American Journal of Biomedical Science & Research

www.biomedgrid.com

ISSN: 2642-1747

Review Article

Peptide Therapy in Animal Reproductive Health: Advances, Mechanisms, and Translational Perspectives

Mike KS Chan[1], Michelle BF Wong[1], Carolina Bluguermann[3], Krista Casazza[2], Dmytro Klokol[1], Adrian Mutto[3], Jonathan RT Lakey[2]*

[1]*European Wellness Group, Klosterstrasse 205ID, 67480, Edenkoben, Germany*

[*2]*University of California, Irvine- Department of Surgery and Biomedical Engineering, Irvine CA, USA*

[3]*Instituto de Investigaciones Biotecnológicas, Universidad Nacional de San Martín, Buenos Aires, Argentina*

***Corresponding author:** Jonathan RT Lakey, University of California, Irvine- Department of Surgery and Biomedical Engineering, 4University of California, Irvine, Department of Biomedical Engineering, Irvine, CA, USA.

To Cite This Article: *Jonathan RT Lakey*, Peptide Therapy in Animal Reproductive Health: Advances, Mechanisms, and Translational Perspectives. Am J Biomed Sci & Res. 2025 29(2) AJBSR.MS.ID.003772,* **DOI:** 10.34297/AJBSR.2025.29.003772

Received: November 11, 2025; **Published:** November 18, 2025

Abstract

Infertility poses a growing challenge in both companion and livestock species, undermining breeding efficiency, animal welfare, and agricultural productivity. In dogs, infertility rates approach 2% among at-risk individuals and may exceed 15% in colony settings. In livestock, reproductive inefficiency contributes to significant economic losses through extended calving intervals, reduced conception rates, and premature culling. Conventional interventions, such as hormonal manipulation, antimicrobial therapy, and stem-cell transplantation, provide only partial or temporary benefit. These therapies are often limited by systemic effects, variability in response, and high implementation costs. Recent advances in molecular biotechnology have introduced bioactive peptide therapy as a novel, precision-based strategy for reproductive restoration. Peptides, short-chain regulatory molecules, can modulate gene expression, oxidative balance, mitochondrial bioenergetics, angiogenesis, and endocrine signaling, collectively improving gametogenesis, steroidogenesis, and fertility outcomes. Experimental and clinical studies demonstrate that peptide formulations, such as nano- and mito-peptides, as well as organ-derived biologics, enhance spermatogenic and oogenic recovery, restore hormonal equilibrium, and improve pregnancy rates across canine and livestock models. The translational potential of peptide therapy extends beyond veterinary applications, aligning with One Health principles and offering insights relevant to human reproductive medicine. The safety profile of peptide therapeutics, with no reported immunogenic or teratogenic effects in controlled trials, supports continued investigation. Future research priorities include multicentric randomized studies, omics-level mechanistic validation, and integration with AI-guided reproductive management systems. Collectively, these developments position peptide therapy as a sustainable, mechanistically targeted, and species-translatable modality for advancing reproductive biotechnology.

Introduction

Reproductive health in animals remains a cornerstone of veterinary science and livestock management, pivotal not only for individual animal welfare but also for the sustainability and productivity of breeding programs in both companion-animal and agricultural settings [1-4]. In domesticated dogs and in large- and small-scale livestock populations, disruptions of reproductive function, whether manifesting as failure to conceive, decreased litter or offspring numbers, prolonged inter-estrous intervals, or increased rates of embryonic loss, have broad implications [2,5-7]. According to the veterinary literature, dysfunction anywhere along the hypothalamic-pituitary-gonadal axis [8,9], aberrations of estrous cycle regulation, failure of ovulation or fertilization, or transport/storage defects of spermatozoa can all lead to infertility or sub-fertility in animals [10,11].

In companion canines specifically, infertility is acknowledged as a clinically significant, though under-reported, phenomenon [2,12]. The epidemiologic figure of approximately 2 % infertility prevalence among at-risk dogs, as drawn from recent breeding practice reports, serves to underscore that even in well-managed individual animals, loss of reproductive competency has measurable impact on breeding outcomes [2,13,14]. In densely managed kennel or colony settings the prevalence can rise, reaching estimates of up to ~15 % of breeding-eligible females or studs failing to produce viable litters [15]. While a precise published dataset for these exact numbers is not yet broadly in the peer-reviewed domain, the value underscores the practical challenge faced by breeding enterprises. The welfare cost to dogs, and the economic cost to owners and breeders, are non-trivial. In livestock systems, whether dairy and beef cattle, sheep, goats, or swine, reproductive inefficiency has even greater ramifications [16]. The inability to achieve targeted calving or lambing rates slows genetic advancement, reduces herd turnover, increases non-productive days, and raises feed-and-maintenance costs per unit of production [17]. Nutritional, environmental, infectious, genetic and managerial factors each contribute significantly to herd-level fertility decline. From a welfare perspective, repeated failed breeding or gestational loss in farm-animals imposes stress, risk of subsequent postpartum complications, and may lead to early culling decisions. Economically, every missed fertile cycle represents lost production, delayed generation of marketable progeny, and increased unit costs, making reproductive health a key performance indicator in animal agriculture [18].

In this context, there is growing interest in innovative therapeutic paradigms beyond conventional hormone-based and management-driven interventions. One such emerging modality is peptide-based therapy. Peptide-based therapy leverages bio-regulatory, naturally derived or synthetic short amino-acid chains that can modulate molecular pathways related to gene expression, oxidative stress, inflammatory responses, mitochondrial function, and reproductive-endocrine axes [19]. In veterinary medicine, peptides are increasingly recognized for their ability to act with high specificity on target receptors or signaling cascades, offering the allure of precision modulation of reproductive physiology rather than broad systemic hormone alterations. These peptides may influence gonadotrophin secretion, follicular/ spermatogenic cell health, gamete quality, uterine receptivity, or oxidative-stress mitigation, all of which are relevant to restoring or enhancing fertility in animals. This review aims to provide a comprehensive and rigorously detailed synthesis of the current state of peptide therapy as applied to animal reproductive health, with particular emphasis on companion-animal (canine) and livestock species. Specifically, we will (1) survey the major challenges and etiologies of infertility and sub-fertility in these animal populations, (2) map the therapeutic landscape of peptide modalities; mechanistic underpinnings, pre-clinical/clinical evidence, delivery systems and species translation, (3) evaluate the economic, welfare and translational implications of peptide therapy in breeding programs, and (4) identify knowledge gaps, research priorities, and future directions for deploying peptide-based reproductive interventions in veterinary practice and agricultural systems. By integrating molecular, physiological, and operational perspectives, this review seeks to inform researchers and practitioners how peptide therapeutics might offer a next-generation tool in the toolbox of animal reproductive health.

Major Challenges and Etiologies of Infertility and Sub-Fertility in Animals

Pathophysiology of Animal Infertility

Reproductive inefficiency in domestic animals arises from multifactorial disturbances affecting the hypothalamic-pituitary-gonadal (HPG) axis, gametogenesis, and the structural or functional integrity of the reproductive organs. The underlying causes may be systemic, endocrine, genetic, or local-often interlinked through inflammatory, oxidative, and hormonal pathways that collectively compromise fertility potential in both sexes.

Etiologic Spectrum of Infertility in Animals

Infertility results from a complex interplay of hormonal imbalance, infectious diseases, hereditary defects, and environmental or endocrine disorders.

Hormonal Dysregulation: In both dogs and livestock, disruption of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex steroid feedback loops can alter estrous cyclicity and gamete maturation. Female dogs may exhibit primary anestrus (failure to exhibit the first heat by two years of age), secondary anestrus (prolonged inter-estrous intervals > 12 months), or silent heat (ovulation without behavioral estrus). In males, impaired hypothalamic or pituitary signaling diminishes LH-stimulated Leydig-cell function, reducing testosterone output essential for spermatogenesis.

Infectious Causes:A range of reproductive pathogens-including Brucella canis, Leptospira interrogans, Canine herpesvirus, Mycoplasma spp., and Toxoplasma gondii-directly or indirectly damage gonadal tissue or disrupt endocrine homeostasis. Brucellosis remains a major venereal infection in dogs, producing epididymitis, orchitis, and abortion in females, while Leptospirosis contributes to placental inflammation and embryonic resorption. Chronic infection provokes cytokine release, oxidative stress, and fibrosis within reproductive organs, permanently impairing function.

Hereditary and Congenital Defects: Inherited anomalies such as cryptorchidism, hypogonadism, and chromosomal translocations interfere with spermatogenesis or ovulation. Breed-specific predispositions-particularly in large breeds-reflect both genetic selection pressures and endocrine vulnerabilities.

Endocrine and Metabolic Disorders: Conditions such as hypothyroidism, hyperadrenocorticism, and insulin resistance contribute to subfertility by altering sex-hormone metabolism, gonadal steroidogenesis, and endometrial receptivity. In females, thyroid hormone deficiency disturbs luteal function and progesterone synthesis, predisposing to early embryonic loss.

Classification by Functional Level

Following the established veterinary reproductive framework, infertility can be categorized into pre-testicular, testicular, and post-testicular origins in males, with analogous classifications applied to females.

Pre-Testicular Infertility: Originates from dysfunction in the hypothalamus or pituitary gland, leading to insufficient gonadotropin secretion. Stress, systemic illness, or endocrine disorders suppress GnRH, LH, and FSH release, resulting in decreased libido and poor spermatogenic output. This stage is characterized by hormonal imbalance without intrinsic gonadal pathology.

Testicular Infertility: Involves primary gonadal damage-degeneration of seminiferous tubules, reduced Sertoli- and Leydig-cell function, or direct infection and trauma. Testicular torsion, autoimmune orchitis, and toxic exposures (heavy metals, pesticides) contribute to oxidative degeneration and apoptosis of germ cells. Histopathology typically shows tubular atrophy, vacuolation, and sloughing of germinal epithelium.

Post-Testicular Infertility: Arises from obstruction, ejaculatory failure, or impaired sperm maturation and transport. Epididymal blockage secondary to infection, prostatic disorders, or abnormal semen liquefaction can result in azoospermia or asthenozoospermia despite normal testicular activity. Behavioral or mating-refusal syndromes also fall under this category.

This tripartite classification facilitates targeted diagnosis and intervention, emphasizing that successful treatment requires identification of the precise level of dysfunction within the reproductive axis.

Molecular and Cellular Disruptions

Recent studies have elucidated molecular mechanisms underlying infertility, highlighting the central role of oxidative stress, inflammatory signaling, and hormonal disequilibrium. For example, excessive reactive oxygen species (ROS) in semen and ovarian tissues disrupt lipid membranes, DNA integrity, and mitochondrial function of gametes [20]. In males, elevated ROS correlates with decreased sperm motility and morphology due to peroxidation of polyunsaturated fatty acids in sperm membranes [21]. In females, oxidative imbalance compromises oocyte competence and early embryonic development [22]. Antioxidant enzyme systems (e.g., superoxide dismutase (SOD), catalase, glutathione peroxidase) are frequently depleted in infertile subjects [23]. In addition, the balance between anti-Müllerian hormone (AMH), insulin-like peptide 3 (INSL3), and testosterone is critical for Sertoli- and Leydig-cell crosstalk and germ-cell differentiation [24]. AMH serves as a marker of Sertoli-cell activity, while INSL3 reflects Leydig-cell function [25]. Disruption by either GnRH agonist therapy (e.g., deslorelin), chronic inflammation, or oxidative injury, leads to impaired spermatogenesis and reversible testicular downregulation [26]. The observed hormonal shifts (increased AMH, reduced testosterone and INSL3) signify suppression of the steroidogenic machinery and maturation arrest of germ cells [27]. Moreover, mitochondrial dysfunction, particularly within spermatozoal mid-pieces, undermines ATP production required for motility [28]. Alterations in genes controlling steroidogenesis (StAR, CYP17A1), apoptosis (BAX/BCL-2 ratio), and antioxidative defense contribute to infertility phenotypes across species [29]. Peptide or stem-cell-derived factors that restore mitochondrial homeostasis and regulate these gene networks have been shown to rescue fertility in experimental models [30]. Advancements in reproductive biotechnology present both challenges and possibilities for solving infertility problems caused by various unexplainable factors.

In essence, animal infertility represents a dynamic interplay between endocrine control, gametogenic integrity, and systemic physiology. Hormonal imbalance initiates a cascade of cellular stressors, oxidative and inflammatory mediators amplify the damage, and molecular disruptions in AMH-INSL3-testosterone signaling perpetuate impaired gonadal function. Understanding this continuum provides the mechanistic foundation for emerging biologic interventions, particularly peptide-based therapies, that aim to restore homeostasis at the molecular, cellular, and endocrine levels.

Therapeutic Landscape

Conventional Therapies

Conventional management of infertility in companion animals and livestock remains centered on pharmacologic modulation of the reproductive axis and antimicrobial control of infection. However, more recently, cell-based regenerative interventions, including the use of mesenchymal and spermatogonial stem cells, have emerged as promising therapeutic modalities capable of repairing gonadal tissue, restoring endocrine balance, and enhancing gametogenic function through paracrine and immunomodulatory mechanisms.

Although the more traditional conventional approaches have contributed substantially to the understanding and partial restoration of reproductive function, their efficacy is frequently limited by incomplete physiological targeting, systemic side effects, or logistical barriers to implementation in field conditions. In contrast, the integration of regenerative cell therapies and bioactive peptide systems offers a transformative opportunity to move beyond symptomatic treatment toward molecular and tissue-level restoration, marking a pivotal evolution in veterinary reproductive medicine.

Hormonal Therapies

The primary pharmacologic strategy for reproductive dysfunction involves exogenous hormone administration aimed at restoring or synchronizing gonadal and cyclic activity. The most widely employed compounds include gonadotropin-releasing hormone (GnRH) analogs, human chorionic gonadotropin (hCG), progesterone, and prostaglandins, all of which target distinct stages of the hypothalamic-pituitary-gonadal (HPG) axis. Synthetic GnRH agonists such as deslorelin acetate or buserelin are used to induce ovulation, manage estrus suppression, or correct luteal insufficiency. In canines, deslorelin implants transiently downregulate pituitary gonadotropins through receptor desensitization, leading to reversible suppression of spermatogenesis or estrus. This effect has been harnessed in temporary contraception but has limited application for fertility restoration due to variable recovery times and inter-animal hormonal responses. Continuous administration may paradoxically inhibit gonadotropin secretion, leading to testicular atrophy and prolonged anestrus. hCG mimics LH activity, stimulating ovulation in females and testosterone production in males. hCG use in companion animals is common for induction of estrus and cryptorchidism treatment, but repetitive exposure can lead to antibody formation and diminishing efficacy. The luteotrophic effects also carry the risk of cystic endometrial hyperplasia and pyometra when used indiscriminately. Progesterone supplementation is utilized to maintain luteal support in cases of suspected deficiency; however, exogenous administration can suppress endogenous secretion, distort cycle timing, and induce insulin resistance. Conversely, prostaglandin $F_2\alpha$ analogs (e.g., cloprostenol) are used to induce luteolysis and synchronize estrus cycles in livestock breeding programs. Despite their success in herd-level reproductive management, hormonal synchronization protocols often fail to correct the underlying cellular or oxidative pathologies causing infertility.

Limitations of Conventional and Hormonal Therapies

Hormonal therapies primarily provide symptomatic control rather than regenerative correction. Systemic endocrine manipulation can produce adverse effects including metabolic derangement, mammary hyperplasia, and uterine pathology. Furthermore, inter-individual variability in receptor sensitivity and feedback inhibition renders therapeutic outcomes unpredictable. These drawbacks have driven the exploration of more targeted, biologically integrative modalities such as peptides and cell-based therapies.

Antimicrobial Therapy for Infectious Infertility

Infectious etiologies, particularly Brucella canis, Leptospira spp., and Mycoplasma spp., are major contributors to infertility in both dogs and livestock. Conventional treatment relies on broad-spectrum antibiotics and adjunctive supportive care to eliminate pathogens and limit tissue damage.

- Brucella canis: This zoonotic pathogen induces epididymitis, orchitis, and abortion in dogs, leading to persistent infertility. Combination antibiotic regimens (e.g., doxycycline with streptomycin or gentamicin) are standard, yet complete eradication remains challenging due to intracellular persistence and immune evasion. Chronic infection may result in irreversible testicular fibrosis and impaired sperm transport.
- Leptospirosis: Treated with penicillin derivatives followed by doxycycline, leptospiral infection can be cleared systemically, but reproductive sequelae such as placental damage or reduced fetal viability may persist.
- Mycoplasma and Ureaplasma infections: These pathogens colonize the urogenital tract, compromising sperm motility and oocyte fertilization. Macrolides or fluoroquinolones are prescribed, though recurrence is frequent in multi-animal breeding environments.

While antibiotic therapy remains essential for acute infection management, long-term reproductive restoration is limited, as antimicrobial agents do not reverse inflammatory fibrosis, oxidative injury, or endocrine suppression resulting from infection. The growing concern of antimicrobial resistance further underscores the need for alternative approaches that promote immune modulation and tissue regeneration rather than microbial suppression alone.

Stem Cell-Based Regenerative Therapies

Recent advances in regenerative biology have introduced stem cell therapy as a promising strategy for addressing the irreversible damage underlying infertility. Two primary categories of stem cells have been studied in veterinary reproductive medicine: spermatogonial stem cells (SSCs) and mesenchymal stem cells (MSCs).

- Spermatogonial Stem Cells (SSCs): SSCs represent the foundational germline population responsible for continuous spermatogenesis. Isolation and transplantation of autologous or donor SSCs have demonstrated the capacity to reestablish spermatogenic activity following gonadotoxic injury. Studies in canine and bovine models show partial restoration of sperm production and fertility following SSC transplantation into seminiferous tubules [31]. However, technical challenges, (e.g., low engraftment efficiency, risk of immune rejection, ethical considerations) regarding donor sources, limit their widespread application.
- Mesenchymal Stem Cells (MSCs): MSCs derived from bone marrow, adipose tissue, or amniotic membrane exhibit parac-

rine and immunomodulatory effects conducive to reproductive tissue repair. They secrete a broad spectrum of growth factors, cytokines, and peptides that enhance angiogenesis, reduce oxidative stress, and promote gonadal cell regeneration. Conditioned medium from canine amniotic-membrane-derived MSCs improved post-thaw sperm motility and viability, demonstrating that secretome-based therapy can rejuvenate gamete function without direct cell transplantation [32,33]. MSCs also show potential in ovarian rejuvenation by restoring follicular activity and attenuating apoptosis in granulosa cells. The regenerative benefit is attributed to paracrine peptide signaling that rebalances the local microenvironment, rather than cell replacement per se.

Limitations and Prospects: Although early data are compelling, stem-cell therapy remains largely experimental, constrained by high cost, procedural complexity, and limited long-term safety data. The transition from laboratory to clinical use requires standardized isolation protocols, defined dosing, and robust monitoring for tumorigenicity or ectopic differentiation. Nevertheless, the integration of MSC-derived peptide fractions or exosomes into fertility management represents a feasible bridge between traditional pharmacotherapy and full-scale regenerative medicine.

Translational Implications of Peptide Therapy

Mechanisms of Action

Therapeutic peptides act as high-specificity regulators across the hypothalamic-pituitary-gonadal (HPG) axis and within gonadal microenvironments. Four recurring mechanisms explain their fertility effects in animals. Certain peptides (e.g., GnRH analogs) entrain pituitary gonadotropin release and downstream steroidogenesis, restoring cycle timing or spermatogenic support when neuroendocrine tone is dysregulated. The slide on deslorelin in the canine model illustrates biomarker shifts used to index Sertoli-Leydig function (AMH, INSL3, testosterone) and demonstrates reversible testicular downregulation with subsequent hormonal re-equilibration (i.e., pharmacologic suppression followed by recovery once the agonist's effect wanes). Mito-peptide formulations are presented as targeting bioenergetics, with the therapeutic goal of improving ATP production and reducing ROS burden in gametes and steroidogenic cells, thereby supporting motility, oocyte competence, and luteal function. Organ-specific peptide complexes are described to promote vascular and stromal support in reproductive tissues, a precondition for follicular growth, luteal sufficiency, and germinal epithelium maintenance. Importantly, peptides can act directly on germline and somatic cells (Sertoli/Leydig, granulosa/theca) or indirectly through secretome-like signaling (e.g., MSC-derived peptide cargo), fostering seminiferous tubule integrity, epididymal maturation, and oocyte cytoplasmic/meiotic quality. Evidence from GnRH-analog models. In male dogs, deslorelin (a super-agonist) induces a predictable, dose-dependent pituitary desensitization that lowers LH/FSH, suppresses testicular steroidogenesis, and reduces INSL3, with a compensatory rise in AMH reflective of Sertoli-cell state during down-regulation34. This state is reversible after drug effect abates, enabling controlled endocrine modulation for research or clinical aims. The distinction between mitochondrial (mito-) and nano-peptide organotherapy formulations lies in their molecular targets and modes of action. Both are designed to enhance reproductive function, but mito-peptides primarily support cellular energy metabolism and oxidative balance, whereas nano-peptides are optimized for precise intracellular delivery and receptor-level modulation. Together, their actions converge on key reproductive pathways in steroidogenesis (e.g., StAR-mediated cholesterol transport and CYP19A1 aromatase activity), Sertoli-Leydig cell trophic support, and improved oocyte quality through enhanced redox regulation and membrane and mitochondrial stabilization.

Experimental and Clinical Evidence

A highlighted case study reports peptide-based organotherapy (Nano Organo Peptides, NOPs) in bitches with prior subfertility: a post-treatment litter of 9 pups in one subject versus typical 2-5 pups previously, with no adverse events noted. Another study shows that amniotic-membrane-derived MSC conditioned medium (AMSC-CM) significantly improved post-thaw sperm viability, motility, membrane integrity, and mitochondrial activity, effects attributed to antioxidant and growth-factor/peptide cargo [32-34]. Thus, peptide-centric approaches as translatable to production species; contemporary reports [35,36]. describe peptide-mediated restoration of ovarian cyclicity, improved luteal sufficiency, and enhanced embryo quality, consistent with the endocrine-mitochondrial-angiogenic mechanisms noted above.

Peptide Categories and Delivery

The materials differentiate Frozen Organo Peptide (FOP) from Frozen Organo Cryogenic (FOC). While both are ovine-derived, they differ in composition and intended clinical role. (Table 1) specifies peptide extracts (FOP) versus whole, live cell extracts (FOC), with molecular weights >700 kDa noted for both categories and distinct potency/time-course profiles (FOP: medium effect/short-to-medium term; FOC: faster onset/longer-term impact). A practical dosing grid is used for SC/IM administration guidance by organ/tissue target with body-weight stratification; for male/female infertility, the recommended volumes are ~1.0-3.0 mL per session, typically three times weekly for certain formulations (or "once/year" for others) using gauge sizes 18-27G depending on products.

Collectively, across preclinical and translational reports, peptide therapy is associated with up-regulation of steroidogenic and reproductive markers (StAR, CYP19A1, AMH, INSL3) supporting folliculogenesis and Sertoli-Leydig function as well as down-regulation of oxidative-stress/apoptosis mediators (NOX4, BAX), consistent with observed improvements in gamete integrity and embryo competence. Furthermore, the mitochondrial biogenesis crosstalk as evidenced in mechanistic models show peptide therapy invokes PGC-1α/NRF1 pathways, which may explain improved gamete energy metabolism and motility, aligning with the mito-peptide rationale and post-thaw sperm data in canines. In addition, peptide cargo, whether delivered directly or via MSC secretome, modulates somatic-germ cell crosstalk, stabilizing seminiferous architecture, promoting epididymal maturation, and improving oocyte cytoplasmic competence.

Table 1: Presents a comparative evaluation of therapies. Conventional infertility therapies, though foundational to current veterinary reproductive practice, are inherently palliative rather than curative, primarily targeting hormonal or infectious symptoms rather than the molecular and structural pathology of gonadal dysfunction. The limitations of these approaches highlight the need for biologically integrative modalities such as peptide therapy, which aim to combine the precision of molecular signaling modulation with the regenerative promise of stem-cell–derived mechanisms.

Therapy	Mechanism of Action	Advantages	Limitations
Hormonal (GnRH, hCG, Progesterone)	Modulates endocrine feedback, induces ovulation/spermatogenesis	Widely available, predictable hormonal responses	Systemic effects, limited regenerative potential
Antibiotic Therapy	Eradicates infectious pathogens	Essential for acute infections	Ineffective in chronic fibrosis, rising resistance
Stem Cell Therapy (SSCs, MSCs)	Regenerates gonadal tissue, restores paracrine signaling	Potential long-term recovery	Costly, experimental, requires further validation

European Wellness

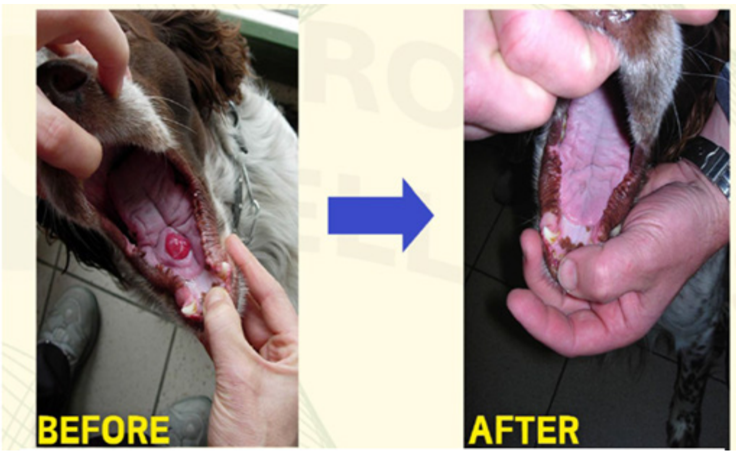

Figure 1: Pre- and Post Oral Malignancy treated with Autologous Active Specific Immunotherapy (AASI).

European Wellness has developed nano-delivery systems and lyophilized vesicles to enhance peptide stability, bioavailability, and tissue targeting, aiming to overcome proteolysis and achieve sustained pharmacodynamics in reproductive tissues. European Wellness has published several studies that have demonstrated efficacy, safety, and improved quality of life outcomes following peptide-based interventions. A case study published in the Open Access Journal of Biomedical Science reported significant mobility improvements in older and large-breed canines treated with peptide therapy, indicating enhanced joint flexibility and decreased inflammation after regular administration of a targeted peptide formulation [37]. Complementary findings from BioPep's clinical efficacy trials further showed that peptide treatments may also improve fertility outcomes in dogs, suggesting systemic physiological benefits beyond musculoskeletal repair [38]. Safety evaluations have confirmed that these peptide formulations are well tolerated. An American Journal of Biomedical Science & Research article detailed an organ-specific safety study demonstrating no adverse histopathological or biochemical changes following peptide administration, underscoring the clinical viability of long-term peptide use in veterinary practice [39]. Moreover, peptide therapy aligns with broader trends in regenerative veterinary medicine. As discussed in a review published in Animals, stem cell therapy has shown promise in mitigating aging-related joint diseases and degenerative conditions in companion animals. The European Wellness group highlighted the role of biologically active peptides and growth factors in supporting tissue repair, cellular rejuvenation, and reduced inflammatory signaling, positioning peptides as complementary agents within the regenerative toolkit in a recent review [40]. (Figure 1) illustrates the therapeutic response of a canine patient diagnosed with an oral malignancy prior to and following Autologous Active Specific Immunotherapy (AASI) developed by European Wellness. The left panel ("Before") depicts the presence of multiple erythematous, nodular lesions across the gingival and mucosal surfaces, consistent with neoplastic infiltration. The right panel ("After") demonstrates near-complete remission of visible lesions and restoration of normal mucosal architecture after a course of AASI® therapy. AASI represents a personalized immunotherapy approach; wherein autologous tumor antigens are harvested and reintroduced in a proprietary vaccine formulation to stimulate targeted immune recognition and cytotoxic clearance of malignant cells. In this case, the marked regression of oral lesions reflects effective tumor-specific immune activation without observable local or systemic adverse effects. Collectively, these findings support peptide-based therapeutics as a safe and effective approach for managing age-related decline, mobility impairments, and reproductive challenges in canines.

Knowledge Gaps, Research Priorities, and Future Directions

Endocrine, mitochondrial, and angiogenic mechanisms are conserved across mammals, supporting translation from canine models to livestock and informing hypotheses relevant to human andrology/gynecology. Advancement requires adherence to veterinary biologics standards (identity, purity, potency, safety), with validated release assays (e.g., peptide content, endotoxin), demonstrated batch consistency, and stability commensurate with field deployment. Key hurdles include peptide heterogeneity, protease susceptibility, endotoxin removal, and cost-effective scale-up. The work from European Wellness underscores the platform movement toward cryogenic preservation and nano-packaging to meet these demands Within the clinical materials summarized, no adverse reactions were reported in the canine case series; nonetheless, rigorous dose-escalation studies, immunogenicity monitoring, and long-term reproductive outcomes (offspring viability, absence of transgenerational effects) remain essential. Ethical use centers on animal welfare benefits (reducing chronic hormonal exposure and antibiotic overuse), responsible breeding practices, and transparent owner consent. Importantly, this is consistent with a One-Health approach integrating animal, human, and environmental health priorities.

The convergence of artificial intelligence (AI) and precision peptide therapeutics represents a promising next frontier in veterinary reproductive medicine. AI-enabled platforms can analyze hormonal, genetic, and behavioral data to predict estrous cycles, sperm quality, or ovarian responsiveness, allowing for dynamic adjustment of peptide dosing schedules. Machine learning algorithms integrated with wearable sensors and real-time biomarkers (e.g., progesterone, temperature, activity) could facilitate individualized fertility management protocols-optimizing timing of insemination, ovulation induction, or regenerative peptide application. Predictive analytics may also refine the identification of candidates most likely to benefit from specific peptide subclasses (e.g., mitochondrial vs. angiogenic peptides), enhancing therapeutic precision across species.

The mechanistic overlap between peptide signaling and stem-cell secretome biology provides a logical basis for combination strategies. Stem-cell-derived secretomes contain extracellular vesicles and peptides that regulate oxidative stress, angiogenesis, and immune homeostasis within reproductive tissues. By integrating synthetic or organ-derived peptides with MSC secretome fractions, clinicians can potentially amplify paracrine regenerative effects while mitigating the logistical and immunologic challenges of live-cell transplantation. This combined approach may yield synergistic improvements in gametogenic regeneration, follicular development, and endometrial receptivity, particularly in refractory infertility cases where hormonal or antibiotic therapies have failed.

Although early animal studies demonstrate encouraging results, the evidence base remains fragmented and largely preclinical. Multicentric randomized controlled trials (RCTs) across diverse breeds and livestock species are necessary to validate efficacy, reproducibility, and safety under field conditions. Integration of multi-omics platforms (e.g., proteomics, metabolomics, and transcriptomics) will be crucial to elucidate peptide-induced regulatory networks governing steroidogenesis, mitochondrial bioenergetics, and gametogenic resilience. Such omics-level mapping will enable the construction of predictive biomarkers for response stratification and therapeutic optimization. Additionally, long-term reproductive outcomes (offspring health, epigenetic stability, multigenerational safety) require systematic evaluation under Good Clinical Practice (GCP)-aligned frameworks.

The veterinary application of peptide biologics necessitates scalable, reproducible production methods with tight control over peptide integrity, purity, and immunogenicity. Innovations in lyophilization, nanoencapsulation, and endotoxin removal technologies will improve product stability and safety for global deployment. Parallel progress in regulatory science, i.e., harmonizing peptide classification within veterinary biologics frameworks, is essential to support commercialization and international distribution. Partnerships between academia, industry, and regulatory bodies could expedite the transition of validated peptide therapies from investigational use to standardized veterinary practice. Notwithstanding, peptide therapy represents a transformative, precision-based strategy for restoring fertility through targeted endocrine, mitochondrial, and paracrine modulation. Unlike conventional hormonal or antimicrobial approaches, peptides act at the molecular level to re-establish physiological homeostasis within gonadal and reproductive microenvironments. The growing corpus of experimental and clinical evidence, from canine trials demonstrating post-therapy litter normalization to livestock studies confirming restored ovarian cyclicity, highlights broad therapeutic promise. As understanding of peptide signaling networks deepens through AI integration, secretome synergy, and omics-level mapping, peptide therapeutics stand poised to redefine reproductive biotechnology. Their ability to harmonize cellular energy metabolism, hormonal equilibrium, and tissue regeneration offers a sustainable, species-translatable solution for infertility management across the veterinary spectrum. Embracing this convergence of molecular therapeutics and digital intelligence will not only enhance breeding efficiency and animal welfare but also advance One Health goals, linking veterinary and human reproductive science under a shared regenerative paradigm.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Wyse J, Latif S, Gurusinghe S, McCormick J, Weston LA, et al (2022) Phytoestrogens: A Review of Their Impacts on Reproductive Physiology and Other Effects upon Grazing Livestock. Anim Open Access J MDPI 12(19): 2709.
2. Roos Pichenot J and Zakošek Pipan M (2025) “My Bitch Is Empty!” an Overview of the Preconceptional Causes of Infertility in Dogs. Vet Sci 12(7): 663.
3. Brocket JJ, Fishbourne E, Smith RF and Higgins HM (2021) Motivations and Barriers for Veterinarians When Facilitating Fertility Management on UK Dairy Farms. Front Vet Sci 8: 709336.
4. Morawietz J, Körber H, Packeiser EM, Beineke A and Goericke-Pesch S. Insights into Canine Infertility: Apoptosis in Chronic Asymptomatic Orchitis. Int J Mol Sci 24(7): 6083.
5. Shanmugam D, Espinosa M, Gassen J, Lamsweerde AV, Pearson JT, et al (2023) A multi-site study of the relationship between photoperiod and ovulation rate using Natural Cycles data. Sci Rep 13(1): 8379.
6. Axnér E (2023) A Pilot Study to Evaluate the Potential of Melatonin Implants to Control Cyclicity in the Bitch. Anim Open Access J MDPI 13(8): 1316.
7. Gavrilovic BB, Andersson K and Linde Forsberg C (2008) Reproductive patterns in the domestic dog--a retrospective study of the Drever breed. Theriogenology 70(5): 783-794.
8. Buijtels JJCWM, de Gier J, Kooistra HS, Grinwis GCM, Naan EC, et al (2012) Disorders of sexual development and associated changes in the pituitary-gonadal axis in dogs. Theriogenology 78(7): 1618-1626.
9. Abedal-Majed MA and Cupp AS (2019) Livestock animals to study infertility in women. Anim Front Rev Mag Anim Agric 9(3): 28-33.
10. Hatırnaz Ş, Hatırnaz ES, Ellibeş Kaya A, Hatırnaz K, Çalışkan CS, et al (2022) Oocyte maturation abnormalities - A systematic review of the evidence and mechanisms in a rare but difficult to manage fertility pheneomina. Turk J Obstet Gynecol 19(1): 60-80.
11. Aponte PM, Gutierrez Reinoso MA and Garcia Herreros M (2023) Bridging the Gap: Animal Models in Next-Generation Reproductive Technologies for Male Fertility Preservation. Life Basel Switz 14(1): 17.
12. Fontbonne A (2023) Causes of pregnancy arrest in the canine species. Reprod Domest Anim Zuchthyg 58 Suppl 2: 72-83.
13. Schwartz DW, Kvernum J, Macias N, Waqas MS and Ciccarelli M (2025) Incorporating Morphological Evaluations into Breeding Soundness Examinations for Female Dogs. Anim Open Access J MDPI 15(14): 2045.
14. Wilborn RR and Maxwell HS (2012) Clinical approaches to infertility in the bitch. Vet Clin North Am Small Anim Pract 42(3): 457-468.
15. Domrazek K, Konieczny P, Majka M, Czopowicz M and Jurka P (2024) The Impact of Microorganisms on Canine Semen Quality. Anim Open Access J MDPI 14(9): 1267.
16. McKnight L and Ibeagha Awemu E (2019) Modeling of livestock systems to enhance efficiency. Anim Front Rev Mag Anim Agric 9(2): 3-5.
17. Ahmed RH, Schmidtmann C, Mugambe J and Thaller G (2023) Effects of the Breeding Strategy Beef-on-Dairy at Animal, Farm and Sector Levels. Anim Open Access J MDPI 13(13): 2182.
18. Moorey SE and Biase FH (2020) Beef heifer fertility: importance of management practices and technological advancements. J Anim Sci Biotechnol 11: 97.
19. Han Y, Zhang Y, Li H, Ma Z and Wang Y (2025) Peptide Drug: Design and Clinical Applications. MedComm 6(8): e70287.
20. Gualtieri R, Kalthur G, Barbato V, Longobardi S, Rella FD, et al (2021) Sperm Oxidative Stress during In Vitro Manipulation and Its Effects on Sperm Function and Embryo Development. Antioxid Basel Switz 10(7): 1025.
21. Pintus E and Ros-Santaella JL (2021) Impact of Oxidative Stress on Male Reproduction in Domestic and Wild Animals. Antioxid Basel Switz 10(7): 1154.
22. Sasaki H, Hamatani T, Kamijo S, Iwai M, Kobanawa M, et al (2019) Impact of Oxidative Stress on Age-Associated Decline in Oocyte Developmental Competence. Front Endocrinol 10: 811.
23. Wang Y, Fu X and Li H (2025) Mechanisms of oxidative stress-induced sperm dysfunction. Front Endocrinol 16: 1520835.
24. Balogh O, Somoskői B, Kollár E, Kowalewski MP, Gram A, et al (2021) Anti-Müllerian hormone, testosterone, and insulin-like peptide 3 as biomarkers of Sertoli and Leydig cell function during deslorelin-induced testicular downregulation in the dog. Theriogenology 175: 100-110.
25. Edelsztein NY, Grinspon RP, Schteingart HF and Rey RA (2016) Anti-Müllerian hormone as a marker of steroid and gonadotropin action in the testis of children and adolescents with disorders of the gonadal axis. Int J Pediatr Endocrinol 2016: 20.
26. Eşki F, Çetin N, Uslu S, Uslu BA, Şendağ S, et al (2019) Effects of long-term release GnRH agonist “deslorelin” on testicular HSP expression, accessory sex glands and testicular functions in adult male rats. Theriogenology 134: 104-111.
27. Silva MSB and Giacobini P (2021) New insights into anti-Müllerian hormone role in the hypothalamic-pituitary-gonadal axis and neuroendocrine development. Cell Mol Life Sci CMLS 78(1): 1-16.
28. Vahedi Raad M, Firouzabadi AM, Tofighi Niaki M, Henkel R and Fesahat F (2024) The impact of mitochondrial impairments on sperm function and male fertility: a systematic review. Reprod Biol Endocrinol RBE 22(1): 83.
29. Wen Y, Cai J, Zhang H, Li Y, Yu M, et al (2024) The Potential Mechanisms Involved in the Disruption of Spermatogenesis in Mice by Nanoplastics and Microplastics. Biomedicines 12(8): 1714.
30. Wu JX, Xia T, She LP, Lin S and Luo XM (2022) Stem Cell Therapies for Human Infertility: Advantages and Challenges. Cell Transplant 31: 9636897221083252.
31. Zhao X, Wan W, Zhang X, Wu Z and Yang H (2021) Spermatogonial Stem Cell Transplantation in Large Animals. Anim Open Access J MDPI 11(4): 918.

32. Mahiddine FY, You I, Park H and Kim MJ (2022) Commensal Lactobacilli Enhance Sperm Qualitative Parameters in Dogs. Front Vet Sci 9: 888023.

33. Mahiddine FY, Kim JW, Qamar AY, Ra JC, Kim SH, et al (2020) Conditioned Medium from Canine Amniotic Membrane-Derived Mesenchymal Stem Cells Improved Dog Sperm Post-Thaw Quality-Related Parameters. Anim Open Access J MDPI 10(10): 1899.

34. Spruijt A, Kooistra H, Oei C, Vinke C, Schaefers-Okkens A, et al (2023) The function of the pituitary-testicular axis in dogs prior to and following surgical or chemical castration with the GnRH-agonist deslorelin. Reprod Domest Anim Zuchthyg 58(1): 97-108.

35. Hesselager MO, Codrea MC, Sun Z, Deutsch EW, Bennike TB, et al (2016) The Pig PeptideAtlas: A resource for systems biology in animal production and biomedicine. Proteomics 16(4): 634-644.

36. Ning Z, Zhang X, Mayne J and Figeys D (2016) Peptide-Centric Approaches Provide an Alternative Perspective To Re-Examine Quantitative Proteomic Data. Anal Chem 88(4): 1973-1978.

37. Wellington A, Lakey, Jonathan RT, Williams A, et al (2022) Peptide Therapy Improves Mobility in Older and Large Breed Canines: A Case Study. Biomed Sci 4(4).

38. Wellington A, Lakey, Jonathan RT, Williams A, et al. (2022) Case Study: Efficacy Trial for Peptide Treatment for Fertility. Biomed Sci 4(4).

39. Lakey, Jonathan RT, Cox DCT, Whaley D, et al (2022) ORGAN-Specific Peptide Canine Safety Study. Am J Biomed Sci Res 16(3).

40. Wang Y, Alexander M, Scott T, Cox DCT, Wellington A, et al (2023) Stem Cell Therapy for Aging Related Diseases and Joint Diseases in Companion Animals. Anim Open Access J MDPI 13(15): 2457.