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

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Abstract

Reproductive and regenerative health remain pivotal determinants of performance, welfare, and economic sustainability in equine medicine. Despite advances in endocrine modulation and assisted reproductive technologies, infertility, chronic metabolic decline, and refractory wound healing persist as major clinical challenges. Conventional hormonal and antimicrobial therapies address functional symptoms but fail to reverse the oxidative, mitochondrial, and inflammatory dysfunction that underlie these conditions.

This review synthesizes emerging evidence for peptide- and organ-based biologics as next-generation tools in equine regenerative and reproductive medicine. Peptides, derived synthetically, from organ extracts, or as stem-cell secretome fractions, act as highly specific molecular regulators of endocrine balance, mitochondrial bioenergetics, and tissue homeostasis. Mechanistically, they modulate key reproductive and regenerative pathways including *StAR*-mediated steroidogenesis, *PGC-1α/NRF1*-driven mitochondrial biogenesis, and angiogenic remodeling of reproductive and stromal microenvironments.

Clinical translation of these principles is illustrated by four equine case studies demonstrating systemic metabolic recovery and localized wound regeneration following administration of precursor stem-cell (PSC), frozen organo-cryogenic (FOC), mito-peptide (MO), and nano-organo-peptide (NOP) formulations. Across cases, therapy induced measurable improvements in body condition, granulation resolution, and epithelial restitution within 8–12 weeks, without adverse reactions.

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These findings support peptide-based therapeutics as safe, biologically coherent interventions capable of restoring endocrine–mitochondrial–angiogenic equilibrium.

Integration of omics-based profiling, artificial intelligence driven estrous and performance prediction, and precision peptide delivery is poised to transform equine reproductive and regenerative management. By harmonizing cellular energetics, hormonal signaling, and tissue repair, peptide therapeutics represent a scalable, welfare-oriented, and One-Health-aligned paradigm for optimizing fertility and recovery in the modern horse.

Keyword
Peptide Therapy; Animal reproductive health; Mechanisms; Translational perspectives.

Introduction
Reproductive health in the horse remains a cornerstone of equine veterinary medicine, breeding management, and performance optimization [1]. Reproductive health underpins both the welfare of individual animals and the genetic and economic sustainability of the global equine industry, spanning Thoroughbred and Standardbred racing to sport, pleasure, and working horses [2]. Infertility or subfertility in mares and stallions carries substantial consequences. The diminished conception rates, extended foaling intervals, early embryonic loss, and reduced foal crop efficiency affect not only breeding success but also herd turnover, genetic progress, and the commercial value of stallions and broodmares [3,4].

In the mare, the cyclic nature of ovulation, combined with a relatively low conception rate per estrous cycle (~60 % in optimal conditions), renders reproductive efficiency particularly vulnerable to disruptions [5,6]. Failure to conceive within the breeding season leads to significant economic loss, given the seasonal breeding constraints imposed by photoperiodicity and performance scheduling. In stallions, alterations in spermatogenesis, semen quality, or libido translate directly into reduced conception rates per cover or per collection, compromising the commercial viability of breeding operations. Epidemiologic data suggest that reproductive inefficiency affects approximately 10–15 % of breeding mares and 5–10 % of active stallions annually in managed programs [7]. This estimate rises under conditions of stress, suboptimal nutrition, infectious exposure, or advancing age.

Etiologic complexity characterizes equine infertility [8]. Dysfunctions along the hypothalamic-pituitary-gonadal (HPG) axis, anovulatory hemorrhagic follicles, luteal insufficiency, uterine endometritis, chromosomal anomalies, or spermatozoal defects can each compromise fertility potential [9,10]. Infectious and post-inflammatory uterine pathologies. Most notably are pathologies caused by Streptococcus equi subsp. zooepidemicus, Escherichia coli, and Pseudomonas aeruginosa [11,12]. Infection by these microorganisms remain leading causes of subfertility in mares, while testicular degeneration, epididymal blockage, or oxidative injury contribute significantly in stallions. At the molecular level, excessive reactive oxygen species (ROS) generation in gametes and reproductive tissues leads to lipid peroxidation, DNA fragmentation, and mitochondrial dysfunction, compromising oocyte competence and sperm motility [13,14]. These oxidative-inflammatory pathways are now recognized as pivotal molecular mediators of equine infertility.

Traditionally, equine reproductive management has relied on hormonal manipulation, through exogenous gonadotropins, prostaglandins, progesterone, and GnRH analogues, to synchronize estrous cycles or stimulate ovulation and spermatogenesis [15]. While these strategies improve reproductive control, they are largely symptomatic and fail to restore underlying cellular or oxidative homeostasis. Similarly, antimicrobial therapy for infectious infertility, though indispensable, cannot reverse fibrotic or degenerative damage to endometrial or testicular tissue [16,17]. Consequently, there is growing scientific interest in peptide-based regenerative therapeutics as a next-generation approach to equine reproductive health. Peptide therapies employ bioactive short amino-acid chains that modulate specific molecular and cellular pathways, including endocrine signaling, mitochondrial biogenesis, oxidative stress response, and angiogenesis [18,19]. Unlike conventional hormone replacement, peptides offer high target specificity and act at multiple regulatory levels, from hypothalamic and pituitary modulation to direct gonadal support. Emerging data suggest that peptide formulations can enhance follicular growth, oocyte competence, luteal sufficiency, and spermatogenic integrity by stabilizing oxidative balance and restoring mitochondrial ATP production [20]. This review aims to provide a comprehensive synthesis of peptide-based strategies in equine reproductive medicine, examining their potential to restore fertility through molecular, endocrine, and cellular mechanisms. Specifically, it will:

1. Characterize the major causes and pathophysiology of infertility and subfertility in mares and stallions, emphasizing oxidative, endocrine, and inflammatory contributors;
2. Map the therapeutic landscape of conventional versus emerging peptide interventions, evaluating mechanistic underpinnings, pre-clinical and translational evidence, delivery technologies, and comparative outcomes;
3. Assess the economic and welfare implications of peptide therapeutics within equine breeding programs; and
4. Identify knowledge gaps and research priorities, including omics-based biomarker discovery, AI-driven estrous prediction, and peptide-secretome synergy for reproductive regeneration.

By integrating molecular endocrinology, bioenergetics, and regenerative biology, this equine-focused review positions peptide therapy as a transformative precision-medicine tool for advancing fertility management, improving reproductive outcomes.

Pathophysiology of Equine Infertility

Reproductive inefficiency in horses is inherently multifactorial, resulting from a complex interaction of endocrine, inflammatory, infectious, and environmental factors that affect gametogenesis, hormone signaling, and the functional integrity of reproductive organs [7,13,14,21]. Mares are seasonally polyestrous, with reproductive activity governed by photoperiod and melatonin-mediated modulation of the HPG axis [22]. Stallions, though less seasonally constrained, exhibit reduced sperm output and libido during shorter daylight periods, highlighting the influence of neuroendocrine seasonality on both sexes. Infertility can manifest through anovulatory cycles, luteal insufficiency, chronic endometritis, early embryonic loss, or defective spermatogenesis [22,23]. These conditions often share overlapping pathomechanisms involving oxidative stress, endocrine dysregulation, and local tissue inflammation. The outcome is reduced conception rate, delayed foaling intervals, or failure to achieve pregnancy despite

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repeated coverings or artificial insemination.

Etiologic spectrum of equine infertility

Hormonal imbalance represents one of the primary contributors to equine infertility. In mares, disrupted pulsatility of GnRH from the hypothalamus alters secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), impeding folliculogenesis and ovulation [25,26]. Seasonal anestrus, transitional irregularities, and luteal-phase insufficiency are frequently linked to suboptimal hypothalamic stimulation or inadequate luteotropic support [22,27]. Elevated prostaglandin $F_2\alpha$ prematurely regresses the corpus luteum, leading to shortened cycles and failed implantation. In stallions, hypothalamic or pituitary dysfunction can depress LH-driven Leydig cell activity, resulting in reduced testosterone and impaired spermatogenesis [28,29]. Aging stallions often exhibit blunted endocrine responsiveness, with decreased Leydig cell number and function, altered aromatase activity, and reduced androgen receptor expression, collectively diminishing sperm quality and libido.

Uterine and accessory gland infections are the leading cause of subfertility in mares. Persistent mating-induced endometritis (PMIE), characterized by failure to clear post-breeding inflammation, results in prolonged uterine fluid accumulation, oxidative damage to endometrial epithelium, and reduced embryo survival [11]. Common pathogens include Streptococcus equi subsp. zooepidemicus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. These bacteria disrupt mucociliary clearance, provoke cytokine release, and trigger fibrotic remodeling of the endometrium [30]. Chronic inflammation compromises vascular perfusion and glandular function, leading to the so-called “endometrosis” phenotype. In stallions, epididymitis, seminal vesiculitis, and orchitis from infectious agents (Taylorella equigenitalis, Klebsiella spp., E. coli) can impair sperm maturation and storage [6,14,31]. Subclinical inflammation alters seminal plasma composition, increases reactive oxygen species (ROS), and damages sperm membranes and DNA.

Genetic or congenital defects, though less prevalent than acquired causes, can profoundly influence fertility. In mares, chromosomal abnormalities such as XO (Turner’s syndrome) and mosaicism result in ovarian dysgenesis and anestrus [32]. Endometrial cysts, uterine adhesions, and cervical incompetence further hinder conception and embryonic retention [33]. In stallions, testicular hypoplasia, cryptorchidism, and segmental aplasia of the Wolffian ducts lead to oligospermia or azoospermia [34]. Structural lesions such as accessory gland obstruction or ampullary stasis are common findings in older breeding stallions and can be reversible with appropriate therapy if detected early.

Systemic endocrine disorders profoundly affect equine fertility. Pituitary pars intermedia dysfunction (PPID), insulin dysregulation, and metabolic syndrome, especially in easy-keeping breeds, interfere with ovarian steroidogenesis and uterine receptivity [35,36]. Hyperinsulinemia alters granulosa cell function and may delay follicular development, while PPID-induced cortisol excess disrupts the HPG axis via negative feedback inhibition [37,38]. In stallions, metabolic stress and systemic inflammation compromise testosterone biosynthesis and impair Sertoli–Leydig communication [39]. Nutritional imbalances, particularly deficiencies in selenium, vitamin E, zinc, and omega-3 fatty acids, exacerbate oxidative stress and reduce gamete quality [40].

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Classification by functional level

As in other species, equine infertility can be classified according to the level of dysfunction along the reproductive axis. Pre-Gonadal (Pre-Testicular/Ovarian) Infertility stems from hypothalamic or pituitary disturbances leading to inadequate gonadotropin secretion. Stress, systemic disease, and chronic pain are potent inhibitors of GnRH release. Seasonally anestrous mares exemplify physiological pre-gonadal suppression. Gonadal Infertility, in mares, ovarian dysfunction due to persistent anovulatory follicles, luteal insufficiency, or granulosa-theca cell tumors directly compromises ovulation and cyclicity. In stallions, primary testicular degeneration, orchitis, or toxin exposure (e.g., fescue endophyte alkaloids, anabolic agents) causes reduced sperm output, abnormal morphology, and decreased motility. In contrast post-Gonadal Infertility, includes disorders of gamete transport, storage, or deposition. In mares, cervical or uterine pathology may prevent sperm passage or embryo fixation. In stallions, ejaculatory dysfunction, ductal blockage, or defective semen liquefaction can impair fertility despite normal spermatogenesis.

Molecular and cellular disruptions

At the cellular level, oxidative and inflammatory stress play central roles in equine reproductive pathology. Excessive ROS within spermatozoa and oocytes damage lipid membranes, mitochondrial DNA, and nuclear chromatin, leading to decreased sperm motility, reduced oocyte competence, and increased embryonic mortality. Mares with recurrent endometritis display reduced antioxidant enzyme activity, particularly superoxide dismutase (SOD) and glutathione peroxidase, within uterine secretions, correlating with poor pregnancy rates. Similarly, in stallions, ROS overproduction in seminal plasma correlates with high sperm DNA fragmentation index (DFI) and reduced ATP content in midpiece mitochondria. Mitochondrial dysfunction underlies much of the age-related decline in stallion fertility, impairing flagellar motility and acrosomal integrity. Dysregulation of key genes governing steroidogenesis (StAR, CYP17A1, CYP19A1), apoptosis (BAX/BCL2), and oxidative defense (SOD2, GPX4) has been documented in sub-fertile equine reproductive tissues.

The intricate hormonal interplay among anti-Müllerian hormone (AMH), insulin-like peptide 3 (INSL3), and testosterone mirrors the regulatory triad observed in other mammals [41]. In stallions, reduced INSL3 and testosterone levels reflect Leydig-cell dysfunction, while elevated AMH indicates Sertoli-cell immaturity or inhibition [42]. Such molecular markers provide diagnostic windows into testicular health and potential targets for peptide-mediated restoration.

Equine infertility thus represents a continuum of physiological, molecular, and environmental disruptions. From hypothalamic dysregulation and oxidative stress to inflammatory fibrosis and metabolic imbalance, the equine reproductive system responds dynamically to stressors that compromise gamete integrity and endocrine equilibrium [43]. The next-generation approach, focused on peptide-based therapeutics, aims to modulate these intersecting pathways at their molecular roots: restoring redox balance, stabilizing mitochondrial function, and reestablishing gonadal homeostasis to enhance fertility outcomes in both mares and stallions.

Therapeutic Landscape in Equine Reproductive Medicine

Conventional management of infertility in horses has traditionally centered on endocrine modulation,

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antimicrobial therapy, and assisted reproductive technologies (ARTs) such as artificial insemination, embryo transfer (ET), intracytoplasmic sperm injection (ICSI), and cryopreservation. These methods have revolutionized breeding efficiency, yet they remain largely symptomatic or compensatory, addressing reproductive manifestations rather than reversing the underlying molecular and cellular dysfunctions that impair fertility. Increasingly, veterinarians and reproductive physiologists recognize that subfertility in equines often stems from chronic oxidative stress, mitochondrial dysfunction, or low-grade inflammatory states that conventional hormone or antibiotic protocols cannot fully resolve. Accordingly, regenerative and peptide-based interventions are gaining traction as complementary or alternative strategies aimed at restoring physiological equilibrium and cellular integrity within reproductive tissues.

The cornerstone of equine reproductive management remains pharmacologic regulation of the estrous cycle and stimulation of ovulation or spermatogenesis. Exogenous administration of GnRH analogues (e.g., deslorelin acetate, buserelin) or human chorionic gonadotropin (hCG) is used to induce ovulation once a dominant follicle (>35 mm) is detected ultrasonographically. These compounds mimic the natural LH surge, promoting follicular rupture within 36–42 hours and enabling precise timing for insemination. Deslorelin implants, in particular, have shown consistent efficacy in mares with irregular cycles, though repeated use can lead to pituitary desensitization and prolonged inter-estrous intervals. Progestin supplementation (e.g., altrenogest) is employed to suppress estrus in performance mares or to support luteal function in early pregnancy. However, chronic or inappropriate administration may disrupt endogenous luteal responsiveness and induce insulin resistance or uterine pathology. Prostaglandin $F_2\alpha$ analogues (e.g., cloprostenol) remain widely used to induce luteolysis and synchronize estrus, particularly in breeding programs requiring coordinated ovulation schedules. While these hormonal protocols enable predictable cycle control, they do not address subclinical uterine inflammation, oxidative imbalance, or follicular senescence, which underlie many cases of unexplained subfertility in mares.

Therapeutic strategies for male infertility often involve stimulating testicular steroidogenesis and spermatogenesis. Exogenous hCG and GnRH analogues are used to increase testosterone secretion and improve libido in stallions with suppressed pituitary output or age-related hypogonadism. However, chronic stimulation risks receptor downregulation and variable long-term outcomes. Adjunctive administration of anabolic agents (e.g., nandrolone) or aromatase inhibitors has been explored experimentally but carries the risk of negative feedback suppression of gonadotropins. Thus, hormonal therapies in stallions must be individualized, balancing transient benefits with potential for testicular desensitization or spermatogenic exhaustion. Despite their indispensable role in reproductive management, traditional hormonal interventions largely offer functional modulation rather than regenerative correction. They do not repair cellular or mitochondrial damage within oocytes, spermatozoa, or endometrial tissue. Prolonged or indiscriminate use can induce metabolic disturbances or alter feedback sensitivity of the HPG axis. Moreover, endocrine responsiveness in mares and stallions declines with age, limiting the efficacy of hormonal protocols in older breeding stock. These limitations highlight the need for therapies that restore reproductive physiology at the molecular level, specifically through antioxidant, angiogenic, and mitochondrial pathways modulated by peptide or stem-cell–derived biologics.

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Antimicrobial Therapy for Infectious and Post-inflammatory Infertility

Infectious endometritis remains one of the most common and economically significant causes of infertility in mares. Conventional treatment protocols combine uterine lavage, intrauterine antibiotic infusion, and systemic antimicrobial therapy, guided by culture and sensitivity testing.

Uterine infection in mares

- Streptococcus equi subsp. zooepidemicus and E. coli infections are managed using penicillin, ceftiofur, or gentamicin-based regimens, often in combination with uterine lavage using isotonic saline or dilute povidone-iodine solutions. PMIE is addressed with oxytocin or prostaglandin $F_2\alpha$ analogues to promote uterine clearance. Adjunctive therapies include mucolytic agents, autologous plasma infusions, or immunomodulators to enhance endometrial defense.

While antimicrobial therapy effectively resolves acute infections, chronic endometrial fibrosis, glandular degeneration, and oxidative damage persist even after bacterial eradication, continuing to impair fertility.

- Seminal Tract Infections in Stallions: Bacterial epididymitis and seminal vesiculitis are treated with prolonged systemic antibiotic courses (e.g., trimethoprim-sulfonamide, fluoroquinolones), combined with sexual rest and anti-inflammatory therapy [44]. Despite clinical resolution, sperm DNA damage and oxidative membrane injury may persist, contributing to subfertility. Consequently, there is increasing recognition that antimicrobial monotherapy must be complemented by regenerative and antioxidant approaches.

Regenerative and Stem Cell–Based Therapies

Recent advances in regenerative medicine have introduced mesenchymal stem cells (MSCs) and their secretomes as promising therapeutic tools in equine infertility. Intrauterine infusion of autologous or allogeneic MSCs has shown potential to restore endometrial architecture, reduce fibrosis, and enhance angiogenesis in mares with chronic degenerative endometritis or endometrosis. These effects are largely mediated through paracrine secretion of bioactive peptides, cytokines, and growth factors, rather than direct cellular engraftment. Experimental studies report increased uterine vascularization, glandular density, and pregnancy rates post-treatment. In stallions with testicular degeneration or idiopathic subfertility, MSC transplantation or conditioned medium infusion has been observed to enhance spermatogenic cell regeneration, improve semen motility, and decrease oxidative biomarkers. Amniotic-derived MSCs (AM-MSCs), in particular, secrete peptide-rich secretomes that upregulate antioxidant enzymes and mitochondrial function in spermatozoa. These findings suggest that stem cell–derived peptide fractions could represent a practical and less invasive alternative to direct cell transplantation.

Peptide-based therapeutics: A regenerative bridge

Peptide therapy occupies a unique niche between conventional pharmacologic management and stem cell therapy. Bioactive peptides, either synthetic, organ-derived, or MSC-secretome–derived, modulate cellular homeostasis and endocrine balance without the logistical and immunologic challenges of live-cell

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administration. In equine models, organ-specific and mitochondrial-targeted peptides have demonstrated enhanced ovarian folliculogenesis and improved luteal sufficiency in sub-fertile mares, restoration of sperm motility, mitochondrial activity, and membrane integrity in stallions, and downregulation of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and upregulation of antioxidant enzymes (SOD, GPx), as well as improved angiogenesis and tissue perfusion within reproductive organs. Notably, experimental formulations derived from amniotic MSC secretomes (rich in peptide and growth factor cargo) significantly improve post-thaw sperm motility and mitochondrial respiration, supporting the translational potential of peptide-based semen extenders and ovarian support agents. Peptide complexes such as Frozen Organo Peptides (FOP) and Mito-peptides developed by translational research groups offer sustained delivery and organotropism via nano-encapsulation, ensuring stability against enzymatic degradation and targeted delivery to gonadal tissues.

Therapy	Mechanism of Action	Advantages	Limitations
Hormonal (GnRH, hCG, Progestins, $PGF_2\alpha$)	Modulates endocrine cycles and ovulation timing	Predictable, field-proven	Lacks regenerative repair, may cause metabolic derangement
Antimicrobial Therapy	Eliminates bacterial pathogens	Essential for acute infection	Ineffective in chronic fibrosis; resistance concerns
Stem Cell Therapy (MSCs, SSCs)	Regenerates tissue via paracrine and immunomodulatory effects	Restores structure and function	High cost; technical complexity
Peptide Therapy (Organ- or Mito-peptides)	Regulates oxidative stress, angiogenesis, mitochondrial activity	Targeted, minimally invasive, regenerative	Limited large-scale trials; dosing optimization ongoing

Table 1: Comparative Evaluation of Reproductive.

Traditional equine infertility treatments, while indispensable, primarily correct endocrine timing or clear infection, without restoring molecular homeostasis [8]. In contrast, peptide therapeutics offer precision modulation of reproductive physiology, acting through cellular bioenergetics, oxidative balance, and endocrine feedback restoration. By bridging molecular biology with clinical reproductive management, peptide-based interventions represent a paradigm shift toward regenerative fertility restoration in mares and stallions, complementing existing ART frameworks and advancing One-Health-aligned veterinary therapeutics.

Translational Implications of Peptide Therapy in Equine Reproduction

Peptide-based therapeutics in equine reproduction act as precision biologics. Peptides are short amino-acid sequences that regulate specific molecular, endocrine, and cellular pathways governing fertility. Their mechanisms of action span from hypothalamic–pituitary modulation to gonadal mitochondrial support, enabling multi-level restoration of reproductive homeostasis.

Four principal mechanistic domains characterize their role in equine fertility restoration:

1. **Endocrine Modulation (HPG Axis Rebalancing):** Certain peptide analogs, notably GnRH mimetics

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and modulators, fine-tune the pulsatile release of LH and FSH from the pituitary, restoring hormonal synchrony critical for ovulation and spermatogenesis [45]. In mares, peptide therapy has shown potential to normalize luteal function and enhance progesterone output during the diestrus phase, thereby improving embryo retention and reducing early pregnancy loss [46]. In stallions, peptide-regulated LH release enhances Leydig cell steroidogenesis and INSL3 expression, reinforcing testosterone-driven spermatogenic maintenance [47].

2. **Mitochondrial Support and Oxidative Stress Mitigation:** Mito-peptides are a class of bioactive peptides targeting mitochondrial integrity. Mito peptides restore ATP production and counteract ROS accumulation in gametes and gonadal tissues [18]. In equine spermatozoa, mitochondrial function is central to motility and fertilizing capacity; peptide-mediated stabilization of the mitochondrial membrane potential ($\Delta\Psi m$) reduces lipid peroxidation, DNA fragmentation, and apoptosis [48]. Similarly, in mares, peptides enhance oocyte mitochondrial biogenesis, supporting cytoplasmic maturation and improved embryonic competence.
3. **Angiogenic and Stromal Support:** Organ-specific peptides exert trophic effects on ovarian and testicular microvasculature by promoting vascular endothelial growth factor (VEGF) expression and endothelial regeneration. This angiogenic support optimizes nutrient and oxygen delivery to the follicular and seminiferous environments—critical for luteal sufficiency, endometrial receptivity, and spermatogenic renewal. Enhanced vascular perfusion also facilitates more efficient hormonal exchange between systemic and local compartments.
4. **Paracrine Regeneration and Secretome Synergy**: Increasing evidence supports the role of peptides as bioactive components of the stem-cell secretome, the ensemble of cytokines, growth factors, and peptides released by MSCs. When delivered exogenously, these peptides replicate many of the regenerative and immunomodulatory functions of MSCs without the risk of cellular overgrowth or immune rejection. In mares with chronic endometritis, for instance, intrauterine peptide infusion can attenuate fibrotic signaling (via TGF-β downregulation), enhance glandular regeneration, and re-establish a receptive endometrial environment.

Collectively, these mechanisms converge to restore gonadal homeostasis through redox regulation, endocrine re-equilibration, and paracrine regeneration, three axes that underlie sustainable fertility improvement in equine species.

Experimental and Clinical Evidence

Although equine-specific peptide research remains emerging, preclinical and translational findings are compelling. Studies adapted from canine, bovine, and ovine peptide therapy models have shown direct applicability to equine physiology due to conserved endocrine and mitochondrial signaling pathways.

1. **Peptide-Enhanced Sperm Function in Stallions:** Equine studies utilizing amniotic-membrane–derived MSC conditioned medium (AMSC-CM), rich in peptide and growth-factor content—have demonstrated significant improvements in post-thaw sperm motility, membrane integrity, and mitochondrial activity [49]. These effects are attributed to the antioxidant and cytoprotective peptide cargo that modulates NOX4, BAX, and PGC-1α/NRF1 signaling pathways, supporting mitochondrial biogenesis and sperm viability after cryopreservation [50]. Such formulations are

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now being explored as adjuncts in stallion semen extenders, enhancing fertility rates following artificial insemination or shipped semen use.

2. **Ovarian Function Restoration in Mares:** Pilot applications of peptide-based biologics have shown promise in restoring follicular activity and reducing the incidence of anovulatory hemorrhagic follicles in mares with subfertility [51]. Nano-encapsulated organ peptides targeting the ovary and uterus enhanced folliculogenesis, luteal progesterone synthesis, and early embryo survival rates in transitional mares [52]. This effect parallels observations in other species where organ-derived peptides upregulate StAR and CYP19A1 (key steroidogenic enzymes) and improve luteal angiogenesis through PGC-1α–dependent mitochondrial pathways [53].
3. **Endometrial Regeneration**: Intrauterine delivery of peptide-enriched MSC secretome fractions has been shown to improve uterine vascularization. The associated reduction in collagen deposition and oxidative markers (MDA, 8-OHdG) supports the hypothesis that peptides act by reprogramming endometrial fibroblasts toward a reparative rather than fibrotic phenotype. This regenerative remodeling enhances the uterine microenvironment for embryo implantation. Case-based studies extrapolated from the European Wellness group and BioPep research indicate broader systemic benefits of peptide therapy (e.g., metabolic resilience, joint mobility, stress tolerance) which indirectly support reproductive function by stabilizing the HPG axis and reducing chronic inflammation. These pleiotropic effects underscore the systemic harmonization achievable with targeted peptide modulation. Equine peptide therapeutics require formulation strategies that accommodate large body mass, variable metabolic rates, and extensive extracellular matrix turnover. Advanced delivery systems have been developed to optimize peptide stability and tissue targeting:

- Nano-encapsulation enhances peptide bioavailability and resistance to enzymatic degradation [54].
- Lyophilized vesicular formulations enable field-stable reconstitution and prolonged release [55].
- Organ-specific complexes (e.g., ovarian, testicular, uterine peptides) exhibit tropism guided by molecular affinity for tissue-specific receptors [56].
- Cryogenic preservation maintains peptide conformational integrity, allowing standardized potency across treatment batches [57].

Dosing regimens vary according to formulation and indication: injectable peptides are typically administered subcutaneously or intramuscularly at 1–3 mL per session, two to three times weekly for fertility protocols, with cumulative effects observed over 2–4 weeks. For reproductive enhancement, some long-acting formulations are applied seasonally or annually to coincide with breeding preparation. Across species, peptide-based interventions have demonstrated excellent safety profiles. Studies in canine and ovine models report no adverse histopathological or biochemical effects following long-term administration. In equines, preliminary safety assessments confirm absence of systemic hypersensitivity, hepatic or renal perturbation, and local injection-site reactions. Importantly, peptide therapy avoids the cumulative hormonal exposure associated with repeated endocrine treatments and reduces reliance on antimicrobial regimens, aligning with One Health and antimicrobial stewardship goals.

Representative equine case studies demonstrate systemic and localized regenerative outcomes following

organ- and peptide-based therapies are presented in (Figure 1). The European Wellness cases highlight the translational efficacy of mitochondrial, organ-specific, and cryogenic peptide formulations across metabolic and wound-healing pathologies that have direct relevance in the antimicrobial, anti-inflammatory and ROS microenvironment. Panel A (Horse [1]) presents an 18-year-old Thoroughbred mare diagnosed with chronic weight loss received three monthly sessions of precursor stem cells (PSCs) containing nine organ-specific cell fractions (placenta, kidney, liver, spleen, adrenal cortex, thymus, pancreas, bone marrow, and intestinal mucosa). Serial photographs demonstrate progressive improvement in muscle mass, body condition, and coat quality from the first injection (11/8/2023; weight: 310 kg) to three months post-initiation (10/11/2023; weight: 368 kg). Incremental gains (+11, +5, +42 kg) were recorded after each subsequent session, reflecting enhanced metabolic recovery and anabolic response. Visual body scoring shows restoration of topline musculature reduced bony prominence, and improved skin and hair luster, consistent with systemic trophic and metabolic effects of PSC therapy. Panel B (Horse [2]) presents a 10-year-old Thoroughbred stallion presenting with a ruptured joint capsule, tendonitis, and suspected osteoarthritis underwent three monthly sessions of Frozen Organo Cryogenic (FOC) injections containing seven organ-derived cell types (mesenchyme, skin, placenta, cartilage & synovial tissue, adrenal cortex, spleen, and bone). Serial imaging between 7/28/2023 and 9/29/2023 documents progressive wound contraction, re-epithelialization, and granulation tissue maturation. Noticeable improvement is observed within seven days post first session, with marked reduction of necrotic tissue and establishment of healthy granulation beds after the second treatment. By the third session, the wound exhibits near-complete epithelial closure with minimal scarring. These findings align with FOC's proposed angiogenic and anti-inflammatory mechanisms, supporting regenerative healing of synovial and periarticular tissues. Panel C (Horse [3]) presents a 16-year-old Criollo gelding (Argentinian Polo breed) diagnosed with non-neoplastic exuberant granulomas ("proud flesh") on both fore fetlocks received 36 sessions (three per week over three months) of Mito Organelle (MO) therapy. The formulation incorporated four organ-derived peptides (skin, placenta, mesenchyme, and thymus) targeting mitochondrial bioenergetics and tissue remodeling. Sequential wound images show rapid resolution of hypergranulation tissue, transition from inflamed to epithelialized surface, and progressive contraction of lesion margins. Mid-therapy improvement reflects downregulation of inflammatory signaling and stimulation of fibroblast mitochondrial recovery. Final photographs depict near-complete epidermal continuity with minimal fibrosis, indicative of mitochondrial stabilization and peptide-driven tissue regeneration. Panel D (Horse [4]) presents a 6-year-old Local Malaysia Pony mare diagnosed with non-neoplastic exuberant granulomas ("proud flesh") on the facial region underwent 27 sessions (three per week) of Nano Organo Peptide (NOP, triple strength) therapy. The protocol utilized seven peptide fractions (skin, placenta, mesenchyme, thymus, spleen, adrenal cortex, and lymph nodes). Serial images captured between 8/2/2023 and 10/6/2023 demonstrate staged regression of the granulomatous lesion from hyperemic, exudative tissue to fully epithelialized, pigment-restored skin. Visible reduction in lesion size and inflammation was observed by week three,

Figure 1: Clinical Response to Peptide- and Cell-Based Therapies in Four Equine Case Studies.

with complete closure by therapy completion. The data support the capacity of NOPs to enhance cellular turnover, angiogenesis, and extracellular matrix remodeling in chronic equine dermal lesions. Across all four equine cases, cell- and peptide-based regenerative interventions demonstrated substantial clinical improvement within 8–12 weeks. The therapies correlated with enhanced tissue regeneration (i.e., epithelialization, angiogenesis, and mitochondrial activity) and reduction of inflammation and hypergranulation (i.e., improved systemic metabolic tone and weight recovery in geriatric horses; absence of adverse events or local injection reactions, supporting therapeutic tolerability). Collectively, these case studies illustrate the translational potential of peptide- and organoid-based regenerative medicine in equine health, highlighting their applicability for chronic degenerative, metabolic, and wound-healing conditions.

Mechanistic and translational framework of MO and NOP in equine regenerative medicine

Recent advancements in mitochondrial and nanopeptide biotechnology have yielded highly refined bio-regulatory formulations designed to restore cellular and organ-level function through targeted molecular signaling. Among these, European Welness MO and NOP represent two complementary regenerative systems that combine organ-specific peptide ultrafiltrates with advanced delivery nanotechnology, enabling precise modulation of oxidative, endocrine, and metabolic pathways across tissues. Their integration into equine veterinary practice provides a mechanistic and translational template for regenerative interventions targeting fertility, metabolic resilience, and tissue repair. The platform centers on mitochondrial rejuvenation, recognizing mitochondria as both the energy hub and signaling nexus of cellular health. Each formulation consists of organ-specific ultrafiltrates (<700 kDa) containing mitochondrial-targeted peptides that promote:

- ATP synthesis and respiratory chain efficiency, enhancing energy metabolism across gonadal, hepatic, and muscular tissues.
- Regulation of redox homeostasis, reducing ROS accumulation and lipid peroxidation damage in gametes and somatic cells.

- Activation of nuclear–mitochondrial communication, restoring gene expression linked to PGC-1α, NRF1, and TFAM-mediated mitochondrial biogenesis.

The therapy operates via the "5R" framework (Repair, Revitalize, Restore, Regenerate, and Regulate/Detoxify) to optimize organ-level mitochondrial performance. Clinically, equine applications align with observed benefits in human and preclinical models, including improved cellular metabolism, fertility enhancement, reduced oxidative stress, and restoration of tissue vitality. The mitochondrial support observed in Horse [3] (mito-peptide therapy) exemplifies this mechanism in vivo, where peptide signaling facilitated granulation resolution and collagen matrix restoration in chronic fetlock lesions.

NOP represents nano-scale progression of peptide biologics, using low-temperature nanotechnology and parallel-extraction processes to produce organo-peptides <10 kDa with superior bioavailability and receptor-level specificity. Derived from fetal organ-specific tissues, these peptides mimic natural paracrine signaling, delivering potent regenerative instructions at the cellular level. Mechanistically, NOP formulations exhibit rapid systemic absorption and tissue tropism due to nanoscale size (~3 nm); multi-organ coordination, particularly across the liver, placenta, gonads, and adrenal cortex, organs central to the HPG and HPA axes; and enhanced anti-inflammatory and angiogenic signaling, accelerating healing and regeneration of soft tissue and dermal structures. The equine case (Horse [4]) treated with NOP demonstrated this translational principle, showing near-complete closure of exuberant granulomatous lesions (proud flesh) on the face after 27 therapy sessions. This response reflects the NOP mechanism of stimulated collagen synthesis, enhanced vascular perfusion, and immune modulation, consistent with the observed peptide actions in human dermal regeneration.

System	Primary Focus	Key Mechanism	Clinical Effect in Equines
Mito Organelles (MO)	Mitochondrial bioenergetics and systemic metabolism	Enhances ATP synthesis, redox balance, and organ-level mitochondrial density	Restores cellular vitality, muscle tone, and reproductive competence
Nano Organo Peptides (NOP)	Nano-delivered regenerative signaling	Stimulates angiogenesis, collagen synthesis, and cellular repair	Accelerates wound closure and soft-tissue regeneration

Table 2: MO and NOP represent a dual-axis regenerative framework.

MO and NOP operate as a complementary, two-axis regenerative system that targets distinct yet synergistic biological domains. MO formulations primarily support mitochondrial bioenergetics, enhancing ATP production, redox stability, and organ-level mitochondrial density. This mitochondrial optimization restores systemic vitality in equines, improving muscle tone, metabolic resilience, and reproductive competence. In parallel, NOP formulations deliver nano-scaled regenerative peptides that act directly at tissue and cellular interfaces, promoting angiogenesis, collagen synthesis, and coordinated cellular repair (Table 2). Together, MO and NOP establish a dual-axis therapeutic model. One axis restores intracellular energy and metabolic balance. The other drives localized tissue regeneration. MO+NOP provides a comprehensive platform for equine recovery across systemic and site-specific pathologies. Together, these platforms demonstrate multi-level rejuvenation, uniting molecular peptide signaling with

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tangible clinical recovery, as seen across your case panels (Horse [1–4]). Their relevance to equine regenerative medicine extends beyond reproductive restoration to encompass systemic performance, musculoskeletal resilience, and wound healing, forming a mechanistic continuum between mitochondrial optimization and nano-level peptide precision.

Despite promising early data, the application of peptide-based therapies in equine reproductive medicine remains largely translational and exploratory. The existing evidence base is composed primarily of preclinical studies, small-scale case series, and extrapolations from canine, bovine, or ovine models. Robust multicentric randomized controlled trials (RCTs) are necessary to confirm efficacy, optimize dosing, and establish standardized safety profiles for mares and stallions under diverse management conditions. For example, variable purity and molecular composition among commercially available preparations hinder reproducibility. To date, few validated surrogate endpoints exist for monitoring peptide efficacy in reproductive tissues (e.g., dynamic changes in AMH, INSL3, or mitochondrial function) [58]. Absorption, tissue distribution, and degradation kinetics in large-bodied equines differ significantly from small-animal models, necessitating dedicated pharmacodynamic studies. Moreover, long-term reproductive outcomes (e.g., foal viability, maternal health, and transgenerational safety) remain under-investigated.

Addressing these gaps is critical to transitioning peptide therapy from an experimental adjunct to a clinically standardized intervention in equine reproductive practice.

Regulatory and manufacturing considerations

The development of equine peptide biologics must align with veterinary biologics regulatory frameworks emphasizing identity, purity, potency, and safety [59]. To move towards regulatory grade validated quality control assays for peptide identity and bioactivity (e.g., high-performance liquid chromatography (HPLC), mass spectrometry, and endotoxin quantification); batch-to-batch consistency testing to ensure stability across production cycles; cryogenic preservation and nano-packaging to maintain peptide conformation and extend shelf-life in field conditions; and clear labeling of origin (synthetic, organ-derived, or MSC-secretome–derived) to facilitate traceability and ethical compliance is essential. Regulatory harmonization, particularly between European, North American, and Australasian veterinary standards, will be critical to enable global distribution and to integrate peptide therapy into mainstream reproductive biotechnology.

Integration with omics and precision reproductive medicine

Peptide therapy represents a new frontier in equine reproductive medicine, bridging molecular endocrinology, mitochondrial biology, and regenerative physiology. Through mechanisms encompassing oxidative stress control, endocrine rebalancing, angiogenesis, and stromal repair, peptide formulations offer targeted, physiologic, and sustainable restoration of fertility in mares and stallions. The convergence of peptide therapeutics, artificial intelligence (AI), and digital biomonitoring represents a transformative step for equine reproductive management. AI-enabled systems integrating biometric, hormonal, and behavioral data can predict estrous cycles, ovulation timing, and stallion libido patterns, enabling dynamic optimization of peptide therapy schedules. By leveraging advanced delivery systems, secretome synergy,

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and AI-guided personalization, peptide therapeutics transcend the limitations of conventional hormonal and antimicrobial approaches. As clinical evidence expands, these biologics are poised to redefine fertility management across the equine breeding industry, aligning high-performance outcomes with welfare, sustainability, and translational regenerative medicine principles. Advances in multi-omics technologies (genomics, proteomics, metabolomics, and transcriptomics) present an unprecedented opportunity to elucidate peptide-induced molecular networks governing equine fertility [60,61]. These tools have the potential to identify peptide-responsive gene clusters involved in steroidogenesis, mitochondrial biogenesis, and angiogenesis and quantify shifts in oxidative and inflammatory proteomic signatures following peptide treatment; to reveal metabolomic correlates of improved gamete energy metabolism and membrane integrity. Integrating omics data with clinical outcomes will facilitate development of predictive biomarkers for treatment response, enabling AI-driven therapeutic personalization [62]. For instance, an algorithmic platform combining serum INSL3, AMH, and ROS indices with real-time behavioral or hormonal data could dynamically adjust peptide dosing to optimize follicular readiness or spermatogenic efficiency [63].

Ethical and welfare considerations

Ethical deployment of peptide therapy in equine practice centers on welfare optimization, responsible breeding, and transparency. Peptides, by virtue of their biological precision and non-hormonal nature, offer distinct welfare advantages. For example, peptides mat provides opportunities for a reduction in chronic hormonal exposure, metabolic stress, and adverse drug effects associated with traditional endocrine therapies. Further, minimized reliance on long-term antibiotics, contributing to antimicrobial stewardship has the potential to enhance long-term health outcomes. Collectively, enhanced reproductive longevity, decreasing premature culling of valuable breeding mares and stallions provides benefit to longevity and quality of life. Notwithstanding, to translate peptide therapy from potential to practice, large-scale, controlled clinical trials assessing fertility outcomes in mares and stallions under field and laboratory conditions. Continued efforts in pharmacokinetic and pharmacodynamic modeling specific to equine physiology, including peptide half-life, tissue penetration, and elimination is essential. Increased number of comparative efficacy studies contrasting peptide monotherapy with established hormonal synchronization or antimicrobial protocols and/or combination therapy research integrating peptides with stem-cell–derived secretomes or antioxidant nutraceuticals for synergistic regeneration will facilitate therapeutic decision-making. Importantly, long-term safety and transgenerational studies tracking offspring health, epigenetic stability, and fertility inheritance across breeding lines is paramount.

The equine model holds translational significance for both veterinary and human reproductive medicine due to shared endocrine, mitochondrial, and angiogenic pathways. Understanding how peptides restore reproductive equilibrium in horses may inform therapeutic development for human infertility and age-associated reproductive decline. Moreover, peptide therapy aligns with One Health principles by promoting:

- Animal welfare and productivity through non-hormonal regenerative strategies;
- Environmental stewardship via reduced drug residues and antibiotic use;

- Human–animal scientific convergence, fostering cross-species insights into fertility, mitochondrial health, and reproductive endocrinology.

Equine peptide therapy represents a paradigm shift in veterinary reproductive medicine, moving beyond symptomatic hormonal control toward molecular restoration of fertility. Through regulation of oxidative stress, endocrine signaling, angiogenesis, and mitochondrial function, peptides offer a biologically coherent and ethically aligned alternative to conventional interventions. Bridging the insights of peptide biology, regenerative medicine, and precision analytics will accelerate the development of evidence-based, welfare-conscious reproductive solutions for horses, enhancing not only breeding efficiency and animal wellbeing but also contributing to the broader scientific pursuit of reproductive resilience across species.

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