods in some spayed dogs (Reichler et al. 2003). No adverse effects were noted.

Long-term use of deslorelin has been reported for treating six dogs for benign prostatic hyperplasia, control of fertility, abnormal reproductive behavior, and urinary incontinence. No short-term side effects were noted during treatment except for the initial flare response. However, a spayed female treated for urinary incontinence developed a pituitary carcinoma, although the authors felt it was unlikely to be related to deslorelin (Romagnoli et al. 2023). A second case involved bladder carcinoma in an intact male dog treated with deslorelin for nine years. This could have been due to the prolonged lack of gonadal hormones – as more commonly occurs in spayed and neutered dogs.

Deslorelin appears to be safe to use in young intact dogs. Two studies reported that pre-pubertal intact male and female dogs were treated safely to postpone puberty (Gontier et al. 2022; Schäfer-Somi et al. 2022), although postnatal deslorelin implants have been reported to cause cryptorchidism in intact males (Faya et al. 2018).

DHEA for spayed and neutered dogs: Uses and side effects

DHEA (dehydroepiandrosterone) and DHEAS (the sulfated "storage" form) are the most abundant steroid hormones in humans. They are produced mainly in the adrenal glands and have the interesting characteristic of being precursors to both estrogenic and androgenic hormones. DHEA is taken up by various tissues, including the liver, kidneys, gonads, and brain, where it is converted to estradiol, estrone, testosterone, androstenediol, androstenedione, or dihydrotestosterone (DHT).

[2] Licensed veterinarians and pharmacists can legally import deslorelin implants into the U.S. for treating dogs through VMD Access. Request an account and fill out an importation request at www.vmdsciences.com

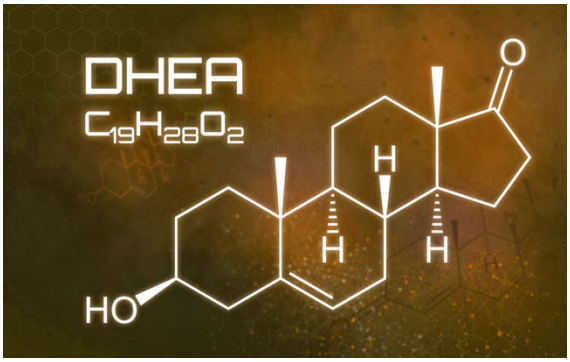
Research on DHEA in humans

DHEA is available over the counter as a human supplement in the US and has been used for anti-aging, sex hormone insufficiency, adrenal support, autoimmune disease, and osteoporosis.

The medication has been used by postmenopausal women, but results vary. Some analyses report little impact on symptoms (Wierman and Kiseljak-Vassiliades 2022), while others have reported that DHEA can address vasomotor symptoms, support immune function, and improve muscle mass and bone health (Tang et al. 2021). Impacts on cognition and cardiovascular disease had inconsistent results. However, recent studies confirm that DHEA can significantly increase testosterone and estradiol levels after menopause, especially at doses of ≥ 50 mg/day (He et al. 2025).

No serious side effects in women have ever been reported. Mild side effects included hirsutism, acne, greasy skin, scalp itching, abundant vaginal discharge, increased sweat, and odor (Rabijewski et al. 2020). There is little information about contraindications and risks of the development of testosterone- or estrogen-dependent tumor progression, but caution is warranted. DHEA has been associated with lower total cholesterol levels but higher HDL cholesterol in women (Qin et al. 2020).

Research on DHEA for dogs



In male dogs, DHEA is usually produced by the testes, and levels increase significantly after puberty. It is mainly secreted by the adrenal glands and less so from the ovaries in females, with decreasing levels with age, especially in spayed females (Mongillo et al. 2014). Given that DHEA is produced in the testes, the levels are significantly lower after castration. However, in females, DHEA is similar in intact vs. spayed females (Frank et al. 2003; Mongillo et al. 2014).

It would be interesting to know if DHEA treatment could address spay-neuter syndrome, but studies in dogs are rare. Research on DHEA supplementation in dogs reported that giving 30-75 or 60 mg/kg/day to obese (mostly gonadectomized) dogs increased weight loss and reduced cholesterol, lipoproteins, and thyroid hormones (Kurzman et al. 1990; Kurzman et al. 1998; MacEwen and Kurzman 1991). The dogs did not reduce food intake, and no toxic effects were reported. Higher doses of DHEA (100 mg/kg) also provided brain protection in older dogs. After 7 months of treatment, elderly dogs showed a two-fold reduction in the percentage of damaged cells in the cerebral cortex (Shen et al. 2001). The doses reported in these studies are orders of magnitude higher than those usually used in humans. It is unclear whether the high dose was needed for the desired effect.

Much more research is needed to identify potential side effects of DHEA treatment in dogs, assess its impact on sex hormone levels, and determine the minimum effective dose. Not enough information is currently available to include it in the hormone restoration protocol, but DHEA could be a promising treatment for spay-neuter syndrome in both male and female dogs.

For veterinarians: Hormone restoration protocols for spayed or neutered dogs

Status of our knowledge and disclaimer

Scientists, veterinarians, and dog parents are at the early stages of understanding how spay and neuter affect individual dogs and how to provide hormone therapy to enhance lifelong health. As an evidence-based organization, the Parsemus Foundation believes that much more research is needed in these areas. We expect that, as the negative health and welfare effects of traditional dog sterilization are appreciated, additional funding will be available for research on hormone restoration.

However, dogs need help today. With the knowledge we have now, the following protocols are presented as examples for veterinarians to consider for their clients suffering from spay-neuter syndrome. It includes our best effort to outline safe and effective treatment options, recognizing that **veterinarians currently offering hormone restoration for dogs use various medications, dosages, and evaluation protocols**.

While the protocol was reviewed by several veterinarians, the Parsemus Foundation is not a veterinary organization. **The information presented here is for educational purposes only**, and is not a substitute for professional veterinary care. It is important for each pet parent to coordinate their dog's care plan with a qualified veterinarian to address their dog's individual needs.

As we learn more about hormone restoration in dogs, our understanding of balancing hormones will advance, and standard protocols will develop.

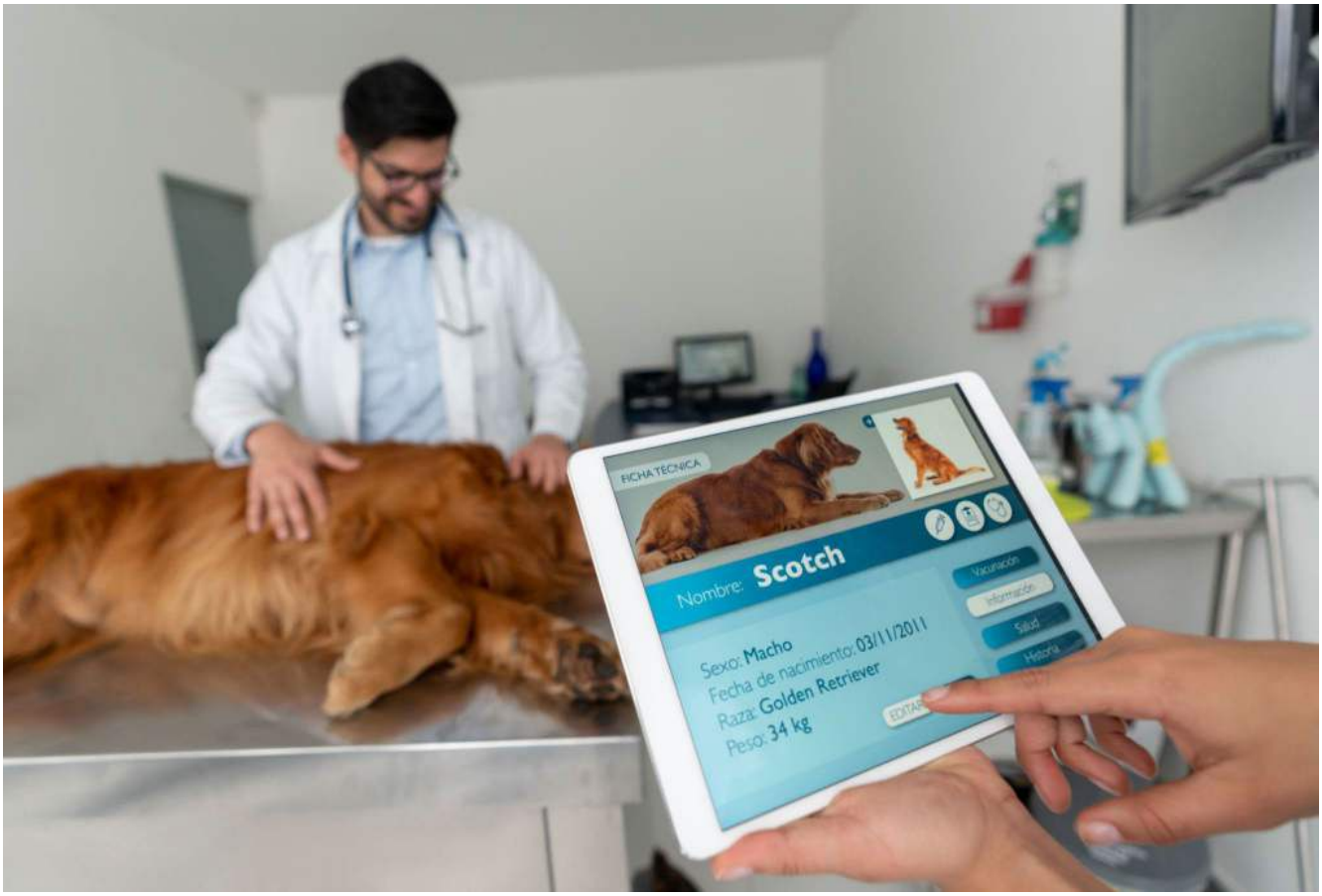
Evaluating a dog for possible hormone restoration

Initial exam: A veterinary examination should be conducted to ensure the dog is generally healthy and hormone restoration is appropriate. This should include history, bloodwork, and physical examination to rule out the need for other medical treatment and to ensure the dog is healthy enough for hormone restoration.

Potential contraindications for hormone restoration: Serious health conditions or breed risks should be evaluated prior to initiating hormone restoration, and likely require additional monitoring:

- Serious health conditions (e.g., hepatic, renal, prostate, cardiovascular disease) could be affected in adverse ways by hormone treatment.
- Epilepsy or history of seizure. Hormones can have opposite impacts on seizures. Research in humans and mice reported that testosterone metabolized to dihydrotestosterone can reduce seizures, but estradiol can increase seizures (Reddy 2004; Rodriguez-Villar et al. 2022).
- High hemoglobin can be exacerbated by testosterone, which has the side effect of erythrocytosis.

Hormone restoration planning: There is **currently no standardized hormone restoration protocol**, and it is important that the dog be under a veterinarian's care to determine the best course of action and provide evaluation and follow-up. The plan is usually created based on the individual dog, the goals, and the pet parents' ability to monitor the dog and support ongoing veterinary care. The following are sample protocols:



Hormone restoration protocols

Step 1. Determine the treatment plan

1. **Dogs with symptoms** – Behavioral or health conditions may be related to the loss of gonadal hormones. These conditions are collectively called spay-neuter syndrome.

   The basic treatment plan for spay-neuter syndrome in males and females involves **replacing gonadal hormones** and **reducing LH levels** to within the normal range for intact dogs. This involves supplementation with testosterone (males/females), estriol (females), and/or deslorelin (males/females). Testosterone supplementation is especially useful for both male and female dogs with muscle loss, frailty, or joint disorders, helping reduce frailty and support joint health for better mobility.

   Veterinarians currently use different treatments based on their experience or the dog's characteristics. Alternative treatments involve only deslorelin or only testosterone (for males and females).

   Research indicates that these treatments are generally safe for dogs (see Background Research section for details); however, we do not have data to determine which method is most likely to reduce health issues. When using both sex hormones and deslorelin, we currently lack

information on whether it is best to start with hormone replacement, with deslorelin, or both at the same time — although starting with hormone replacement is currently more common.

2. **Dogs without symptoms** –
    a. **Adult dogs:** In some dogs that were spayed or neutered, hormone restoration may be implemented to reduce the risk of health or behavior issues related to the loss of gonadal hormones.

        Some veterinarians use deslorelin alone to reduce elevated LH levels in healthy dogs. Others prefer to use sex hormone supplementation (testosterone or estriol) alone or in combination with deslorelin. Research indicates that these treatments are generally safe for dogs (see Background Research section for details); however, we do not yet have data to determine which method is most likely to reduce future health issues.

    b. **Young dogs:** In cases of pre-pubertal gonadectomy, the risk of joint disorders increases due to delayed growth plate closure from the lack of adolescent gonadal hormone stimulation. Large-breed dogs are at higher risk of joint disorders, possibly due to later puberty. Other conditions are also more common in particular breeds when spayed or neutered before six months of age (Hart et al. 2020a, 2020b).

        Thus, there may be interest in initiating hormone replacement therapy around puberty. Estriol has been used in female dogs over 12 months of age. Testosterone has been used safely for 3 months in neutered male dogs as young as 10 months (Brent et al. 2025). Estriol or testosterone cypionate could be used in dogs around puberty or 12+ months of age with careful monitoring. Deslorelin has been used safely in intact pre-pubertal dogs (Gontier et al. 2022; Schäfer-Somi et al. 2022), but will not address growth plate closure.

What about progesterone? *Female reproductive hormones are dependent on multiple hormones, including estrogen, LH, and progesterone. Hormone restoration is unlikely to replicate this delicate cycle. Progesterone is not considered here due to its influence on the uterus and the possibility of stimulating stump pyometra.*

What about DHEA? *Some veterinarians are using DHEA for hormone restoration. Due to limited basic research on its use in dogs, we are unable to provide recommendations on dosing or outcomes at this time.*

To address the gaps in our knowledge about implementing hormone restoration protocols, the Parsemus Foundation is developing a registry of individual cases. Over time, this will support the evaluation of long-term effects, side effects, and dosing differences for various breeds, ages, and sizes of dogs with different conditions. Additionally, our goal is to support research on estriol or DHEA for female dogs to better understand safety, dosing, and impact on other hormones.

Step 2. Dosing and implementing the plan

Depending on the treatment plan determined for the individual dog, the basics of dosing for replacing gonadal hormones and/or lowering LH include:

Testosterone: Subcutaneous injections of testosterone cypionate may be initiated at 0.5 mg/kg/week for males and 0.25 mg/kg/week for females[3]. The dose may need to be adjusted over time, depending on symptoms and hormone levels, but many male dogs perform well in the lower half of the normal range for intact dogs. Some veterinarians use higher doses at longer intervals (every 2-4 weeks), although side effects are more likely with infrequent dosing.

The injection can be given subcutaneously with an insulin syringe (such as a 30G 0.3-0.5cc 5/16-Inch [8mm] insulin syringe available on Amazon), often in the back of the neck. Testosterone cypionate is a viscous product and takes some time to draw into the syringe. The veterinary care team can provide instruction on giving the subcutaneous injection in a sterile manner if the dog's caregiver will give the weekly injections (this video provides the basics). Testosterone cypionate can be obtained from most pharmacies, but availability varies by country. In the US, testosterone is a controlled substance, so a Drug Enforcement Administration (DEA) license is required for dispensing. For small dogs requiring a very small amount of testosterone, it may be necessary to obtain diluted testosterone from a human compounding pharmacy so it is more easily administered.

Estrogen: Estriol has been safely used for spayed female dogs to treat urinary incontinence, under the brand name Incurin®. It is available in the US, Canada, EU, UK, and many other countries. For urinary incontinence, it is given orally once daily, starting with 1mg. Dosage should be adjusted up or down at 1-2-week intervals to achieve the desired effect, with a maximum dose of 2 mg/day. Dosage reduction can be achieved by providing ½ tablet and/or dosing every other day. For treatment of other conditions related to gonadectomy, veterinarians may consider starting at a lower dose for smaller dogs and titrating the dose as needed.

Deslorelin implant: As part of hormone restoration, many dogs will need a deslorelin acetate implant (brand name Suprelorin®) to reduce LH to within the normal range of intact dogs. Suprelorin is a GnRH agonist marketed as a 9.4 mg 12-month implant for dogs in the EU, Australia, and New Zealand. A 4.7 mg Suprelorin implant is available for dogs in Canada (the 9.4 mg implant can be requested with an emergency drug release application). In the US, the 4.7 mg Suprelorin implant is marketed for ferrets (see below for more information on use in dogs). Suprelorin is a small, degradable implant injected into the area between the shoulder blades of dogs every 6 months (4.7 mg) or every 12 months (9.4 mg). It can be implanted near the umbilicus the first time for easier retrieval if any side effects occur.

The timing of providing the first deslorelin implant when also providing exogenous sex hormones has not been studied for hormone restoration. For simplicity, they can be initiated simultaneously. Another method is to wait for about 3 months after testosterone or estriol replacement has been initiated to evaluate any side effects, then start deslorelin. Research has shown that weekly subcutaneous higher-dose testosterone injections can reduce LH levels after 3 months of treatment,

[3] Some veterinarians are using higher doses in males and females. Research has demonstrated safety of testosterone cypionate up to 5X the recommended dose over 3 months in male dogs, but data is not yet available for female dosing.

but for most dogs, they did not lower LH levels to those of intact dogs (Brent et al. 2025). So, deslorelin will usually be necessary to bring LH levels back to within the normal range for intact dogs.

Note: Importing deslorelin implants to the US

Suprelorin is not approved specifically for dogs in the US. While some practitioners use the ferret implant off-label, licensed veterinarians and pharmacists can legally import deslorelin implants into the US for the treatment of dogs through VMD Access. Go to vmdsciences.com or use the QR code to request an account or submit an importation request form.

Monitoring

To maintain good health during hormone therapy, routine clinical assessment and bloodwork are important and should be performed prior to and at regular intervals. Measurement of testosterone, estrogen, and LH levels is also helpful for dose adjustment before and during treatment. For the treatment of specific disorders, dosages can be adjusted to the minimum effective level, keeping in mind that levels usually take time to stabilize. It is also critical for pet parents to closely monitor their dog for any changes in behavior or health. Keeping a log of such changes to discuss with the veterinarian can be especially useful for hormone restoration.

Hormone measurements

- **Testosterone** assays are commonly available, and testosterone should be measured several times during the first year of use (for males or females). There is no need to measure baseline levels as they will be near zero for gonadectomized dogs. It takes several months of treatment for testosterone levels to stabilize. Thus, we recommend taking a measurement 3-4 months after treatment initiation. This measurement can be used to determine whether testosterone is within the normal range for intact dogs, enabling dose adjustments as needed. Additional testosterone tests may be completed over time, taking samples at the same number of days since dosing (about 4 days after weekly injection) and at the same time of day for best results.
- **Estrogens** can be measured in a total estrogen test. Estriol does not convert to estradiol, so a standard estradiol test will not provide accurate results for estriol treatment. As with testosterone, the level in a gonadectomized female will be near zero, so no baseline evaluation is necessary. The post-treatment measurement should be compared with the normal range for intact females and adjusted as needed. In obese male dogs, testosterone can be aromatized in adipose tissue to estradiol. While testosterone may help improve body condition over time, you may want to monitor estradiol levels in these dogs.

- **Luteinizing hormone** (LH) varies between individual dogs, but it is likely that a spayed or neutered dog will have LH above the normal range for intact dogs. LH can be measured prior to treatment as a baseline, and again 3-4 months after hormone treatment is initiated, to evaluate LH levels and the need for deslorelin. An LH test can also be completed 2-3 months after the deslorelin implant to gauge the effect. However, **if LH testing is not available in your**

area, the assumption can be made that LH is above the normal limit for intact dogs, even after hormone therapy is initiated, and will drop within the normal range after the deslorelin implant. Thus, testing may not be critical for implementing LH reduction treatment.

Different LH tests: Veterinary endocrine diagnostic laboratories that conduct canine LH assays have reference ranges for intact and neutered male and female dogs. There is currently no lab in the US that provides quantitative LH testing. It is **not recommended** to test LH levels using the following:

- Most veterinary reference laboratories (Antech, Idexx) do not provide reference ranges because their results are NOT quantitative.
- LH tests used to determine breeding timing in female dogs (e.g., Witness LH Test) only measure low levels and are not applicable to gonadectomized dogs.
- Human LH tests are not predictive of canine levels.

Routine health monitoring

Routine clinical assessment and hematology/biochemistry bloodwork are important before and at regular intervals during treatment. Assessment of behavioral changes should be included, as the addition of hormones can increase hormone-related behaviors (e.g., mounting, roaming, resource guarding, urine marking) and may decrease other behaviors (stranger aggression, anxiety, fear).

Hormone-dependent diseases

Hormone restoration is likely a long-term treatment, underscoring the importance of regularly monitoring health parameters. The following conditions deserve mention due to their relationship with gonadal hormone levels:

Benign prostatic hyperplasia (BPH): High levels of testosterone cypionate and testosterone propionate have experimentally induced BPH in neutered dogs (Berry et al. 1986; Li et al. 2018). However, when testosterone was replaced in previously castrated dogs of different ages, BPH did not develop to the same extent as in intact dogs (Juniewicz et al. 1994). The development of an enlarged prostate in neutered dogs treated with hormone therapy may depend on the timing of the neuter and when testosterone administration begins. Therefore, regular assessment of the prostate before and during testosterone therapy is recommended, especially as the dog ages.

Erythrocytosis (polycythemia): Hemoglobin and hematocrit should be evaluated regularly for dogs on testosterone therapy. The most common effect of testosterone therapy in men is higher hemoglobin or hematocrit levels, although there is little evidence that this causes health concerns (Ahmad et al. 2022). Dosing frequency is related: infrequent doses of high testosterone levels result in an increased risk of erythrocytosis, which is more common with infrequent intramuscular injection and pellet delivery (White et al. 2022). Dogs receiving weekly testosterone cypionate, at low or high doses, did not develop erythrocytosis in a 3-month study (Brent et al. 2025).

Stump pyometra: Spayed females may have residual uterine tissue (the uterine stump). Estradiol exposure can alter the stump and may cause stump pyometra. Estriol is short-acting, so it has a lower risk of producing stump pyometra than estradiol. See the **Background Research section on estrogen for spayed female dogs** for research on this topic. Routine screening (vaginoscopy and ultrasonography) was not generally recommended for dogs on estriol, but monitoring plans can be tailored to the individual. Veterinarians should alert clients to watch for any vaginal discharge.

Mammary tumors: Mammary gland development and the development of mammary tumors are influenced by estrogens. However, the weak estrogen estriol and the conjugated equine estrogens have not been related to the development of mammary tumors in spayed dogs treated for urinary incontinence (Veronesi et al. 2009). Evaluation of mammary tissue should nevertheless be part of a routine health assessment.

Hormone restoration notes

1. Restoring lost hormones is the goal

Hormone restoration aims to return balance to the HPG axis by replacing the sex hormones and reducing luteinizing hormone to within **the normal range for intact dogs**. This is an important concept, because sometimes people think that hormone therapy is doing something unnatural to the dog. In fact, the opposite is true. The goal as described in this document is to return the system to a natural balance.

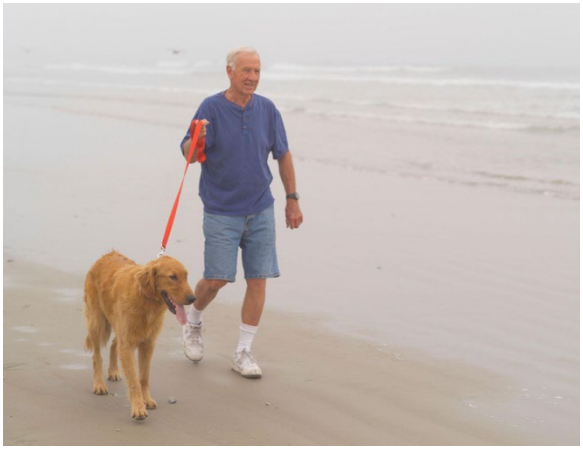
2. There are many preparations of sex hormones

As noted in the Research Review, there are pros and cons to different application methods and compounds. The protocols presented here use the best available scientific information, which is sometimes based on human medicine when canine studies are lacking. Some hormone preparations are unavailable in some countries, so it is important to research the risk profiles of any compound used outside the protocols and determine appropriate doses.

3. Individual variation requires personalized treatment

Every dog will respond differently to the same dosage of medication. Hormone restoration is no different. Tailoring the plan to the dog requires monitoring their health and behavior. Keep in mind that sometimes it takes time for hormone restoration methods to show results, and some effects (such as increased sexual behavior) may subside when the body becomes used to natural hormone levels. Complex problems, such as aggressive behavior, may require additional behavior therapy.

Share your experience



Given the early stage in our knowledge about hormone restoration therapy, keeping careful records of treatments and outcomes can assist the broader community. Consider sharing your experience through presentations, collaborations, and discussions. Also, veterinary clinics can join the free Parsemus Foundation Veterinary Directory so that clients can more easily find hormone restoration care for their pet: https://www.parsemus.org/vet-directory/

A hormone restoration registry system is currently being developed so that veterinarians and pet parents can share data about hormone restoration. This will ultimately enable more detailed analysis, a better understanding, and updated protocols.

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