



## The Use of Melatonin Implants as a Method for Estrus Suppression in Cats

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**Abstract:** Melatonin implants have gained attention as an effective and reversible method for estrus suppression in female cats. As seasonally polyestrous animals, cats exhibit cyclic reproductive behavior influenced by photoperiod, with melatonin playing a crucial role in regulating the hypothalamic-pituitary-gonadal axis. Subcutaneous melatonin implants mimic short daylight conditions, leading to a temporary suppression of ovarian activity and estrus-related behaviors. Studies have demonstrated that melatonin implants extend the interest interval for 2–4 months with minimal adverse effects. However, variations in estrus suppression duration and occasional induction of ovulation and pseudopregnancy highlight individual variability in response to treatment. Compared to traditional hormonal contraceptives, melatonin offers a safer alternative without the severe side effects associated with progestins and androgens. Despite these advantages, concerns regarding application challenges, cost, and temporary efficacy persist. Further research is needed to refine dosage protocols, evaluate long-term effects, and address individual response differences. Melatonin implants represent a promising tool for feline reproductive management, particularly for cat breeders and owners seeking a non-surgical alternative to sterilization.

**Keywords:** Contraceptive implant, Estrus suppression, Feline reproduction, Melatonin, Non-surgical contraception, Ovarian activity, Reproductive cycle.

### Kedilerde Östrus Baskılama Yöntemi Olarak Melatonin İmplantlarının Kullanımı

**Özet:** Melatonin implantları, dişi kedilerde östrus baskılanması için etkili ve geri döndürülebilir bir yöntem olarak kullanılmaktadır. Mevsimsel polioestrik hayvanlar olan kediler, üreme döngülerini ışık periyoduna bağlı olarak düzenler ve bu süreçte melatonin, hipotalamik-hipofizer-gonadal aksın kontrolünde kritik bir rol oynar. Subkutan melatonin implantları, kısa gün uzunluğu koşullarını taklit ederek ovaryum aktivitesinin ve östrusla ilişkili davranışların geçici olarak baskılanmasını sağlar. Yapılan çalışmalar, melatonin implantlarının interöstrus aralığını 2–4 ay boyunca uzattığını ve minimal yan etkilere sahip olduğunu göstermektedir. Ancak, östrus baskılanma süresinde görülen bireysel farklılıklar ve bazen ovulasyon ile psödogebelik oluşumu, değişken bireysel yanıtları ortaya koymaktadır. Geleneksel hormonal kontraseptiflerle karşılaştırıldığında, melatonin, progesterinler ve androjenlerle ilişkili ciddi yan etkiler olmadan daha güvenli bir alternatif sunmaktadır. Bununla birlikte, uygulama zorlukları, maliyet ve geçici etkililik gibi konular endişe yaratmaktadır. Melatonin dozaj protokollerinin iyileştirilmesi, uzun vadeli etkilerin değerlendirilmesi ve bireysel yanıt farklılıklarının ele alınması için daha fazla araştırmaya ihtiyaç vardır. Melatonin implantları, özellikle cerrahi sterilizasyona alternatif arayan kedi yetiştiricileri ve sahipleri için umut vadeden bir üreme yönetimi aracı olarak öne çıkmaktadır.

**Anahtar Kelimeler:** Melatonin, östrus baskılanması, kedi üremesi, kontraseptif implant, reproduktif döngü, cerrahi olmayan kontrasepsiyon, ovaryum aktivitesi.

## Introduction

Cats are seasonal polyestrous animals, and ovulation in these species is induced mating. If mating does not happen and ovulation is not induced, cats will eventually return to estrus. During estrus, various behavioral changes such as vocalization, frequent urination, rolling, rubbing against their owner, and an increased desire to escape outdoors can be observed. These symptoms, along with the potential pregnancies resulting from escaping, pose significant challenges for cat owners (Goericke-Pesch, 2010; Johnston et al., 2001; Kutzler, 2007). Due to these issues, cat owners seek various methods to control reproduction (Goericke-Pesch, 2010; Kutzler & Wood, 2006). Estrus suppression can be achieved through surgical and non-surgical methods. Surgical methods permanently eliminate reproductive functions. However, many cat owners hesitate to opt for surgical sterilization due to the need for anesthesia, potential postoperative complications, the risk of obesity and diabetes mellitus, as well as the irreversible and costly nature of the procedure. Instead, they prefer medical treatments to suppress or delay the behavioral changes observed during estrus (Goericke-Pesch, 2010; Howe, 2006; Kutzler & Wood, 2006; Verstegen, 2000). Hormonal methods such as progestins (Romagnoli & Concannon, 2009; Tamada et al, 2003), androgens (Johnston et al., 2001; Tamada et al, 2003; Verstegen, 2000), gonadotropin-releasing hormone (GnRH) analogs (Munson et al., 2001), and melatonin are employed reproduction suppress reproduction temporarily.

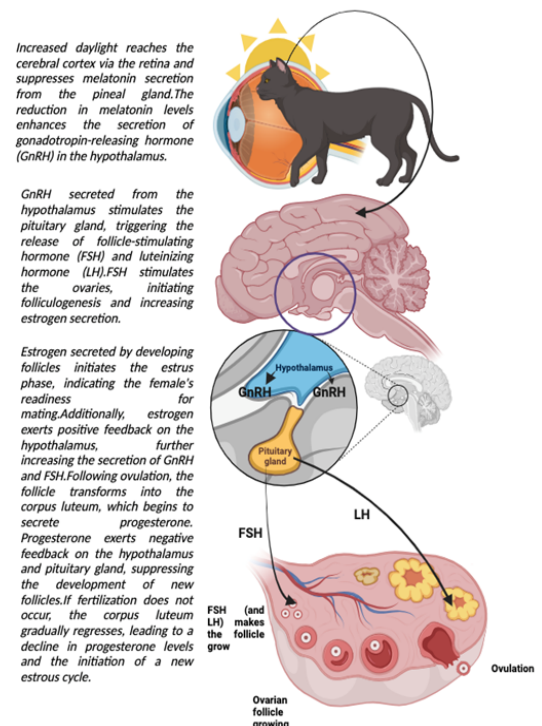
**Melatonin Synthesis, Secretion, and Metabolism:** The pineal gland, also known as the epiphysis, is a neuroendocrine organ according located in the brain that regulates various bodily functions, primarily within the endocrine system, in response to environmental light-dark cycle. Working in conjunction with the suprachiasmatic nucleus, the pineal gland is considered a biological clock that synchronizes bodily activities with natural rhythms. The primary substance secreted by the pineal gland, melatonin, was identified in the late 1950s (Arendt & Aulinas, 2019).

Melatonin (N-acetyl-5-methoxytryptamine) is a neuromodulatory substance involved in numerous physiological processes in mammals. It is produced and secreted by the pineal gland of the central nervous system (Abecia et al., 2019). As a result of photoperiodic changes, melatonin synthesis and secretion follow both circadian (daily) and annual (yearly) rhythms, which are directly influenced by light-dark and day-length cycles (Cassone, 1990). Melatonin secretion duration is proportional to nighttime length (Schäfer-Somi, 2017).

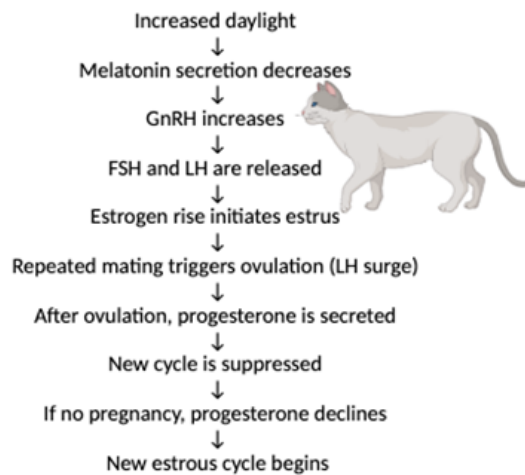
In the pineal gland, melatonin production remains at low levels during the day and increases significantly at night. This synthesis involves the hydroxylation of tryptophan into 5-hydroxytryptophan, which is subsequently converted into serotonin. This process also plays a role in regulating ovarian activity in seasonally polyestrous animals like cats (Al-Hamedawi et al., 2020; Al-Shammary & Al-Yasiri, 2023). In cats, the highest melatonin concentrations are observed during anestrus and interest periods (Kassim et al., 2019). Exogenous melatonin, administered orally or via injection,

has been shown to suppress estrous cycles in cats. Melatonin may serve as a signal for domestic female cats to detect exogenous melatonin levels, mimicking the effects of decreasing photoperiod-induced melatonin (Graham et al., 2004). A subcutaneous application of an 18 mg melatonin implant has been reported to suppress estrus for 2-4 months, without initial signs of estrus (Fontaine, 2021).

**Estrous Cycle in Cats and the Role of Melatonin:** The estrous cycle in female cats consists of four phases: proestrus, estrus, diestrus, and anestrus. The estrus phase, commonly referred to as vocalizations, increased affection, and restlessness, which can be challenging for cat owners exposure. Under long-daylight long daylight conditions (14–16 hours), estrous cycles occur more frequently (Hughes & Olson, 2000). Photoperiodic changes in reproductive capacity were first recognized in the 1930s (Baker & Ranson, 1932). Seasonal variations in photoperiod alter the duration of daily melatonin secretion, leading to behavioral changes associated with seasonal cycles (Wehr, 1997). Once it was discovered that seasonal differences influenced melatonin secretion, researchers established a connection between melatonin and the hypothalamic-pituitary-gonadal axis, demonstrating its critical role in both male and female reproductive systems (Shi et al., 2013) (Figures 1 and 2).



**Figure 1.** Effect of increasing day length on the hypothalamus–hypophysis–ovarian axis. The increasing light during early spring directly affects the cerebral cortex; consequently, melatonin secretion from the pineal gland is suppressed resulting in the suppressive effect on hypothalamic secretion of gonadotropin-releasing hormone (GnRH); the secretion of gonadotropins is increased, leading to an increase in serum sexual steroid hormone concentration. FSH = follicle-stimulating hormone; LH = luteinising hormone.



**Figure 2.** Estrous cycle in cats and the role of melatonin.

Melatonin, a hormone synthesized by the pineal gland, plays a crucial role in regulating reproductive cycles through its interaction with the hypothalamus. Melatonin production increases in darkness and decreases during long daylight periods. Elevated melatonin levels suppress gonadotropin-releasing hormone (GnRH) secretion, thereby inhibiting the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This hormonal regulation is utilized in female cats to induce anestrus and suppress estrous behavior (Romagnoli & Concannon, 2003).

Increased daylight exerts a stimulatory effect on the hypothalamic-pituitary-ovarian axis. At the onset of spring, longer daylight exposure directly influences the cerebral cortex, leading to the suppression of melatonin secretion from the pineal gland. As a result, the inhibitory effect on GnRH release from the hypothalamus is diminished, causing an increase in gonadotropin secretion, which subsequently elevates serum sex steroid hormone concentrations (Leyva et al., 1984; Leyva et al., 1989). A reduced photoperiod is associated with elevated endogenous melatonin concentrations, followed by decreased sexual activity. Exogenous melatonin administration can mimic this effect. Oral or parenteral administration of exogenous melatonin or melatonin receptor agonists effectively suppresses reproductive function in cats (Kutzler, 2015).

#### **Melatonin Implants and Their Mechanism of Action:**

Melatonin implants are subcutaneously placed devices that provide a continuous release of melatonin into the bloodstream. These implants mimic the natural effects of melatonin during short daylight periods, signaling the reproductive system to enter a state of quiescence. Consequently, ovarian activity is temporarily suppressed, leading to a reduction or complete elimination of estrus behavior. Sustained-release subcutaneous formulations of melatonin have been tested as a more practical alternative

to oral administration in cats (Faya et al., 2011; Gimenez et al., 2009; Griffin et al., 2001). The interscapular space is typically used as the implantation site, and the implant can be administered to an unsedated patient with local anesthetic infiltration (Figure 3). Melatonin implants (18 mg, Melovine; Ceva Santé Animale) are commercially available for veterinary use in many countries. The application of an



**Figure 3.** The subcutaneous melatonin implant is administered via an applicator that is positioned in the interscapular region.

18 mg melatonin implant in female cats has been reported to extend the interest interval to 2–4 months (Gimenez et al., 2009).

**Duration of Induced Anestrus:** In female cats implanted during the interestrus phase, anestrus duration ranges from 1 to 3 months (Faya et al., 2011; Gimenez et al., 2009;

Schaefer-Somi, 2017), with the widest reported range in the literature being 21–277 days (Furthner et al., 2020). In female cats implanted during estrus, the suppression lasts approximately 2 months (Gimenez et al., 2009).

**Estrus Symptoms Immediately Following Implantation;** No estrus symptoms have been observed in female cats implanted during seasonal anestrus (Gulyuz et al., 2009) or very early interestrus (Faya et al., 2011). In female cats implanted during interestrus, estrus symptoms are rare, with an incidence of approximately 35% (Faya et al., 2011; Gimenez et al., 2009; Schaefer-Somi, 2017). In contrast, in female cats implanted during estrus, estrus symptoms are quite common, occurring in approximately 80% of cases (Gimenez et al., 2009).

**Ovulation and Pseudopregnancy;** Ovulation and pseudopregnancy have been observed in 43% of female cats implanted during interestrus (Faya et al., 2011).

#### **Advantages of Melatonin Implants:**

- Non-surgical nature: Provides a temporary alternative to sterilization, making it suitable for owners who wish to avoid permanent sterilization.
- Reversibility: Normal estrus cycles resume once the implant's effects diminish.
- Long-term efficacy: A single implant can be effective for several months, reducing the need for frequent interventions.
- Minimal side effects: Melatonin implants are generally well tolerated, with no significant adverse effects reported in clinical studies (Durán Frías, 2021).

#### **Disadvantages of Melatonin Implants**

- High individual variability in suppression duration: Estrus should be carefully monitored before administration.
- Application limitations: The subcutaneous insertion of an 18 mg melatonin implant can be performed using the applicator provided with the product; however, this applicator is designed for sheep, allowing multiple implants to be loaded and administered sequentially. If several queens are implanted on the same day, each requires a sterile needle, making needle availability a limiting factor. In some countries, implants are only available in packs of 2 × 25 with a single needle, necessitating additional purchases. The applicator, designed for sheep, must be bought separately, and obtaining extra needles can be challenging. Consequently, surgical placement via an incision after local anesthesia is often preferred, making repeated treatments less desirable (Romagnoli et al., 2022).
- Timing constraints: If the implant is not administered precisely during the interestrus phase, fertility cycles may resume shortly after implantation (Schaefer-Somi, 2017).
- Temporary nature: The effects of the implant are not permanent, requiring repeated applications for long-term estrus suppression.
- Cost: Melatonin implants may be more expensive than other hormonal methods.

Individual response variability: The efficacy of melatonin implants can vary among individual cats.

- Application procedure: Implantation requires veterinary expertise to ensure proper placement and dosage (Mason et al., 2015).

## **Conclusion**

Melatonin implants provide a safe, effective, and reversible method for suppressing estrus in female cats. They are particularly beneficial for breeders needing reproductive control or cat owners seeking a non-surgical alternative to sterilization. Despite some limitations, such as temporary effects and cost, melatonin implants present a promising tool for feline fertility management. Further studies are needed to optimize dosage, understand individual variability, and evaluate long-term effects.

## **Conflict of Interest**

The authors declare that there is no actual, potential or perceived conflict of interest for this article.

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