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Nanotechnology in Reproductive Health Care

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Mini Review Article

Boomi Manivannan[1], Reena Sharma[2*] and Shipra Goyal[3]

[1,2]*Shandi Global Pte Ltd. Singapore*

[3]*Kanoria P G Mahila Mahavidhyalaya, Jaipur. Rajasthan India*

***Correspondence author**

Reena Sharma
Shandi Global Pte Ltd.
Singapore

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Abstract

In Reproductive healthcare and its management, nanomaterials and the nanotechnology have a tremendous impact in improving the therapeutics, treatment, imaging, and diagnosis. The technology is useful in conception, contraception, assisted reproduction, treatment of postmenopausal syndromes and in the treatment of Sexually Transmitted Infections. The present review summarizes, the use of nanotechnology in reproductive health care and the regulatory implications in commercialization of the technology.

Introduction

Nanotechnology, a biomedical application involving sub micro sized nonmaterial's as carrier molecules of size ranging from the atomic level at around 0.2 nm (2 Å) up to around 100 nm" [1] has a tremendous impact on human reproduction in improving the therapeutics, imaging, diagnosis and presentation, through its inherent nature of controlled and targeted delivery at site, increased permeability through biological barriers and increased bioavailability, thus enhancing its efficiency [2, 3].

Nanotechnology in reproductive health care is applied to fertility/ infertility related issues including assisted reproduction and contraception, detection, treatment and prevention of Sexually Transmitted Diseases (STDs), cancer screening and therapeutics and on hormone therapies [4]. Nanotechnology in reproductive medicine plays a significant role in diagnosis and treatment without or minimal surgical involvement. Gold nanoparticles, Iron oxide nano particles, Silica coated gold nano particles with cadmium selenide quantum dots and PEGylated lysosomes have been successfully demonstrated with enhanced sensitivity in detection of Ovarian cancer [5, 6, 7]. Magnetic nano particles have been used in the treatment of cervical cancer and uterine leiomyoma [8, 9]. Gold nano particles conjugated to Prostate Specific Antigen (PSA) antibodies and Silicon Nano wires enhance sensitivity in detection of PSA in Prostate Cancer Patients [10, 11, 12]. Super paramagnetic iron oxide nano particles (SPION) encapsulated to Anti Prostate Specific Membrane Antigen (PSMA) used to increase the sensitivity of MRI in Prostate Tumour Detection [13].

Nanotechnology in Contraception

Topical vaginal application, using Copper-Curcumin- B Cyclodextrin nano formulations exerted potential *in vitro* spermicidal activities, suggested potential of this nano complex as a topical vaginal formulation for contraception in women [14]. Antifertility properties of nanocomposite containing Copper low density polyethylene as an intra-uterine device [15], polymeric nano formulation of sustained release Follicle Stimulating Hormone -receptor binding inhibitor-8, an octo peptide nanoparticles (OPNP) [16], contraception through gene silencing, by means of chitosan conjugated Gonadotrophin Releasing Hormone (GnRH), using chitosan as nano vehicle for the targeted delivery of DNA to silence the GnRH expressing cells [17], spermicidal action of iron oxide copper Styrene Maleic Anhydride (SMA) with Dimethyl Sulphoxide (DMSO), through drug-sperm interaction/inhibition, mediated by pulsed magnetic field for sustained release spermicidal action in human vas deferens/fallopian tubes of male/female [18], silver nano particle coated condoms with antimicrobials action [19] have been reported. The SMA-DMSO formulation, RISUG (Reversible Inhibition of Sperm Under Guidance) in male offers long term reversible contraception, when injected in vas deferens, *in situ*, the procedure is currently under Phase III Clinical Trials [20, 21].

Nanotechnology in Management of Sexually Transmitted Diseases (STDs)

Nano formulations in antiretroviral therapy through sustained release and targeted delivery in HIV/AIDS patients helped to improve mortality/morbidity of infected individuals. An experimental nano formulation MK-1439 with MK-1439 film coated tablet, nano formulation of efavirinze and lopinavir containing non nucleoside reverse transcriptase inhibitor TMC-278 LA and integrace inhibitor GSK 1265744, nano formulation of HIV antigen conjugated with polyethylamine mannose coding the DNA Plastid dermavir patch vaccine, a non nucleoside reverse transcriptase inhibitor MC 1220 formulated with lecithin/ cholesterol based liposomes and nano particle PLGA carrying rilpivirin are few of the nano formulations against HIV/AIDS therapy, currently under various stages of Clinical Trials [22-26].

Carbosilane dentrimer and nanoparticles in film have been tested in animal models for the treatment of HIV infections [27, 28].

Reports on nano materials and the nano technology, predominantly improve diagnosis, detection and treatment of STDs are well documented. Enhanced HIV-1 detection using nano technology, viz., vertically confirmed electrical detection based on Scanning Tunnelling Microscopy (STM), HIV-1 virus detection by Optical Detection System based on Localized Surface Plasma Resonance (LSPR), Electrochemical detection of HIV-1 virus based on Direct Electron Transfer (DET) in the virus and HIV-1 detection by Surface Enhanced Raman Spectroscopy (SERS) using plasmonic nano particles are currently under progress [29].

A genosensor based on polyaniline-iron oxide carbon nanotubes (PANI-nFe3O4, CNT) and chitosan-iron oxide nano composite bioelectrode have been shown to be effective in diagnosis of STD by *Neisseria gonorrhoea* [30, 31]. A rapid, cost effective diagnosis and detection of Human Papilloma Virus (HPV) with accuracy and sensitivity has been demonstrated using a nano based biosensors [32].

Clinical diagnosis of *Ureaplasma parvum* and *Chlamydia trachomatis* by visual protein micro array method using gold nano particles and silver enhancement technology [33], detection of syphilis by quantum dot based point of cure tests [34], nano particle based colorimetric assay using gold mag immune probes for syphilis [35] and syphilis immunoassay based on polyelectrolyte coated gold nanoparticles [36] have also been reported.

Protective immunity against *Chlamydia trachomatis* by recombinant Major Outer Membrane Protein (MOMP), encapsulated in PLGA Nano particle has been reported in mice [37] and sustained delivery of MOMP Peptide in vivo in mice [38]. *Chlamydia trachomatis* DNA Vaccine, formulated from rMOMP encapsulated in chitosan nano particle shown to offer better protection from enzymatic digestion, enhanced stability, increased delivery and expression of DNA of MOMP peptide *in vitro* as well as in vivo in mice [39]. A nano device, 4 -polyamidoamine (PAMAM) dentrimer-azythromycin conjugate for the treatment of *Chlamydia trochomatis* infection showed enhanced intracellular drug delivery *in vitro* [40].

Nanotechnology in Assisted Reproductive Technology (ART)

In Assisted Reproduction, gold, silver, carbon and magnetic nano materials are used in Preimplantation Genetic Screening (PGS) and Preimplantation Genetic Diagnosis (PGD) for a faster, easier, specific and sensitive method development [41]. Silica nano particles, magnetic iron nano particles, halloysite clay nano tubes and poly (vinyl alcohol) coated iron oxide nano particles have been shown to enhance the delivery of nucleic acids to produce genetically modified embryos via gene transfer in bovine spermatozoa [42-45].

In bovine oocyte culture, nanoencapsulated melatonin in *in vitro* maturation medium (IVM) showed decreased apoptosis, decreased Reactive Oxygen Species (ROS), increased cleavage and increased blastocyst production rate [7]. Nano encapsulated tretinoin in Lipid Core Nano Capsules (LNC) is also showed higher cleavage and blastocyst, decreased ROS of bovine oocytes in IVM [46]. IVM medium supplemented with melatonin loaded LNC showed increased embryo quality and blastocyst hatching [47].

Nanotechnology in reproductive medicine, particularly in assisted reproduction, although closer to commercial application, the nano toxicity may be detrimental to embryo development and embryo quality, as these nano materials can cross the placental barrier and can cause anatomical defects in the foetuses, particularly, silver nano materials and carbon nano tubes can cause damage in live foetuses and increase foetus resorption, thus use of nano materials in assisted reproduction is not viewed encouragingly [48-51].

Nanotechnology in Postmenopausal Management

Significant role of nanotechnology in the infertility management has also been well documented. Among infertile women, endometriosis is the major problems, affecting 25 to 30% of infertile women of reproductive age. Paramagnetic iron oxide nano particle (IONP), magnetic oxide nanoparticle modified with Hyaluronic acid (HA-Fe3O4), lipid grafted chitosan micelles loaded with Pigment Epithelium Derived Factor (PEDF), cerium oxide nano particles Nanoceria, are few of the nanotechnology associated imaging and treatment of endometriosis reported in literature [52-56].

In treatment of uterine fibroids , during cryosurgery, nanoparticles conjugated with Tumour Necrosis Factor – alpha (TNF Alpha NP) as a cryoadjuvant showed reduced recurrence of tumour growth than the conventional cryosurgery [57]. As an alternative to hysterectomy, to deliver the 2 methoxy estradiol, a biologically active metabolite of estradiol having anti tumour and anti angionic properties into human leiomyoma cell line, poly L Lysine PLGA nano particle have been used [58]. Treatment of uterine fibroids with conjugated adenovirus containing magnetic nano particle has shown suppression of cell proliferation and induced apoptosis, when adenovirus was used as a gene delivery vector [59].

In menopausal women, in order to reduce the risks associated with hormone therapy, viz., breast cancer, pulmonary embolism, coronary disorders etc., nano particulate transdermal hormone therapy has been investigated using nano particulate estradiol and nano particulate progesterone. This therapy results in to consistent delivery of therapeutic levels of the hormones and shown to reduce adverse local side effects, lower incidences of stroke, venous thromboembolism and reduced vasomotor symptoms [60, 61]. Non structured composite ceramics, metals and polymers have shown to possess greater surface area, roughness to promote osteointegration and enhance osteoblast function in management of post-menopausal osteoporosis [62]. Risedronate/ zinc hydroxyapatite nano particle and calcium phosphate nano particle have been shown to be suitable vehicle for bone specific drug delivery [63, 64]. Water dispersible magnetic nano particle conjugated to biphosphonate (Bis) conjugated iron (II and III) oxide (Fe3O4) has been shown to reduce the activity of osteoclasts through thermolysis [65].

In diagnosis, imaging and management of post menopausal cardio vascular diseases, nano particles conjugated to 5-(4-carboxyphenyl)-10,15,20 triphenyl-2,3-dihydroxychlorin and perfluro carbon nano particles conjugated to fumagillin have been successfully applied in MRI imaging [66, 67].

Conclusion

Based on the above literatures, although it has been proven that nano medicine and nano technology are promising and may provide a better therapeutic application for physicians of Reproductive Health Care, there are associated challenges till to be addressed. Many of the nano technology are in initial stages and there are potential pitfalls in converting them to clinical applications and finally to marketing. The ligands and composition of nano particles are known to show variable degrees of cytotoxicity to human cells which need to be primarily addressed.

In a nanomaterial-based drug delivery system, it is very crucial to study the ratio of carrier bound drug or encapsulated drug to free the drug after purification, which determine the quality and the biological activity of the product. This property has to be tested either *in vivo* or in a relevant physiological medium *in vitro* to assess the efficiency and safety of the nanomedicine and comparison of pharmacokinetics of the nanomedicine formulations and of the free drug.

The major hurdles, limiting the nano medicine in the worldwide market for sale and distribution are the practical challenges in transforming the nano medicine development from R&D to commercialization. The major challenges being the Intellectual Property Rights, Safety of Nano formulations to its acceptable level by Regulatory Agencies, Compatibility issues at biological level, viz., blood, inter and intra cellular, tissues and organs, etc., Scale up and characterization of nano materials during manufacturing and lack of reliable and validated quality control methods for regulatory certification as a drug/device irrespective of their therapeutic benefits at developmental stages. To enhance the International level of acceptance, the design and system of nanomedicine should be reproducible at commercial scale under cGMP Standards.

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