Role of Nanotechnology in Treatment of Uterine Infections

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Abstract

Health of reproductive system, both in human and animals, is of prime importance. In animals, the major portion of farm profitability is determined by the reproductive health status of the animals. The reproductive health is determined by the reproductive cyclicity, conceptions, pregnancies and giving birth to healthy young ones. In human, reproductive problems in females have immense impact on their social life. Conventionally, hormone and antibiotic based therapies are used for the treatment and management of reproductive disorders. With the progress in nanotechnology, there has been utilization of nanomedicine for more efficient treatment of anomalies. The conventional treatments are being combined with nanomedicine to produce improved effects. This chapter aims to review recent applications of nanotechnology in diagnosis and treatment of reproductive disorders, regulation of hormones involved in reproduction and adverse effects of using nanotechnology on ecosystem. The drawbacks of conventional therapies are also discussed to understand the significance of nanotechnology.

Keywords: Reproductive system, Disorders, Hormones, Antibiotics, Nanomedicine

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Introduction

1. Introduction to Nanotechnology and Nanomedicine

The nanotechnology, modifying and innovating matter at nanometric scale, has become the talk of the town in twenty-first century (Toumey, 2014). The pre-historic people used nano-particals, ranging from 1nm to 100nm in size, for various purposes. For example, craftsmen used nanoparticles to give lustre or iridescence to ceramic pottery. The carbon nanotubes found in pottery of Keelandi, an Indian city of Tamilnadu, carbon dated as 6th century BC, is thought to be the first evidence regarding use of nanotechnology in any human society (Kokarneswaran et al., 2020). In modern times, Richard Feyman's talk "There's plenty of room at the bottom" at the 'American Physical Society Meeting' at the California Institute of Technology (CalTech) is thought to be the foundation of nanotechnology. Back in 1974 the term "Nanotechnology" was first used by a Japanese Professor Norio Taniguchi. Since then, there is an extensive use of nanoparticles in electronics, healthcare, medicine and agriculture (Gupta et al., 2013).

Nanomedicine dawned in 1990s (Krukemeyer et al., 2015). Greater therapeutic efficacy of nanomedicines is enabled due to their small size, greater surface area and surface functionalization's adaptability (Zhou et al., 2018). Menjoge et al. (2010) have broken down historical development of nanomedicine into three stages. The first stage spans 30 years from liposomes' discovery in 1964 to the approval of first nanomedicine-doxorubicin by the Food and Drug Administration (FDA). The clinical validation and commercialization marked the second stage (1995-2007). The third stage (2008 through present) has involved development of new nanotherapeutics like smart nanotherapeutics. Smart nanotherapeutics actively target pathological tissue and thus protect healthy tissue.

Nanomedicine are classified on the basis of nanomaterials used and includes liposomes, polymeric nanomaterials, inorganic nanoparticles, drug nanocrystals and protein based nanoparticles.

2. Conventional Therapies

2.1 Hormonal Treatments

Currently, exogenous hormone based therapies cannot be excluded from farming practices, since they are effective tool to improve fertility and profitability (Hashem and Gonzalez-Bulnes, 2021). In England, 80% of 714 inorganic dairy farm practitioners affirmed the significance of hormones for controlled and effective reproductive management (Higgins et al., 2013). The most common hormones used are gonadotrophins, estradiol, progesterone, prostaglandins, melatonin and testosterone (Hashem and Gonzalez-Bulnes, 2021). Gonadotrophin realeasing hormone and prostaglandin $F_2\alpha$ are lighter in molecular weights and hence have short half-life which restrains the delivery of hormones to the targeted tissues. Others such as human chorionic gonadotropin, luteinizing hormone (LH), follicle stimulating hormone (FSH) and equine chorionic gonadotropin (eCG) stimulate the formation of antibodies. Also, repeated treatments with these result in low fertility and other reproductive problems. Use of hormones for fertility management also raises animal welfare issues. For example, eCG is obtained by bleeding pregnant mares. In future, due to societal pressure, the production of this hormone may face shortage (Manteca et al., 2019). Conventional hormone delivery systems may also disrupt environmental ecosystem. For example, progesterone impregnated intravaginal devices have the potential to cause hormone emissions in the environment, direct transmission to workers or indirect transmission to consumers through animal products (De Graaff and Grimard, 2018).

2.2 Antibiotics Based Therapy

Currently the most widely advised course of treatment for a variety of microbial/protozoan diseases is antibiotic based therapy, including the reproductive illnesses (De Castro et al., 2009; Sturmey et al., 2009). The rate of absorption and distribution of antibiotics determines whether they will reach the infected site or not (Hippen et al., 2008). This rate is affected by a variety of biological factors; antibiotics resistance to gastrointestinal enzyme degradation when administered orally, drug solubility, blood hydrolytic enzymes when given parenterally, and consequent cellular absorption and bioavailability. Antimicrobial resistance is not only detrimental for public health but also results in treatment failures, recurrent infections and related economic consequences (Khalil et al., 2019).

3. Nanotechnology Approaches

There have been numerous studies that demonstrated the potential to overcome limitations of antibiotics based therapies (Vallejo-Timaran et al., 2020; Gurunathan et al., 2018) by using various engineered nanomaterials (such as liposomes, solid lipid nanoparticles, nanogels, nanoparticles of polymers and inorganic nanoparticles) synthesized with specific physiochemical properties (Sánchez-Sánchez et al., 2018; Zhou et al., 2018). Using nanoformula in antibiotics based therapies reduces antibiotic dosage, shorten duration of therapy, enable effective delivery of medicine, and minimize side effects and degeadation of antibiotics (Piotr et al., 2013; Olsen et al., 2006). Nanoparticles can be made to prevent bacterial adhesion, colonisation and biofilm formation (Algharib et al., 2020). Also, pharmaceuticals can be incoporated into nanostructures without changing compond's structure and hence increasing its pharmacological efficacy (Gholipourmalekabadi et al., 2017).

Antibiotic enrofloxacin is used to treat various bacterial infections of reproductive system. The intramuscular dose for swine is 2.5 to 5 mg/kg bw/day for three to five days. Drinking water with suspension of enrofloxacin loaded poly (lactic-co-glycolic acid) nanostructures would result in 23% decrease in minimum inhibitory concentration against *E. coli*, when compared to enrofloxacin alone (Paudel et al., 2019; El-Zawawy et al., 2015). Another study demonstrated that atovaquone nanosuspensions coated with sodium dodecyl sulphate improved transition through GIT and blood-brain barrier and improved the efficiency against toxoplasmosis (Shubar et al., 2011). In S*taphylococcus aureus* lactation infection tilmicosin-loaded castor oil at a lessened dosage showed better therapeutic efficacy because of increased bioavailability and sustained-release performance (Wang et al., 2012). Yang et al. (2009) showed that using amoxicillin nanoparticles extended the duration of post-antibiotic effects and the intervals between doses, in bovine mastitis. Hussein & Hussein (2022) treated a group of Iraqi breed cows with intrauterine infusion of silver nanoparticles and observed that 70% of cows were cured as compared to 20% cured cows of untreated group.

Nanoparticles also have the potential to combat the challenges posed by multiple drug resistant pathogens. The effect of silver nanoparticles (AgNPs) of 10 nm size was evaluated on endometritis causing multiple drug resistant bacteria *Prevotella melaninogenica* and *Arcanobacterium pyogenes* isolated from uterine secretion samples. The AgNPs inhibited cell viability and and biofilm formation (Gurunathan et al., 2018).

4. Diagnosis of Female Reproductive System Related Disorders

4.1 Diagnosis of Cancers

The reproductive system of female has different types of cancers including ovarian cancer, cervical cancer, vaginal and endometrial cancers (Ventriglia et al., 2017). Researchers have created nanoparticles that specifically target cervical cancer cells that overexpress the CD44. These particles use near-infrared fluorescence imaging (FI) to study tumors *in-vivo* and track cancer cells that have spread (Choi et al., 2021). Zhang et al. (2022) have developed photoacoustic imaging platform using nanocomposites having strong near-infrared absorption, hence detecting strong signals and making it easy to observe drug accumulation within tumors. The photoacoustic imaging is different from conventional ultrasound imaging in a way that it offers better spatial resolution, thereby assisting in diagnosis of early lesions. By using photoacoustic imaging together with fluorescence imaging or ultrasound imaging, multimodal imaging strength can be achieved, thereby facilitating the acquisition of data or information from multiple perspectives.

For ovarian cancer, the fluorescence imaging (FI) is effective and non-detrimental method for preliminary screening, intraoperative surgical assistance, and postoperative monitoring of prognosis (Jung et al., 2014). The inorganic nanoparticles, small molecule flurophores, quantum dots and carbon nanotubes are extensively used fluorescence agents in biological visualization. The near-infrared flourescence provides excellent tissue imaging capabilities because of better tissue penetration and weak tissue absorption (Leblond et al., 2010). For imaging of ovarian cancer, indocyanine green has been approved by FDA as a near-infraref fluorescence probe (Reinhart et al., 2016). Additionally 'Plasminogen Activator Inhibitor' (PAI) can also be used for diagnosing ovarian cancer.

4.2 Diagnosis of other Related Disorders

In endometriosis, there is ectopic proliferation of cells of endometrium outside the borders of uterine cavity. The MRI and ultrasound are commonly used for diagnostic purposes. A nanoparticle comprising silicon naphthalocyanine dye, developed by Taratula and his team which upon internalization by endometric cells exhibit better contrast (Moses et al., 2020). To diagnose deep proliferating endometriosis, ultra-small super-paramagnetic iron oxide has been used as an MRI contrast agent by Lee et al. (2012).

The polycystic ovarian syndrome (PCOS), an endocrine and metabolic disorder, is most prevelant in premenopausal women. The disrupted androgen levels result in alopecia, acne, hirsutism, and seborrheic skin. There is decrease in ovulation causing menstrual disruption, reduced fertility, and endometrial hyperplasia. There is also evidence of insulin resistance and metabolic complications (Conway et al., 2014). In the diagnosis of PCOS, nanoparticles have widespread application including MRI, ultrasound imaging, MRE and optical imaging (Duseja et al., 2015).

5. Nanotechnology for Regulation of Female Reproductive Hormones

Ovarian hormones (estrogen and progesterone) along with luteinizing and follicle-stimulating hormone play a critical role in the regulation of normal reproductive functions. Nanotechnology can potentially regulate production, release and effect of these hormones (figure 1).

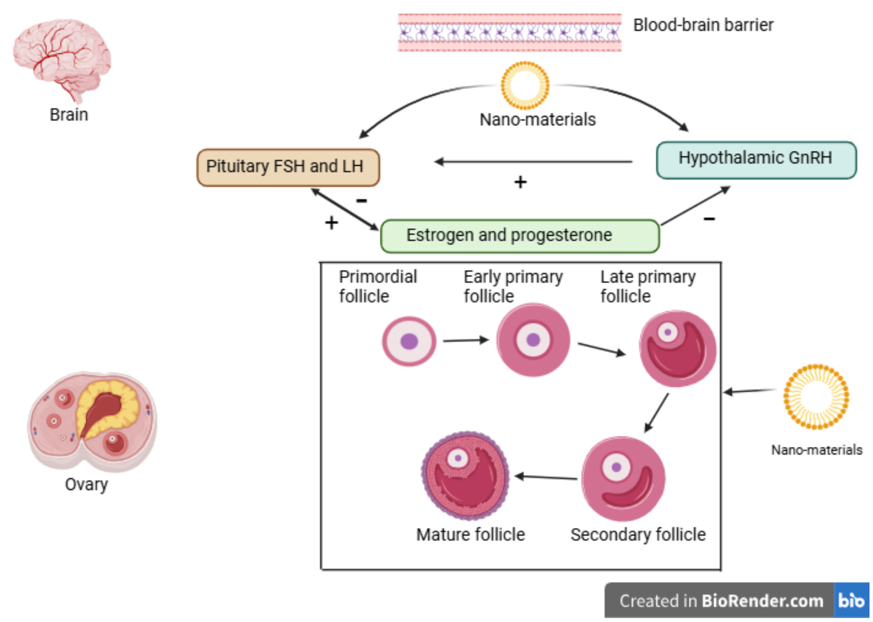

Fig. 1: Nanotechnology for the regulation of female reproductive hormones. 1) Nanoparticles can cross blood brain barrier and influence hypothalamus and pituitary gland 2) Direct circulation towards ovaries can result in unsettled steroidogenesis

5.1 Estrogen

Estrogen is involved in the regulation of ovulation, implantation of embryo, thickening of endometrium and cervical mucus production. The nucleic acid nanoparticles can be potentially used to inhibit the estrogen synthesis' factors, hence reducing its production and release. Abdelgader et al. (2023) studied the application of nanocarriers for delivery of anti-estrogen drugs. These carriers significantly increase bioavailability, drug stability and targeted delivery hence reducing the dose of drug and its side effects. Gene therapy drugs like siRNA have reportedly been delivered using nucleic acid nanomaterials (Cui et al., 2021).

5.2 Progesterone

Progesterone not only influences physiological processes but also has implication in disorders such as osteoporosis and breast cancer (Song et al., 2024). The nanoparticles, nanocapsules and nanofibers have been extensively used for progesterone drugs delivery (Tagde et al., 2022).

5.3 FSH and LH

The FSH and LH, released by pituitary gland, regulates the ovarian hormones. The nanotechnology can potentially influence release and synthesis of FSH and LH, thus interfering ovarian hormones release. Temperature sensitive hydrogel based nanocapsules have been developed for controlled FSH delivery, in order to enhance ovarian reserve function (Huang et al., 2019). These nanocapsules suggest excellent prospects for improving ovarian reserve.

6. Nanotechnology for Vaginal Drug Delivery

There are a number of reasons why vagina is used as route for drug delivery. These include high blood flow, large surface area of vaginal mucosa, preferential distribution to uterus, avoidance of liver's first-pass metabolism and potential for sustained drug release.

6.1 Nanoparticles

Healthy women's vaginal pH is 4-5 which is neutralized by semen and changes in vaginal disorders. This fact has enabled the use of pH sensitive nanoparticles that retain drug at normal vaginal pH and release in response to pH increase. Many studies have devised vaginal nanoparticles based on Eudragit S-100, a FDA approved anionic copolymer (Mandal et al., 2017 and Yoo et al., 2011). The Eudragit S-100 dissolves at pH 7 or greater than 7 and remains insoluble at low pH, thus making it an ideal polymer for intravaginal nanocarriers.

Nanoparticles can also be used for intravaginal delivery of nucleic material. In a recent study, siRNA-polyethylenimine (PEI)-encapsulated NP for the knockdown of PDGFR-β expression has been fabricated as an approach to decrease sexually transmitted chlamydia infection in females (Kim et al., 2018).

6.2 Liposomes

The antibiotics like metronidazole (Pavelić et al., 2005), chloramphenicol (Pavelić et al., 1999) and clotrimazole (Pavelić et al., 2004) were the first medicinal substances to be tested in liposomal intravaginal delivery. These studies showed that in order to obtain nano-sized vesicles having enhanced capacity of drug loading and particle diameter ranging from 200 to 400, techniques like polyol dilution and pro-liposomes can be used. Furthermore, drug's affinity and physicochemical traits are appeared to determine the entrapment efficiency of the drug.

The bioadhesive gels incorporated with liposomes have been developed such as carbopol hydrogels (Vanić et al., 2014). These ensure optimum release of drug at vaginal site and increase retention time.

6.3 Nanoemulsions

The O/W type of nanoemulsions-based compositions have been studied for intravaginal delivery. A gel system was devised comprising poloxamer 407 (20%, w/v) and carbopol 934 (0.3%, w/v) and used in the formulation of a thermosensitive nanoemulsion-based gel (Mirza et al., 2013). For a stable nanoemulsion formulation, the mixture of surfactant and cosurfactant is carefully choosen. The hydrophilic lipophilic balance (HLB) value should be greater for o/w emulsions.

7. Challenges of Nanotechnology in Medicine

7.1 Safety and Toxicity

Materials of nanoscale render unique variations in their chemical, biological and physical characteristics compared to macroscopic materials (Ravindran et al., 2018). It is necessary to understand particle size effects to ensure safety of nanomaterials. As we know, smaller size of nanoparticles increases their surface area and hence contact area with biological system (Hall et al., 2007). Some nanomaterials can cause cell toxicity and they may induce oxidative stress and inflammation (Chang et al., 2014). Factors influencing these traits include dosage, chemical composition and structural traits. When released into the environment, nanomaterials pose seripous consequences to ecosystem by interacting with organisms, water, soil and other constitutes (Koelmans et al., 2015).

7.2 Obstacles to Clinical Translation

Toxicity and safety assessment is a bigger obstacle for clinical translation of nanotechnology. Tang et al. (2019) demonstrated that nanoparticles can cross blood-testis barrier and accumulate in supporting cells, interstitial cells and spermatozoa. Also there are evidences of nanoparticles crossing placenta (Nakamura et al., 2019) and impact of nanoparticles on immune system (Bhise & Green, 2014). There is a lack of unified standardized methodologies and regulations for their characterization, quality control, and batch consistency assessment due to diversity of nanotechnology (Bayda et al., 2018). This poses a series of challenges for the clinical translation of nanomaterials, impeding comparability and reproducibility of outcomes.

High costs of nanomaterials production is another challenge and it is essential to address issues related to large scale preparation, cost control, production scalability and affordability. There are ethical concerns related to research on nanoparticles due to safety concerns; whether the research and application has any adverse effects on health and lives of researchers and users.

Conclusion

The conventional therapies in reproductive medicine are not only disadvantageous for the animals itself but also their overuse may result in body to become unresponsive to them e.g. antimicrobial resistance through unwise use of antibiotics. Nanotechnology when combined with those conventional therapies reduces the drawbacks they can cast when used alone. It also alleviates the pressure mounted by animal welfare over the excessive use of hormones. Nanotechnology when combined with diagnostic tools, facilitates the early diagnosis of reproductive cancers and endometriosis in women. The vaginal drug delivery is a safe and efficient route for delivery of drugs to uterus and nanocarriers are subjected to serve there as well. The safety concerns include toxicity, oxidative stress, inflammation and environmental effects. The lack of regulation and research on toxicity assessment are the obstacles to clinical translation.

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