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Nanotechnology application in overcoming the reproductive disorders in livestock

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Abstract

The profitability as well as productivity of livestock farming operations are significantly impacted by the reproduction rate of farm animals. Applying several techniques, such as dietary, hormonal, and biological methods together with controlling reproductive diseases, is the foundation of optimal reproductive management. These tactics ought to adhere to ethical and practical standards in addition to providing adequate reproductive results. For instance, a number of biological parameters and an animal's physiological state are primarily related to the effectiveness of biological and hormonally based reproductive tactics. Additional aspects, such as digestion and absorption, may also play a role in the effectiveness of nutritional strategies. Concerns about the overuse of antibiotics or the emergence of antibiotic-resistant bacteria further complicate the management of illnesses connected to reproduction.The use of nanotechnology in fields such as cattle farming systems could offer novel and creative ways to address problems with reproductive control. Nanotechnology can give several pharmaceuticals (including hormones and antibiotics), molecules from biology, and nutrients with new physicochemical qualities. These include enhanced bioavailability, increased cellular absorption, regulated sustained release, and decreased toxicity as compared to conventional versions. In this review, it will be demonstrated how nanotechnology has advanced the most popular reproductive management systems while taking into account the ongoing difficulties associated with each strategy.

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1. Introduction

Reproductive efficiency in cattle farming systems has a direct impact on farm output, profitability, and sustainability. The effectiveness of producing milk and/or meat is determined by the reproduction rate of farm animals. This can be done directly or indirectly through management choices like replacement and harvesting rates. Applying precise techniques is the cornerstone of optimal reproductive management, which also requires taking costs, animal welfare, environmental effects, and human health into account. Following the selection of a strategy that aligns with each farm's objectives, the majority of reproductive management techniques are prepared for use in economic livestock farms(Olynk and Wolf 2008; Smith et al. 2018). These tactics could involve nutritional management, reproductive aided techniques (mostly artificial insemination and estrous synchronisation), a number of bio stimulating instruments (like the male effect), and the prevention or treatment of reproductive illnesses (Caraviello et al. 2006; Delgadillo and Martin 2015; Hassanein et al. 2021). Despite being widely and primarily used in various livestock production systems, the effectiveness of these reproductive management techniques is called into question by a number of pragmatic and moral considerations. For instance, hormone-based reproductive medicines are the recommended approach to managing reproduction; yet, the pharmacokinetics and pharmacodynamics of these treatments are critical to their efficacy and can be influenced by biological factors (Hashem and Gonzalez-Bulnes 2020; Hassanein et al. 2021). The male effect is a method of sexual biostimulation that offers the chance to do away with the heavy reliance on hormones for reproductive management and the creation of hormone-free animal products. Agriculture is another industry that has seen a transformation because of artificial insemination (AI). AI has significantly improved cattle raising in particular in a variety of ways. This technology has the potential to raise animal welfare standards, boost sustainable farming practices, and increase output (Gulzar and Hussain 2023). Nevertheless, the male to female ratio, age, and experience of the male all pose challenges to the method's effectiveness (Chasles et al. 2016; Tejada et al. 2017; Ungerfeld 2007). Similarly, inadequate delivery of necessary nutrients and low nutrient bioavailability may have a negative effect on nutritional management strategies aimed at enhancing farm animal reproductive performance (Hashem

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and El-Zarkouny 2014; Izquierdo et al. 2015). Last but not least, worries about the widespread use of antibiotics and the emergence of bacterial resistant to antibiotics pose a barrier to the treatment of illnesses connected to reproduction (Algharib et al. 2020; Cerbu et al. 2021; Yang et al. 2009). Taking these factors into account, the development of new technologies, such as nanotechnology, opens up a world of possibilities for livestock and agricultural output.

Nano-drug delivery systems represent the most significant and promising use of nanotechnologies in the animal production industry. By utilising nanotechnology, a variety of pharmaceuticals, biological molecules, and nutrients can gain new physicochemical characteristics, including enhanced bioavailability, greater mobility and uptake by cells, regulated sustained distribution of the medicine at the target site, decreased toxicity in comparison to other compounds, enhanced enzymatic actions, and elevated mucoadhesive properties (Osama et al. 2020). With the use of nanotechnology, this review aims to demonstrate potential advancements in the most popular reproductive management techniques.

2. Hormone based treatments

Even with current efforts to control reproduction in animals used for agriculture using biological methods, the practices—including exogenous hormone therapy, cannot be completely eliminated from the farming sector. Treatments based on hormones are a useful tool for increasing fertility and the profitability of farming operations. Numerous survey investigations supported the importance of hormonal-based procedures for reproductive management; for example, 87% (103 of 153) of managers from large milking herds (average herd size of 613 cows) in the USA confirmed the use of hormonal synchronisation or timed artificial insemination in their reproductive management (Caraviello et al. 2006). Similarly, about 80% of practitioners from 714 inorganic dairy farms in England confirmed the crucial role of hormones for efficient reproductive management (Higgins et al. 2013). Hormones are frequently utilised because they are necessary for the implementation of many assisted reproductive techniques such as timed artificial insemination (Hashem et al. 2015), superovulation, and estrous synchronisation/induction (Hashem et al. 2015) for increasing the efficiency of reproduction and for treating disorders related to reproduction in both males and females (Hashem et al. 2015; Hashem and Aboul-ezz 2018). Progesterone, oestrogen, testosterone, melatonin, prostaglandins, and gonadotropins are the primary hormones used to regulate fertility in farm animals. The pharmacokinetics and pharmacodynamics of these hormones are primarily responsible for their efficacy. Certain hormones, like prostaglandin F2α (PGF2α) and gonadotropin-releasing hormone (GnRH), have short half-lives and low molecular weights, which limits their ability to be delivered to target areas over time. Certain hormones, like glycoprotein gonadotropins (follicle-stimulating hormone – FSH; luteinizing hormone – LH; human chorionic gonadotropin – hCG; equine chorionic gonadotropin – eCG), can trigger the immune system and the production of particular antibodies, which can make some farm animal species resistant to repeated gonadotropic treatments (Castro et al. 2009). Additionally, reduced fertility and other biological consequences are linked to recurrent administration of these hormones. Anti-eCG antibodies have been demonstrated to impede eCG bioactivities through two different methods. The first method involves blocking eCG's interaction with its receptors; the second involves anti-eCG antibodies changing eCG's structure, which can block eCG bioactivities. It is important to note that after repeated treatments, fertility is impacted since these modifications of eCG biological activity by its antibodies mostly affect the FSH bioactivity of eCG (Herve et al. 2004; Kara et al. 2019).

In this instance, ewes receiving up to three rounds of eCG/FSH based super ovulatory treatments displayed decreased rates of fertilisation and less viable embryos overall at the subsequent recoveries in comparison to the first flushing (Forcada et al. 2011). In a different study, the kidding rate (41.3%) was lower in goats with high eCG levels of antibodies following repeated eCG treatments than in other females (66.7%). The preovulatory LH surge and delayed estrous rate were linked to these goats' reduced fertility (Roy et al. 1999). Similar results were seen in rabbits, where repeated administration of recombinant human FSH elevated the levels of FSH antibodies in the females at the time of the third and fourth superovulation treatments. Concerns about animal health and welfare, the environment, and managing reproduction and fertility in farm animals present additional difficulties to the usage of hormones. For instance, since eCG is derived from bleeding pregnant mares, a shortage is anticipated owing to concerns about animal welfare. Future hormone production may be halted by the persistent social pressure placed on corporations producing the hormone (Manteca Vilanova et al. 2019). Lastly, because hormone residues and carrier materials are released into the environment, conventional hormonal delivery methods may also throw off the equilibrium of the surrounding ecosystem.The employing of progesterone-impregnated intravaginal gadgets which were created to regulate the estrous cycle in various agricultural animals, is the most obvious example (Rathbone and Burke 2013). The progesterone-loaded silicon polymers that make up the majority of these devices must have high concentrations of progesterone in order to release enough hormones to the genital area mucosa. This raises the possibility of hormone emissions into the environment, direct hormone transmission to workers or breeders, and indirect hormone transmission to shoppers through animal products (de Graaff and Grimard 2018).

3. Reproduction related diseases

Reproductive illnesses are typically linked to the phase of animal production, and more especially, reproduction (Casares-Crespo et al. 2018; Fernandez-Serrano et al. 2017; Hashem and Sallam 2020). Reduced conception rate and an increased risk of reproductive culling are two associated symptoms of postpartum diseases, particularly endometritis caused by various bacterial species (primarily *Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Prevotella melaninogenica*, *Arcanobacterium pyogenes*) (Helbling et al. 2014; Oliveira et al. 2013; Rather et al. 2013). When compared to their healthy herd mates, the risk of pregnancy and the number of days from calving until pregnancy were 40 %; HR = 0.60; 69 %; HR = 0.31; 76 %; HR = 0.24 in cows with metritis, clinical endometritis, as well as subclinical endometritis, respectively (Fogolari et al. 2016; Remiao et al. 2016). Protozoan illnesses linked to pregnancy-associated disorders, like toxoplasmosis (*Toxoplasma gondii*) and neosporosis (*Neospora caninum*), cause large financial losses in farm ruminants. Globally, neosporosis infections is a prevalent zoonosis (Li et al. 2018; Mahdasht et al. 2020) that results in abortion in cattle, while toxoplasmosis infection primarily produces reproductive dysfunction in small ruminants (Helbling et al. 2018). Bovine mastitis, primarily caused by Staphylococcus aureus, is a major source of economic losses in dairy farms. The disease results in steep drops in milk yield (about 380 tons of milk are lost globally annually), tainted milk, reproductive disorders, and additional costs for replacing tainted milk and replacing infected animals (Cordova-Izquierdo 2016; Santos-Jimenez et al. 2020). Furthermore, *Staphylococcus aureus* contamination of raw milk poses a threat to public health along the entire food chain (Cannas et al. 2019; Zhao et al. 2021). In general, these illnesses have detrimental effects on population health, animal welfare, and the ultimate profit from the manufacturing process (Scaramuzzi and Martin 2008; Wu 2010). The majority of these bacterium and/or zoonotic diseases include clinical symptoms that are either directly caused by tissue damage and microbial products (endotoxin) or indirectly caused by mediators of oxidant stress (nitric oxide) and/or inflammation (cytokines and eicosanoids) (Penagaricano et al. 2013).

Antibiotic-based therapy is currently the most widely advised course of treatment for a variety of microbial/ protozoan diseases, including illnesses connected to reproduction (Castro et al. 2019; Sturmey et al. 2009). The metabolism of the medication regulates the efficacy of antibiotic-based therapy.The rate at which antibiotics are absorbed and distributed determines whether they will reach the intended infected sites or not (Hippen et al. 2008; Hosny et al. 2020; Shin et al. 2012; Zereu 2016). This rate can be influenced by a variety of biological factors, including the antibiotics' resistance to gastrointestinal enzyme degradation when administered orally, blood hydrolytic enzymes when administered parenterally, drug solubility, and consequent cellular absorption and bioavailability. Furthermore, some infections cause fibrous damage in the infected tissues, which limits the reach of the medications into infected regions when regional therapy is administered—for example, when a medication is directly infused into the female reproductive organ in cases of endometritis or administered through the teats in cases of mastitis (Boerman and Lock 2014; El-Sherbiny et al. 2016; Gawad and Fellner 2019; Hackmann and Firkins 2015; Hammon et al. 2005). It is important to consider the risks associated with the emergence of new wild pathogenic microbial species, the spread of infectious and cross-transmitted microbial species, the accidental spillage of antibiotics into the environment, and the transfer of antibiotic residues into livestock products (meat and milk) (Jahanbin et al. 2015). In addition of being detrimental to the general public's health, antimicrobial resistance increases the chance of treatment failure, recurrent infection, and related economic consequences (Khalil et al. 2019). In fact, because of these variables, using antibiotics to treat disorders associated with reproduction (such mastitis, toxoplasmosis, and neosporosis) is a contentious approach. Therefore, new, secure, and efficient antibiotic therapy based strategies are required, especially when treating farm animals that are used for food production (Albuquerque et al. 2020; Shahin et al. 2020).

4. Nanotechnology approaches

Numerous studies have demonstrated the potential to overcome the therapeutic limitations of antibiotic-based therapies (Gurunathan et al. 2018; Vallejo-Timaran et al. 2020) by employing a variety of engineered nanomaterials (such as liposomes, nanoparticles of polymers, solid lipid nanoparticles, nanogels, and inorganic nanoparticles) that are synthesised with specific physicochemical properties (Sanchez-Sanchez et al. 2018; Zhou et al. 2018). The use of nano-formula for antibiotic-based therapies may also reduce the dosage of the antibiotic, enable effective delivery of the medication to the infected sites, shorten the duration of therapy and minimise side effects and antibiotic degradation (Olsen et al. 2006; Piotr et al. 2013). Nanomaterials have the potential to enhance the transport of antibiotics to diseased sites and provide protection against their rapid degradation (Wang et al. 2017). Additionally, nanomaterials can be made to exhibit cytotoxic and destructive capabilities against microbes.

Furthermore, certain nanoparticles cause harm to the bacterial cell membrane, enzymes, and structural and functional proteins of the cell primarily by inducing oxidative pathways in the cell that alter gene expression and promote both innate and adaptive immunity.It is possible to tailor nanoparticles so that they prevent bacterial adhesion, colonisation, and biofilm formation (Algharib et al. 2020). Additionally, pharmaceuticals can be incorporated into nanostructures without changing the compound's structure, thereby enhancing its pharmacological efficacy (Gholipourmalekabadi et al. 2017). In particular, the antibiotic enrofloxacin is used to treat a variety of bacterial illnesses in pigs, including Salmonella, Pasteurella, Mycoplasma, and *Escherichia coli*. The suggested intramuscular dose for swine is 2.5 to 5 mg of enrofloxacin/kg Bw/day for three to five days. It has been demonstrated that drinking water with a suspension of enrofloxacin-loaded poly (lactic-co-glycolic acid) nanostructures could be administered orally, and that this would result in a 23% decrease in the minimum inhibitory concentration against *E. coli* when compared to enrofloxacin alone (El-Zawawy et al. 2015; Paudel et al. 2019). In a different investigation, atovaquone nanosuspensions coated with sodium dodecyl sulphate significantly improved the transit through gastrointestinal and blood–brain barriers, hence increasing the therapeutic efficacy against experimentally acquired and reactivated toxoplasmosis (Shubar et al. 2011). Similarly, for *Staphylococcus aureus* lactation infection, tilmicosin (a semi-synthetic macrolide antibiotic) - loaded hydrogenated castor oil at a decreased dosage has shown superior therapeutic efficacy than free tilmicosin due to its greater bioavailability and sustained-release performance (Wang et al. 2012). In order to address intracellular persistence of *Staphylococcus aureus* and multi-drug resistance, which are linked to the subclinical and recurrent infection of bovine mastitis, nanoparticle medicines have also been employed as a tactic recently. Yang demonstrated how the use of amoxicillin nanoparticles in the treatment of bovine mastitis may extend the duration of the post-antibiotic effects and, consequently, the intervals between doses (Yang et al. 2009).

Innovative healthy and secure antibiotic alternatives are becoming possible due to the recent convergence of the benefits of nano-drug delivery methods and alternative medicine, which relies on the use of natural compounds with antibacterial activity. Levamisole and morantel are two examples of imidazothiazole medications that have been widely used to treat *Haemonchus contortus* infections; however, the development of resistance has called into question their continued efficacy (Qamar and Alkheraije 2023). Probiotic species, microbial extracts from plants, and botanical secondary metabolites (polyphenols and essential oils) have all been identified in numerous studies as possible antibacterial agents (Garzon et al. 2021). In a different investigation, the use of poly (lactic-co glycolic) acid (PLGA)-epigallocatechin gallate-doxycycline nanoparticles as an aided endometritis therapy proved beneficial (Garzon et al. 2021). In this case, mastitis has been treated with chitosan-TPP nanoparticles (Rivera Aguayo et al. 2020). Moreover, certain metal nanoparticles, such as copper oxide (CuO), zinc oxide (ZnO), silver oxide (Ag_2O), gold (Au), and titanium dioxide (TiO_2) have shown strong antibacterial activity against a variety of microorganisms. These alternatives may offer a chance for patients to completely replace out antibiotic-based medications for safer ones (Ferreira-Silva and Burnett 2017). Because nanometals (silver) can be synthesized biologically while meeting environmental and therapeutic standards, the use of nanomaterials as an antibiotic substitute has been promoted. The anthelmintic closantel belongs to the class of medications known as salicylanilide. Target blood-sucking parasites such the Haemonchus species have plasma proteins that salicylanilide binds to with a strong affinity and high specificity. Moreover, Closantel may interfere with the parasite's defense systems to preserve pH imbalance (Qamar and Alkheraije 2023). The natural reducing agents such as flavonoids, polyphenols, and other flavonoids and phenolic acids molecules of life of Camellia, green tea, when black tea leaf extracts are used, along with microorganisms like *E. Coli*, a type of Acinetobacter, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* for the nanoparticle synthesis (Das et al. 2020). In this case, the manufacture of silver nanoparticles measuring 10 nm was accomplished through the use of apigenin, a polyphenolic molecule. By preventing the viability of cells and creation of biofilm in a dose-and time-dependent manner, these nanoparticles demonstrated antibacterial efficacy against pathogenic bacteria *Prevotella melaninogenica* and *Arcanobacterium pyogenes* found in an endometrial infected uterine discharges.

Similarly, Yuan verified that two triple drug-resistant strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* obtained from goat milk samples afflicted with mastitis could be inhibited by biologically synthesised silver nanoparticles (Yuan et al. 2017). Radzikowski confirmed the ability of readily available silver nanoparticles, metal nanoparticles, and the combination of them to reduce the viability about mastitis-borne pathogenic organisms without exhibiting harmful impacts on mammary gland tissues, in reference to the toxicity of such nanotechnologies to animal tissues (Radzikowski et al. 2020). Additionally, Paudel verified that the drug's integration into the PLGA matrix reduced the amount of reactive oxygen compounds that the antibiotic induced, indicating that enrofloxacin-entrapped nanoparticles are less harmful to mammalian cells than the free drug (Paudel et al. 2019).

5. Conclusions

This review highlighted the current drawbacks and restrictions of the most widely used reproductive management techniques in farm animals. As demonstrated, factors limiting the effectiveness of reproductive management strategies include ease of field-scale application, animal behaviour and physiological state, drug availability and uptake, and environmental factors like antibiotic/hormone residue release. Innovative and unconventional solutions are provided by nanotechnology. Nanotechnology has the potential to limit the emergence of antibiotic-resistant microbial species by increasing the effectiveness of antibiotics and/or developing natural antibiotic substitutes. However, in light of the information now accessible, this study offers bold remedies for the problems with reproductive management; further research is needed to determine the efficacy of these tactics.

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