NANOTECHNOLOGY
AND REPRODUCTIVE HEALTH



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Nanotechnology and Reproductive Health

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FOREWORD I



It is with great pleasure and academic appreciation that I write this foreword to the timely and comprehensive book Nanotechnology and Reproductive Health, edited by the esteemed scholar, Professor Mohammad Mehdi Ommati. As a professor with deep expertise in nanomedicine and drug delivery systems, I have witnessed firsthand the transformative impact of nanotechnology on modern healthcare. Among its many applications, its role in reproductive health stands out as one of the most promising—and yet, underexplored—frontiers. This book arrives at a crucial time, when global challenges in reproductive medicine demand innovative, precise, and interdisciplinary solutions.

Professor Ommati has assembled a distinguished team of international experts to produce a scientifically rigorous and forward-looking exploration of how nanomaterials interact with reproductive biology. This volume offers a multidisciplinary perspective, integrating insights from nanotechnology, reproductive physiology, toxicology, biomedical engineering, and ethics. The result is a holistic and timely contribution to a rapidly evolving field.

The chapters span a broad and interconnected landscape—from foundational applications of nanotechnology in diagnostics, therapeutics, and tissue engineering (Chapter 1), to the critical issue of nanomaterial-induced reproductive toxicity (Chapter 2). This dual lens—innovation and caution—reflects the maturity of a field poised to strike a balance between promise and responsibility.

Chapter 3 presents a compelling analysis of the environmental impact of nanoparticles, particularly their potential reproductive toxicity in both sexes and across generations. Chapter 4 then shifts focus to the translational potential of nanomaterials in addressing male and female reproductive disorders. The discussion of Nano-enhanced Assisted Reproductive Technologies (NARTs) in Chapter 5 is particularly insightful, offering novel strategies to enhance gamete selection, improve embryo implantation, and increase overall clinical success rates.

Chapter 6 examines the often-overlooked interface between nanoparticles and gamete biology, shedding light on how these materials may impact fertilization processes at the molecular level. Chapter 7 further advances this discussion by examining the emerging role of nanoparticle-based delivery systems in treating reproductive cancers and inflammatory conditions, with enhanced precision and minimized side effects.

Among the book's most significant contributions are the chapters addressing mechanistic and translational concerns. Chapter 8 explores the endocrine-disrupting effects of nanomaterials on the neuroendocrine axes. In contrast, Chapter 9 examines the permeability of the placental barrier to nanoparticles, highlighting the potential risks to both maternal and fetal health. These chapters are essential reading for researchers and clinicians seeking to understand the long-term implications of nanomaterial exposure.

Chapter 10 provides a forward-looking analysis of nanotechnology-based contraception, signaling a shift toward more innovative, reversible, and user-friendly approaches. The inclusion of Chapter 11, which explores the ethical dimensions of reproductive nanotechnology, is especially valuable. It underscores the importance of robust ethical frameworks, regulatory oversight, and public engagement as these technologies continue to evolve.

Finally, Chapter 12 offers a glimpse into the future of reproductive nanomedicine, highlighting the integration of artificial intelligence and personalized medicine. These concluding chapters point toward a new era of innovation—one that is not only scientifically advanced but also ethically grounded and environmentally sustainable.

This book is more than a technical reference; it is a visionary roadmap for the future of reproductive nanomedicine. The contributors' scientific excellence, combined with Professor Ommati's editorial leadership, has resulted in a seminal work that will guide researchers, clinicians, educators, and policymakers alike.

I offer my heartfelt congratulations to all the contributors and wholeheartedly recommend this volume to anyone seeking to understand, apply, or ethically govern the integration of nanotechnology in reproductive health.

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FOREWORD II



Science, at its most transformative, is not only the pursuit of knowledge but the pursuit of hope. Few areas embody this truth more deeply than the meeting point of nanotechnology and reproductive health—a place where the smallest materials known to humanity hold the power to shape the most profound beginnings of life.

Nanotechnology and Reproductive Health, edited by Professor Mohammad Mehdi Ommati, is more than a scientific compendium; it is a testament to what can be achieved when innovation, curiosity, and responsibility walk hand in hand. Across its pages, the reader will encounter a spectrum of insight—discoveries that promise to heal, technologies that aim to protect, and ethical reflections that remind us of our duty to use science wisely.

The early chapters explore the vast potential of nanotechnology in reproductive medicine—how engineered materials can illuminate disease at its earliest whisper, deliver therapies with unprecedented precision, and even guide the regeneration of life-giving tissues. Yet the volume does not shy away from the shadows. It directly addresses the pressing questions of nanomaterial safety, the subtle ways these particles may alter fertility, and their capacity to cross generational boundaries.

Here, innovation is tempered with vigilance. The discussions move from the clinic to the environment, from the intimacy of gamete interaction to the complexity of endocrine regulation and placental protection. The middle sections introduce us to nano-enhanced assisted reproductive technologies, to strategies that could one day make infertility treatments gentler, more effective, and more accessible. The later chapters turn to the horizon—examining AI-assisted contraception, and precision nanomedicine as part of the next chapter in reproductive care.

What makes this book exceptional is not just the breadth of its science, but the unity of its vision: a future where technology does not replace the human touch in medicine, but strengthens it; where the tools of the nanoscale are wielded with the wisdom of the heart as well as the rigor of the mind.

• To the scientist, this work offers a roadmap for discovery.

• To the clinician, it offers tools for healing.

• To the policymaker, it offers guidance for governance.

• And to every reader, it offers a reminder that the smallest things we create may one day safeguard the most precious beginnings of life.

It is with deep respect that I commend this volume to all who seek to explore, advance, and safeguard the union of nanotechnology and reproductive health.

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PREFACE



Nanotechnology has opened an unprecedented chapter in biomedical sciences, reshaping how we diagnose, treat, and prevent complex health challenges. Nowhere is its transformative potential more profound than in the field of reproductive medicine, where nanoscale innovations meet the intricacies of life's beginnings. *Nanotechnology and Reproductive Health* brings together leading global experts to explore this intersection and offers a comprehensive examination of nanotechnology's roles in reproductive physiology, pathology, and therapeutics.

As the editor, I draw on more than a decade of research in reproductive toxicology, endocrinology, and nanopharmacology, with a focus on xenobiotic-induced infertility, mitochondrial dysfunction, oxidative stress, and endocrine disruption; topics increasingly relevant in the age of engineered nanomaterials. My editorial work, from biology for students to leadership roles in journals including scientific reports, reproduction and fertility, trends in pharmaceutical sciences and technologies, and frontiers in veterinary science, has further deepened my commitment to advancing knowledge across these interconnected domains.

This volume would not have been possible without the exceptional contributions of distinguished scholars from around the world. I am especially grateful to Professors **Reza Heidari, Hong-Wei Wang**, and **Socorro Retana-Márquez**, whose expertise as Advisory Editors ensured the coherence and scholarly rigor of this work. I am deeply honored to include Forewords by two internationally renowned scholars, Professor **Soodabeh Davaran** and Professor **Rovshan Khalilov**, whose visionary perspectives on nanotechnology and its biomedical applications greatly enrich this volume. Their willingness to contribute despite having no prior professional connection to me reflects their generosity and commitment to advancing global scientific discourse. Their thoughtful essays frame this work with scholarly depth and inspire readers to engage with nanotechnology's transformative potential in reproductive health. As I transition to my new position, I am grateful to Linyi University for welcoming me into their academic community. I extend my sincere gratitude to Professor **Zhen Wang** (Department Head), Professor **Xinyue Song** (Dean's Assistant), and Mrs. **Ronghua Liu** (Faculty Secretary) at Linyi University for their invaluable support and guidance during my transition. Their dedication to fostering international collaboration and their warm welcome into the School of Medicine community have been instrumental in making this move possible. I also extend my appreciation equally to Shiraz University of Medical Sciences, Shiraz, Iran, for its steadfast support. I offer my deepest thanks to my colleagues at both Linyi University and Henan University of Science and Technology, whose encouragement has sustained this effort.

Structured to guide readers from foundational principles to clinical applications and future directions, this book is designed for researchers, clinicians, graduate students, and policymakers alike. By integrating cutting-edge science with ethical and practical considerations, it aims to serve as both a definitive reference and an invitation to innovate responsibly.

As we stand on the new era in reproductive medicine, we must pair scientific ambition with ethical foresight to ensure that nanotechnology's benefits are realized inclusively and sustainably. I hope this volume inspires collaboration, drives discovery, and makes a meaningful contribution to a healthier, more equitable, and more sustainable future.

Finally, I wish to express my deepest gratitude to my wife, *Samira Sabouri*, and to our two wonderful children, *Adrian* and *Ariana*. Their unwavering love, patience, and the peaceful home they create have been my constant source of strength and inspiration. It is through their presence that I find the calm and joy necessary to bring this work to life.

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CHAPTER 1

Nanotechnology in Reproductive Medicine

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Abstract: Nanotechnology has become an innovative advancement in medical sciences, providing novel approaches for diagnosing, treating, and preventing diseases. Nanomaterials possess distinct properties, including enhanced surface area and high reactivity, which increase their interactions with biological systems. These features have allowed great progress in diagnostic technologies, leading to the creation of highly sensitive molecular probes to enhance signal detection, as well as biosensors for the early detection of diseases. Nanotechnology allows drugs to be delivered precisely to specific locations during therapy, thereby increasing treatment efficacy and minimizing systemic side effects. Nanoparticles are also critical in gene therapy, allowing the precise delivery of genetic material to specific cells, and in tissue engineering, where nanomaterials promote tissue repair and regeneration. This chapter highlights essential topics exploring the wide-ranging applications of nanotechnology in diagnostics, targeted drug delivery, gene therapy, tissue engineering, and personalized medicine. Despite its significant potential to advance healthcare, nanotechnology faces challenges such as nanoparticle toxicity, biocompatibility issues, and lagging regulatory oversight, which must be addressed to ensure its safe and effective use in clinical settings.

Keywords: Advanced therapeutics, Biomedicine, Drug development, Fertility, Reproductive system.

INTRODUCTION

Nanotechnology is a rapidly evolving field that has gained considerable application in medical sciences. Nanomaterials have physicochemical properties that differ significantly from those of other molecules. They enhanced surface

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area and increased reactivity, offering new opportunities for diagnosing, treating, and preventing diseases. The use of nanotechnology in medicine, known as "nanomedicine," can provide precise, targeted, and highly effective solutions to patients' needs. So, nanotechnology is introducing innovative diagnostic and therapeutic strategies, thus reshaping the medical landscape [1].

Nanotechnology has demonstrated high utility in diagnostics, particularly in developing highly sensitive imaging agents and biosensors. Due to their physicochemical properties, nanoparticles are able to interact with biological molecules, facilitating the creation of imaging agents that specifically target disease biomarkers, enabling early detection of conditions such as cancer, cardiovascular diseases, and neurological disorders. For instance, magnetic nanoparticles are being used as contrast agents in magnetic resonance imaging (MRI), enhancing the resolution and clarity of diagnostic images [2].

Moreover, gold nanoparticles offer high sensitivity for detecting trace amounts of biomarkers, with promising results in optical imaging [3]. These advancements are critical for the early diagnosis of various diseases.

Traditional drug administration methods often show low efficacy due to the inability of drugs to target specific tissues, causing systemic side effects and limited efficacy. In comparison, Nanotechnology has the potential to enhance drug delivery systems significantly therapeutically. So, nanoparticles could be engineered to deliver therapeutic agents directly to disease sites [4]. In cancer therapy, nanoparticles can carry chemotherapy drugs directly to tumor cells and minimize the damage to healthy tissues. This demonstrates that targeted delivery of therapeutics significantly improves treatment outcomes and decreases side effects [4, 5]. Additionally, nanomaterials may be designed to release drugs in response to specific stimuli (*e.g.*, changes in pH), ensuring drug release is controlled and precisely delivered. This approach improves therapeutic results, reducing the need for frequent dosing and decreasing adverse drug reactions.

Gene therapy is one of the most promising applications of nanotechnology in medicine. This involves the introduction or modification of the genetic material inside a patient's cells in order to treat or prevent diseases [6]. Nanoparticles, such as liposomes and dendrimers, have arisen as key tools for such delivery of genetic materials into cells [7]. Thus, nanoparticles can encapsulate nucleic acids (DNA and RNA), protecting them from degradation and increasing cellular uptake [7]. This capability provides the potential to treat various disorders, including reproductive system diseases [8]. Furthermore, the use of nanoparticles for gene delivery can improve precision in gene editing techniques (*e.g.*, CRISPR) by ensuring the precise delivery of editing components to specific cells [9].

Plus, nanotechnology has applications in tissue engineering and regenerative medicine [10]. Part of tissue engineering entails the creation of synthetic or biological scaffolds that support the growth of new tissues and organs. Nanostructured materials are especially advantageous in this context [11]. Use of nanomaterials as scaffolds enhances tissue regeneration, such as bone, cartilage, and skin, while promoting greater efficiency in the healing of wounds. In addition, nanomaterials may stimulate stem cells, directing their differentiation into specific cell types as needed for tissue repair. This strategy holds great potential for the facilitation of organ transplants, and the treatment of injuries and degenerative diseases [10, 11].

In the future, nanotechnology will play a pivotal role in the development of medical treatments that can be tailored for each patient. Nanotechnology can potentially customize therapies with the utmost precision, thus enabling the creation of specific treatments designed to meet individual needs. For example, nanoparticles can be engineered to target specific mutations in cancer cells, thus ensuring that treatment will be highly effective while minimizing damage to healthy cells. This method could remodel disease treatment, leading to more effective and less invasive therapies.

Nanotechnology in Reproductive Medicine

The integration of nanotechnology and nanomedicine in the reproductive sciences has enabled new approaches for the improvement of fertility treatments, prenatal care, and the overall management of reproductive diseases [8]. The ability of nanotechnology to precisely deliver exact drugs and gene therapies is especially beneficial for the management of various reproductive disorders. As an example, nanoparticles have been used for precise drug delivery to the ovaries and testes. This technical approach can potentially improve the efficacy of treatments for conditions such as polycystic ovary syndrome (PCOS), endometriosis, and male infertility [8, 12, 13]. In the field of assisted reproductive technologies (ART), myriad research has documented enhanced delivery of hormones, growth factors, and genetic material to specific sites through nanomedicine and improved success rates of In Vitro Fertilization (IVF) and embryonic implantation [14]. The use of nanomaterials as diagnostic tools holds high promise in reproductive medicine. These tools could be used as biosensors for the earliest detection of reproductive cancers (*e.g.*, ovarian and cervical cancer) by the identification of specific biomarkers at significantly lower concentrations than those of traditional methods [3] Fig. (**1**). Furthermore, nanotechnology facilitates the creation of cutting-edge drug formulations and systems for controlled release. Formulations such as these could significantly reduce the adverse effects of drugs and improve therapeutic results. In addition, the use of nanomaterials in gene therapy for the precise

CHAPTER 2

Nanomaterial-Induced Reproductive Toxicity: Mechanisms, Mitigation, and Future Directions

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Abstract: The swift expansion of nanotechnology has modernized diverse fields in recent years, such as medicine, agriculture, and environmental science. Nevertheless, alongside its transformative potential, concerns about the unintended toxicological effects of engineered nanomaterials (ENMs) on human and animal health have emerged as a serious focus of studies. This chapter examines ENM-induced reprotoxicity, synthesizing mechanistic insights, experimental evidence, and translational perspectives. The chapter explores how nanoparticles (NPs) impair reproductive system physiology through key pathways, including oxidative stress, mitochondrial dysfunction, apoptosis, and endocrine disruption. Although there is a good body of literature on NP-induced toxicity in the reproductive systems of both males and females, a notable gap remains in comprehensively understanding sex-specific responses. Addressing this gap is essential, as hormonal and physiological differences between sexes may influence susceptibility to NP exposure and its long-term consequences. Recent progress in multi-omics research highlights further mechanisms, including autophagy, inflammation, and gut microbiota dysbiosis, that mediate NP-induced reproductive toxicity. This chapter also sought to uncover the roles of placental transfer and fetal developmental impacts, underscoring the risks NPs may pose to future generations. Moreover, it assesses emerging therapeutic strategies,

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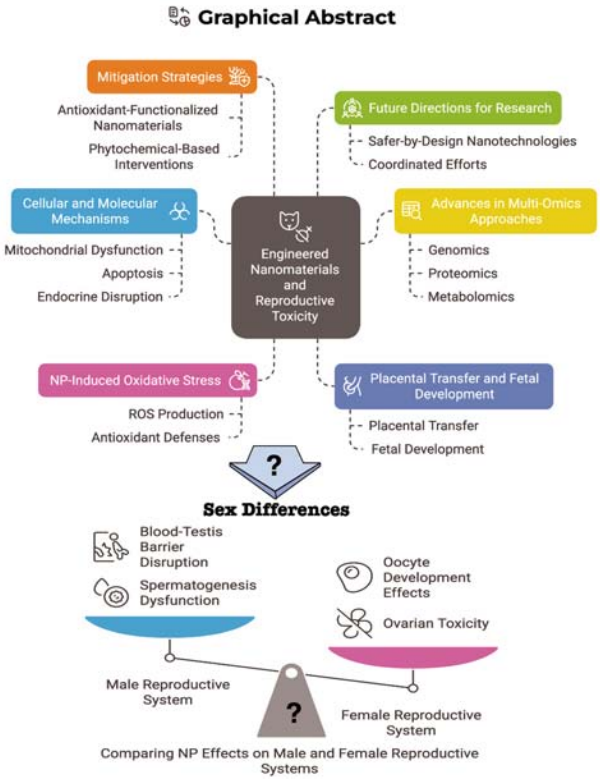
such as antioxidant-functionalized nanomaterials and phytochemical-based interventions, which offer promising avenues for counteracting oxidative injury and restoring hormonal balance. Structured into thematic sections, the chapter begins with an overview of NP-induced oxidative stress, progresses through cellular and molecular mechanisms of toxicity, and concludes with future directions for research and the development of Safer-by-Design (SbD) nanotechnologies. By integrating cutting-edge scientific advances with practical considerations, this work highlights the urgent need for coordinated efforts to mitigate reproductive risks and ensure the responsible application of nanotechnology in the 21st century.

Keywords: Apoptosis, Autophagy, Endocrine disruption, Epigenetic modifications, Mitochondrial dysfunction, Nanodiagnostics, Oxidative stress, Placental transfer, Reproductive barriers, Safe-by-design, Sex-specific toxicity, Steroidogenesis, Transgenerational effects.



Graphical Abstract. Engineered nanomaterials and reproductive toxicity.

INTRODUCTION

In recent decades, nanotechnology has ushered in transformative innovations across numerous sectors, with healthcare emerging as the most commercialized application. As of 2020, it accounted for approximately 19.5% of global

nanotechnology investment, a trend primarily driven by rapid advances in nanodiagnostics, nanosurgical systems, and targeted drug-delivery platforms [1]. By 2022, nanoparticles (NPs) had become the dominant nanomaterial category, accounting for 74% of capital investment, with drug delivery comprising 25.1% of clinical applications [1]. Although more recent market-wide figures are still emerging, current research trajectories and funding priorities strongly suggest the continued expansion of nanomedicine into the mid-2020s. Despite its remarkable benefits, concerns about unintended consequences, particularly human health, have grown. Among these, the impact of engineered nanomaterials (ENMs) on reproductive health represents a critical yet underexplored dimension of nanotoxicology. As societies increasingly integrate nanotechnology into daily life, understanding its potential risks to fertility and generational health becomes timely and imperative. For instance, recent studies have demonstrated that NPs such as single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) induce spermatotoxic effects in male mice, disrupting spermatogenesis and mitochondrial function through oxidative stress pathways [2].

Within this expansive domain, the subfield of reproductive toxicology has gained heightened attention due to accumulating evidence linking NP exposure to adverse outcomes in both male and female reproductive systems. These systems are particularly vulnerable to NP exposure due to their dynamic cellular turnover, intricate endocrine regulation, and specialized physiological barriers such as the blood-testis and placental barriers [3 - 9]. While significant insights have been gained, critical gaps persist in our understanding of how NPs affect gametogenesis, hormone signaling, embryonic development, and long-term fertility. A growing body of research implicates a constellation of mechanisms, including oxidative stress, mitochondrial dysfunction, inflammation, and endocrine disruption, as central drivers of these toxicological outcomes [10 - 14]. Recent advances in multi-omics methodologies have further revealed additional layers of complexity, including autophagy, apoptosis, and gut microbiota dysbiosis, as mediators of NM-induced gonadal injury [15, 16]. These emerging insights underscore the urgency of deepening our mechanistic understanding of NP-induced reproductive toxicity, an endeavor this chapter aims to advance.

This chapter specifically focuses on the toxicological impacts of NPs on reproductive health, synthesizing recent mechanistic insights, experimental findings, and translational perspectives. Drawing on a comprehensive synthesis of current literature and experimental studies, the chapter elucidates how various nanomaterials, ranging from metal oxides (*e.g.*, TiO_2, ZnO, AgNPs) to carbon-based structures (*e.g.*, CNTs), interfere with reproductive physiology *via* oxidative damage, hormonal dysregulation, mitochondrial injury, and apoptotic or

CHAPTER 3

Nanoparticles in the Environment and their Effects on the Reproductive System

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Abstract: Nanoparticles are insoluble, bio-persistent, microscopic particles that range in size from 1 to 100 nm and have one or more exterior dimensions exhibiting unique physical, chemical, and biological properties. Nanoparticles, ubiquitous in modern technology and consumer products (food, clothes, cosmetics, and medicines), have raised concerns about their potential toxicity to human health, particularly reproductive health. Examples of NPs are TiO_2, ZnO, SiO_2, CuO, Cd, Sb, As, and nano-polyethylene. NPs enter the body through different routes, *e.g.*, ingestion, inhalation, skin penetration, and needling. By increasing the level of ROS, NPs have adverse effects on DNA and mitochondria. In the last couple of decades, modifications in the field of nanotechnology have promoted the need to minimize the dangerous effects of NPs on the reproductive system, which has major health concerns. Many researchers have confirmed the deleterious effects of NPs by interpreting deposition points, but few studies have mainly focused on NPs deposition of NPs in reproductive organs. Based on composition, NPs may be lipophilic or hydrophilic; they can cross cell membranes through diffusion and active transport. Some studies dealt with the effects of NPs on the male reproductive system by interpreting the sperm parameters (sperm number, motility, viability, quality, morphology, and concentration), histopathology of seminiferous tubules, and the level of male hormones, mainly testosterone. Numerous investigations have demonstrated that nanoparticles combine in the ovary, uterus, and placenta and induce ovarian toxicity, alter the hormonal balance, and increase the risk of reproductive tract cancer and epigenetic modifications. NPs affect ovarian cells and cause ovarian toxicity by increasing the level of ROS production. There is a significant reduction in pregnancy rate due to cyst formation and follicular atresia. In this review, we will understand how NPs enter the body and their effects on the male and female reproductive systems.

Keywords: Nanoparticles, Ovarian toxicity, Pregnancy rate, Seminiferous tubules, Sperm quality.

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INTRODUCTION

Nanoparticles vary in size from 1 to 100 nm and have one or more exterior dimensions [1]. Because of their tiny size, NPs exhibit various unique mechanical, electrical, optical, thermal, and magnetic capabilities. NPs are widely used in industries such as material science, engineering, physics, chemistry, medicine, pharmacology, and biology, among other domains of life. As a result, they frequently target humans in many ways [2]. NPs have harmful effects on multiple critical organs, such as the liver, kidney, brain, and reproductive organs, like the testes and ovaries [3]. NPs are utilized in 1,814 products, including textiles, antibiotics, sports, and numerous food items, and their number is rising daily. The overuse of NPs across all aspects of life has prompted researchers to focus on the health issues arising from their use [4]. Overuse of silver nanoparticles occurs in a variety of industries, including textiles, wound treatment, and electrical and medical appliances. Ag toxicity in humans is of interest to researchers due to the widespread use of Ag-NPs in human health [5]. NPs can form in two different modes: "bottom up" and "top down." In a top-down scenario, NPs are deliberately fabricated because characterizing their precise size and chemical properties. The parameters known as NPs' kinetic properties are designed to measure how much material is absorbed and how it happens in living organisms [6]. Almost 72 NPs have been identified in food and beverage products in the past few decades. Several NP types, including SiO_2, TiO_2, ZnO, and Ag NPs, are utilized as drug-resistant agents in food.

NPs can enter the body by ingestion, inhalation, or injection. Once inside, the circulation carries the NPs to several organs, including the ovaries in women and the liver, spleen, and testicles in men. NPs can cross both the Blood-Brain Barrier (BBB) and the Blood-Testis Barrier (BTB) [3]. Male reproductive organs are more susceptible to exogenous toxins and NPs. Due to their small size, NPs can cross the blood-testis barrier and concentrate in reproductive organs. NPs are employed in both fluorescence imaging and medication delivery systems. For targeted therapy, nanomaterials are used as drug carriers that directly approach sensitive materials in the environment, leading to the production of pollutants. The research showed that Titanium dioxide NPs can pass BTB and induce inflammation and changes in gene expression, thereby impairing the reproductive system [7]. Plastic particles ranging in size from 1 to 1,000 nm are referred to as nanoplastics, while those smaller than 5 mm are called microplastics [8].

Polyethylene(PE), polypropylene (PP), polystyrene (PS), polyvinylchloride (PVC), and polyethylene terephthalate (PET) are the most common types of microplastics [9]. NMs can pass the blood-brain and blood-testes barriers, which has raised worries among professionals concerning the male reproductive system.

Male infertility is one of the greatest difficulties in modern health, affecting about 70 million people worldwide. A high ratio of affected people in industrialized countries [10]. Different NPs have different roles in our daily lives. The world's most engineered metal oxide NPs are TiO_2-NPs. TiO_2-NPs are utilized to eliminate contaminants from wastewater. TiO_2 degrades many polycyclic aromatic hydrocarbons, chlorinated organic chemicals, dyes, cyanides, arsenic, and heavy metals-NPs [11]. According to research, these metal oxide nanoparticles (MONPs) can cross the blood-testis barrier and accumulate in the testis. Although some MONPs have been shown to protect male germ cells, multiple studies suggest that these nanoparticles harm male fertility by interfering with spermatogenesis. *In vitro* and *in vivo* studies show that exposure to MONPs may induce overproduction of reactive oxygen species, leading to oxidative stress, which is the primary molecular mechanism proposed to cause germ cell damage. The latter damages proteins, cell membranes, and DNA, which may eventually lead to dysfunction of the male reproductive system [12]. The reproductive system is a highly delicate biological system composed of reproductive tissues and gametes, and its main function is to transfer genetic information to offspring. This system is very delicate to environmental toxicants and NPs [13].

ENVIRONMENTAL EXPOSURES OF NANOPARTICLES AND REPRODUCTIVE TOXICITY

NPs produced by both industrial and natural processes are always present in human environments. The primary natural sources of NPs include forest fires, volcanic eruptions, crustal erosion, and photochemical processes in the troposphere. Additionally, NPs are created as hazardous byproducts [14]. The use of plastic items has grown dramatically worldwide in recent years, and by 2050, annual plastic manufacturing is projected to exceed 590 million tons [15]. Through physical abrasion and UV radiation, plastics in the environment can break down into tiny particles called microplastics (MPs), which are less than 5 mm in size and have the properties of being hard and brittle, colorless and transparent, and easily foam [16] as shown in Fig. (**1**). Polystyrene MPs are the most commonly found in the environment, coming from cosmetics, purses, and industrial and agricultural items [17, 18]. MPs represent a novel class of environmental pollutants that can enter the body *via* bioaccumulation and eventually impair human health [19]. According to earlier research, MP exposure may cause inflammation, metabolic problems, and reproductive system impairment [20]. When used in medical applications, single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT) are reproductive toxic. (SWCNT) and (MWCN) cause sperm toxicity, reproductive system injury, mitochondrial impairment, and ROS production [21].

CHAPTER 4

Nanomaterials in Male and Female Reproductive Health: Impacts and Opportunities

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Abstract: Nanomaterials have developed into effective tools for reproductive health because they provide new methods to identify, treat, and prevent medical conditions. The unique characteristics of these materials, which include their nanoscale size, surface alteration abilities, and precise delivery systems, enable them to effectively solve major issues in reproductive health research. The chapter examines how nanoparticles can be used to treat male infertility, female reproductive disorders, detect reproductive cancers, and develop contraceptive methods. The research examines toxicological and safety aspects of nanomaterials while also studying their ethical implications, which require scientific research and the formation of regulatory frameworks. The field shows strong potential since the scientific community needs to conduct research and comprehensive evaluations to establish safe and effective methods for using nanotechnology in reproductive health. The future holds enormous potential for nanotechnology to bring novel answers, as long as these hurdles are addressed wisely and systematically.

Keywords: Biocompatibility, Cancer detection, Diagnostic nanotechnology, Drug delivery, Ethical considerations, Female reproductive disorders, Infertility, Male infertility, Nanomaterials, Nanomedicine, Nanoparticles, Nanotechnology applications, Pharmacokinetics, Precision medicine, Reproductive disorders, Reproductive health, Safety, Targeted therapy, Therapeutic outcomes, Toxicity.

INTRODUCTION

Nanomaterials, identified by their size varying from 1 to 100 nanometers, express unique chemical and physical properties that differentiate them from bulk materials. Hence, they have applications across various fields like electronics, medicine, and environmental science. Their characteristics, including high surface area-to-volume ratio and different quantum effects, result in behaviors that are not seen in larger-scale materials, fostering innovations in different areas like imaging, drug delivery, and tissue engineering [1, 2]. As nanotechnology is conti-

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nuously advancing, it is becoming increasingly important to understand its potential effects on human health, particularly in the context of reproductive health.

Reproductive health is an important aspect of overall well-being, including the ability to maintain sexual health, reproduce, and ensure the health of future generations. Issues related to reproductive health, such as infertility and complications during pregnancy, are widespread around the world and have significant consequences for public health and quality of life [3]. The increasing applications of nanomaterials in consumer, medical, and industrial products are growing concerns regarding their impact on reproductive health. Research suggests that nanoparticles cross biologically established critical barriers, including the blood-testis and blood-placenta barriers, potentially leading to side effects on reproductive organs and functions [4].

The amount of research that has been done on nanomaterials in relation to their positive and/or negative impacts on reproductive health has been vast and thorough, and therefore nanomaterials have great potential in the development of imaging techniques, therapies, and contraceptives, and therefore there is the potential danger of exposure to nanomaterials, which has not been known up to this point and has the ability to cause reproductive damage such as DNA/genetic damage, inflammation, and oxidative stress, which would have negative impacts on fertility, hormonal balance, and the outcome of the pregnancy. Therefore, it is necessary to find the right balance in the opportunities that nanomaterials have to offer in terms of treatment and the right amount of knowledge regarding the dangers of using nanomaterials.

This chapter aims to discuss the current state of knowledge pertaining to the impact of nanomaterials on male and female reproductive health. It also aims to identify the mechanisms by which nanomaterials can affect the reproductive functionalities and the benefits and risks, and the opportunities for the applicability of nanotechnology.

As shown in Fig. (**1**), nanotechnological strategies are being developed to tackle emerging challenges in reproductive health [5]. By providing a thorough overview, this chapter aims to refine future research directions and contribute to the development of safe and effective applications of nanotechnology in reproductive health.

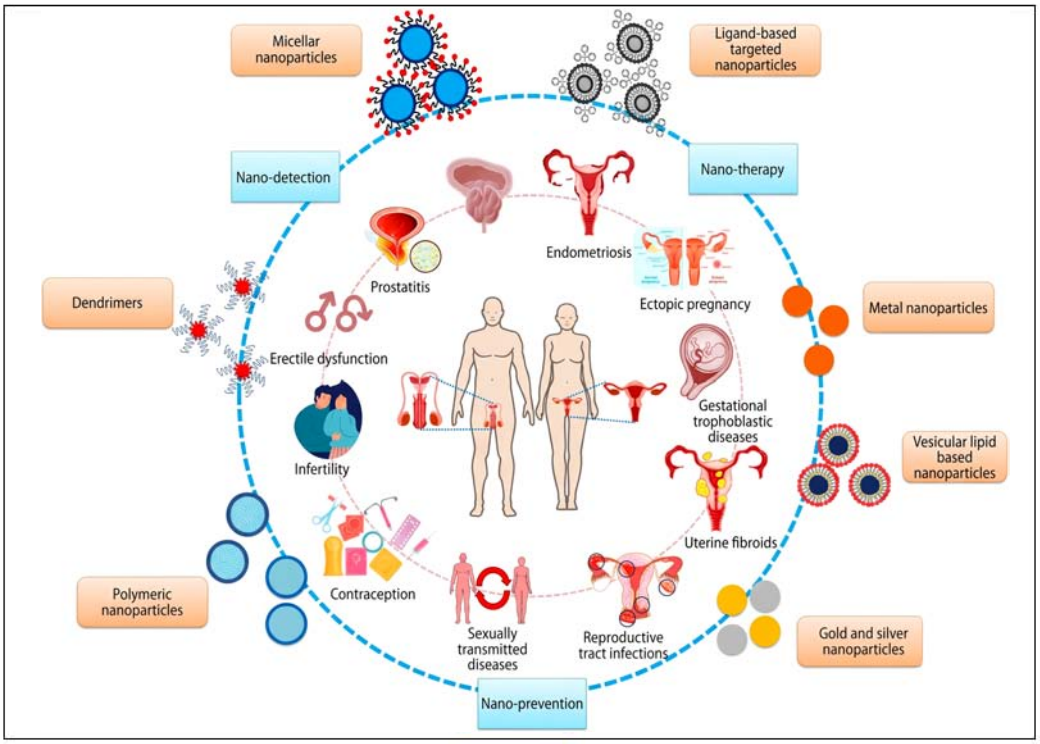

Fig. (1). Nanotechnological strategies for tackling the emerging challenges in reproductive health. Adapted from Shandilya[5].

TYPES OF NANOPARTICLES

Nanoparticles are promptly being utilized to alter the reproductive health market, supported by their small size to surface area ratio, their general size range is around 1-1000 nm, and the most active range for applicability of nanoparticles is 10-100 nm. These features of nanomaterials and particles are critical in their selection as appropriate carriers for medicines and controlled drug release. As shown in Fig. (**2**), various types of nanocarriers and nanoparticles are utilized for targeted drug delivery [24], which are further summarized in Table **1**.

CHAPTER 5

Nano-Enhanced Assisted Reproductive Technologies (NARTs)

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Abstract: Nanotechnology-Assisted Reproductive Technologies (NARTs) is an emerging, innovative technology in reproductive medicine. It has improved the accuracy, efficacy, and success rates of Assisted Reproductive Technologies (ART). The conventional ART methods, despite their excellence, have drawbacks in the form of low success rates, inability to implant embryos, and poor quality gametic selection. These challenges can be addressed through nanotechnology integration, which offers new solutions, including nano-based gametes and embryo selection, nano-based drug delivery, and improved implantation techniques. Metallic nanoparticles, polymer nanoparticles, quantum dots, and carbon-based nanostructures are two nanomaterials that have shown enormous potential for reproductive applications. These nanomaterials are endowed with special physicochemical characteristics: they have high surface area-volume ratios, are biocompatible, and exhibit controlled release, which enhances drug delivery, imaging, and diagnostic accuracy. Besides, NARTs have been developed as nanobiosensors and nanoinaging tools, providing real-time monitoring of reproductive cells and processes and enabling accurate intervention in ART, despite the following challenges: nanotoxicity, bioaccumulation, immune response, regulatory issues, and ethical considerations. Safety, efficacy, and affordability of fertility treatments that are based on nanotechnology are still of concern. Recent research has sought to further refine nanomaterials and non-invasive diagnostic tools, and to integrate NARTs with artificial intelligence and regenerative medicine to achieve more successful outcomes in the reproductive context. This chapter describes the principles, current practice, and

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future vision of NARTs and how they are revolutionizing reproductive medicine. Even though there are still issues, interdisciplinary studies and regulation will be vital to optimally exploit the advantages of nanotechnology in fertility therapies. As technology advances, NARTs have the potential to transform ART, enhancing success rates, reducing complications, and increasing fertility worldwide.

Keywords: Bioaccumulation, Fertility, Gamete, Nanomaterial, Nanotechnology.

INTRODUCTION

Assisted Reproductive Technologies (ART) have transformed reproductive medicine by providing a solution to infertility, which is a reproductive condition affecting millions of people and couples across the globe [1]. Conventional ART incorporates different medical practices and interventions that are designed to fight infertility, including *In Vitro* Fertilization (IVF), intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), and embryo freezing [2]. Assisted Reproductive Technologies (ART) in the American Centre of Disease Control and Prevention (CDC) are defined as all the procedures that involve the manipulation of eggs or embryos in relation to fertility issues. The term does not cover such procedures as intrauterine insemination, which only manipulates sperm. Missing also are the procedures that include the use of ovarian stimulation, yet the purpose of carrying out the procedure is not to extract eggs [3]. The technologies have assisted in significantly enhancing the ability to conceive children and give hope to people who are put off by their reproductive power. Conventional ART does not have its limits, but it is generally successful. The success rates also vary widely, depending on factors such as the patient's age, medical conditions, and the accuracy of the procedure. Moreover, ART procedures can be obtrusive, costly, and emotionally taxing to the patients. Such restrictions highlight the importance of continuous innovation to maximize outcomes and reduce the risks of reproductive medicine [2, 4].

The use of nanotechnology in ART is a significant advancement in addressing the flaws of traditional methods [5]. Nanotechnology refers to the manipulation of materials at the nanoscale (1-100 nanometers) that delivers unsurpassed precision and performance to biological systems. In reproductive medicine, nanotechnology has been used to develop Nano-Enhanced Assisted Reproductive Technologies (NARTs) to improve the efficacy, accuracy, and success of traditional ARTs [6]. One such area is nanoscale imaging and diagnostics, which have also enhanced gamete and embryo quality and facilitated better decision-making during the IVF procedure. Besides, the nanoparticles have advanced to develop drug delivery systems that target reproductive tissues, reducing systemic side effects of hormonal therapies. As such innovations have been introduced and continue to be introduced, they have the potential to revolutionize the field of reproductive

medicine, opening new horizons for overcoming the challenges of infertility [7]. No matter how great the breakthroughs in ART are, there are several problems in the sphere of reproductive medicine. The success rates of IVF and other internal training procedures are not yet optimum, especially where the patients are elderly and have complicated underlying conditions. Moreover, the high cost and lack of affordability of ART services limit the access of many people to these services, which contributes to the widening of disparities in reproductive health care [7, 8]. Even more crucial is the introduction of less harmful and more effective methods due to the possibility of negative outcomes, including ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Also, the ethical and social perceptions of ART continue to affect its adoption and application. All these issues underscore the need for new, innovative technologies such as NARTs, which are desperately needed to address the scientific and social concerns of reproductive medicine [8].

Nanotechnology has a revolutionary capability in terms of dealing with the constraints of the traditional ART. Nanotechnology enables the creation of focused, effective, and minimally invasive solutions by enabling accurate manipulation and interaction with biological structures at the molecular scale. Nanomaterials, for example, can enhance cryopreservation of gametes and embryos and post-thaw viability and survival rates by inhibiting ice crystal formation [9]. In addition, the superior and unmatched insights into the health of gametes and embryos offered by imaging methods based on nanotechnology, such as quantum dot labeling, exceed diagnostic accuracy. Minimization of system exposure and side effects, enabled by the delivery of therapeutic agents into reproductive tissues *via* nanoparticles, paves the way for safer hormonal and non-hormonal therapy. These innovations can improve clinical outcomes while addressing patient issues related to safety, affordability, and accessibility [10]. The aim of this chapter is to provide an informative overview of Nano-Enhanced Assisted Reproductive Technologies (NARTs), their development, their applications, and their potential contributions to the existing sphere of reproductive medicine.

Fundamentals of Nanotechnology in Reproductive Medicine

Nanotechnology is an interdisciplinary field that deals with the manipulation, engineering, and utilization of materials at the nanoscale, which is usually one to one hundred nanometers. In this order, materials may exhibit unique properties, *e.g.*, high reactivity, optical activity, and mechanical strength, which may not exist in their bulk form. Such properties make nanotechnology an effective means of solving complex biological issues, among them reproductive medicine [11]. Nanoscale processes are also consistent in reproduction as compared to molecular

CHAPTER 6

Nanoparticles and Gamete Interaction: Bridging the Gaps

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Abstract: Nanoparticles are rapidly expanding materials; they have small dimensions and large surface area, which possess electrical, mechanical, magnetic, chemical, optical, and biological characteristics that allow them to be used in a wide variety of technical and scientific fields. Consequently, the potential toxic effects of nanoparticles on vital health aspects such as reproduction should be considered and assessed. The central event of reproduction is fertilization, which is the fusion of male and female gametes to give rise to a new organism. Despite the number of studies on the toxic effects of nanoparticles in different reproductive aspects, to date, their effects on gamete competence and interaction have been poorly studied. Due to their very small size, nanoparticles can disrupt biological barriers, enter cells, mainly sperm, oocytes, and cumulus cells surrounding the oocyte, inducing oxidative stress, DNA damage, and apoptosis in those cells, leading to low fertilization rates. However, the molecular mechanism by which nanoparticles disrupt fertilization is poorly known. Membrane proteins such as JUNO and CD9 decrease, as well as Ovastacin. Therefore, the study of how nanoparticles can disrupt fertilization mechanisms should be one of the main objectives in future studies.

Keyword: Fertilization, Gamete interaction, Nanoparticles, Oocyte, Sperm.

INTRODUCTION

Fertilization Mechanisms

For reproduction to occur, a series of complex processes, including the production of gametes by spermatogenesis in male testis and oogenesis in female ovaries, are

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needed, culminating in sperm-to-oocyte interaction, leading to zygote formation [1].

The success of reproduction depends on molecular mechanisms during the fusion of the oocyte and sperm to generate an embryo.

Sperm

Before fertilization, sperm must acquire the competencies to fertilize the oocyte, namely capacitation, hyperactivity, and acrosome reaction [2]. Capacitation occurs within the female reproductive tract [3]; during this process, cholesterol outflow from the sperm membrane occurs, thus increasing permeability to calcium (Ca^{2+}) and bicarbonate ($HCO3^{-}$) ions, as well as protein phosphorylation.

These ions enter the cell and activate soluble adenyl cyclase, which synthesizes cyclic adenosine monophosphate (cAMP). This second messenger activates Protein Kinase A (PKA), leading to indirect tyrosine phosphorylation of proteins [4]. During capacitation, the sperm develop a unique motility pattern called Hyper-Activated Motility (HAM), which is essential for successful fertilization. The main Ca^{2+}-channel that mediates HAM is the sperm-specific CatSper located in the sperm tail [5]. During capacitation, the increase of intracellular Ca^{2+} activates a membrane-bound phospholipase C (PLC), which hydrolyzes phosphatidyl-inositol-4,5-bisphosphate (PIP_2) to diacylglycerol, which activates Protein Kinase C (PKC), activating a Ca^{2+} channel in the plasma membrane, and inositol-trisphosphate (IP_3), which activates the Ca^{2+} channel in the outer acrosomal membrane, leading to Ca^{2+} depletion from the acrosome. As a result, the plasma-membrane store-operated Ca^{2+} channel (SOCC) is activated to increase cytosolic Ca^{2+} concentrations, enabling completion of the acrosome reaction [5]. The acrosome reaction is triggered by several factors, such as zona pellucida glycoprotein and calcium flux induced by progesterone. During the acrosome reaction, the outer acrosomal membrane fuses with the sperm's plasma membrane; the fused membranes vesiculate and fenestrate, the acrosomal matrix disperses to release proteolytic enzymes, and intracellular calcium increases [6]. The acrosome reaction allows the sperm to penetrate the cumulus oophorous cells and the Zona Pellucida (ZP), reach the perivitelline space (PVS), and fuse with the oocyte membrane. After the sperm fuses with the oocyte, its nucleus enters the oocyte cytoplasm [6], followed by syngamy and zygote formation. The fusion of sperm membrane with oocyte plasma membrane occurs in the membrane region covered with microvilli [7]. The acrosomal reaction is facilitated by the interaction of proteins from the sperm membrane and zona pellucida receptors. It is controlled by SNARE complexes, leading to the exocytosis of acrosomal contents upon fusion of the plasma membrane with the outer acrosomal membrane [4]. In the

sperm plasma membrane, there is a protein that is necessary for adhesion and fusion during oocyte fertilization, named IZUMO1. This is a type I transmembrane protein that is expressed exclusively in sperm and is found predominantly in the acrosome of sperm [8]. After the acrosomal reaction, IZUMO1 is relocated to the membrane surface in the equatorial segment of the acrosome [9]. In the absence of this protein, sperm can undergo acrosomal reaction and penetrate the ZP but fail to fuse with oocytes [6].

Oocytes

Microvilli are found on the surface of the mammalian oocyte; they participate in the initial contact of sperm and oocyte plasma membranes; sperm bind to the region of the oocyte with a high concentration of microvilli. CD9 is an oocyte protein located in the microvillar membrane, and is required for sperm–oocyte fusion. Microvilli concentrate adhesion/fusion proteins and/or provide a membrane protrusion with a low radius of curvature. They interact with the sperm and bring it into close contact with the oocyte plasma membrane [10]. Another important protein for fertilization is JUNO, which is the oocyte receptor for IZUMO1. It is a protein located in the oocyte membrane. JUNO is present in unfertilized oocytes, but it is internalized after fusion with sperm, probably as a mechanism to prevent the entry of more than one sperm into an oocyte. In the absence of this protein, females are infertile because their oocytes are unable to fuse with sperm, avoiding fertilization [11]. It has been proposed that CD9 and JUNO proteins have a proximity within the microvillar oolemma, but not in the planar membrane of the microvilli-free region, indicating an interaction between both proteins prior to sperm attachment. Possibly, JUNO and CD9 interact as a requisite for JUNO binding to IZUMO1 for gamete membrane fusion [12]. Once sperm have fertilized the oocyte, the Zona Pellucida (ZP) undergoes biochemical modification to prevent other sperm from penetrating and fusing with the oocyte, which is known as polyspermy [13]. One of the enzymes necessary for the degradation of the ZP is Ovastacin, to ensure that only one sperm fertilizes the oocyte, ensuring successful oocyte fertilization [14]. Considering the molecular precision for all these reproductive events to occur, it is important to understand that gamete interaction can be disturbed by numerous environmental factors.

Impact of Environmental Factors on Gamete Quality

Currently, there are several substances derived from manufacturing processes, known as xenobiotics, which can alter gametes. Among xenobiotics are metals, herbicides, pesticides, persistent organic pollutants, antifoulants, pharmaceuticals, plastics, and nanoparticles [1, 15]. Most of the xenobiotics act as endocrine disruptors (EDs), disturbing the function of different organs, interfering with their

CHAPTER 7

Nanoparticle-Based Delivery Systems in Reproductive Therapeutics: Advances and Challenges

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Abstract: Nanoparticle (NP)-based delivery systems are a transformative tool for reproductive therapeutics. In diagnostic applications, novel nanoparticle-based contrast agents, used with advanced imaging techniques such as Fluorescence Imaging (FI) and Magnetic Resonance Imaging (MRI), improve early cancer detection and disease monitoring by increasing the sensitivity and specificity. On the therapeutic side, photodynamic therapy (PDT) and photothermal therapy (PTT) have been shown to be effective for targeting reproductive cancers and inflammatory conditions while causing minimal off-target effects seen with traditional therapies. However, the application of nanomaterials in reproductive medicine faces challenges, including long-term safety and biocompatibility concerns, as well as regulatory issues. This chapter describes recent advancements in nanoparticle-based reproductive therapeutics, assesses potential hazards, and considers future efforts needed to improve their clinical translation. The potential for nanotechnology to transform reproductive health is immense, with the possibility of increasing diagnostic accuracy, optimizing therapeutic specificity, and mitigating systemic side effects.

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Keywords: Biocompatibility, Drug delivery systems, Nanomedicine, Nanoparticle-based therapy, Reproductive cancer treatment, Graphical abstract.

INTRODUCTION

The survival of humans, therefore, depends on both the male and female reproductive systems, through which a wide range of gametes are produced, and on the roles of these systems in reproduction and fertilization. These systems also control hormones that influence sexual development, reproduction, and regulate homeostasis, collectively modulating physiological, psychosocia, and social well-being. Recently updated epidemiological data show a cause for concern: Reproductive system diseases are becoming more frequent and more premature in both men and women. These diseases can even have severe consequences and complications, including infertility, loss of function, and organ damage, as well as decreased reproductive capacity. The ripple effects go well beyond physical health, affecting emotional well-being and family dynamics. These challenges result in stress, frustration, and heartache for many, making it harder to juggle personal and career lives. Clinical reproductive medicine can help here, but it is challenging. As these conditions become increasingly prevalent, the need for solutions to support reproductive health, both within and outside of the body, has become more pressing than ever before.

Female Reproductive System: The reproductive system is an essential body function for generating new life, and the female reproductive system has a major influence on women's health. It is also responsible for producing ova (oocytes), which are needed for reproduction. The female reproductive system is also crucial in shaping women’s health and helps maintain the population balanced. This complex system, which includes ovaries, fallopian tubes, uterus and vagina, as well as external genitalia, has one main function: to give birth to new life. That being said, it is also associated with several medical problems that are global threats to women's health. Reproductive health issues over time are unfortunately common and continue to be a global issue. Uterine-linked problems, including pregnancy complications, endometriosis, uterine fibroids, and cervical cancer, are common. Millions of women suffer from ovarian disorders, with a high incidence of the polycystic ovary syndrome (PCOS) [1], and the worst is ovarian cancer. Reproductive health is also complicated by infections, such as vaginitis and HIV-related diseases, as well as pelvic inflammatory disease [2]. Beyond impairing reproductive function, these pathologies impose a significant physiological and psychosocial burden. Estrogen hormones are essential for regulating the reproductive cycle and facilitating the metabolic adaptations necessary to support

the physiological requirements of gestation [3, 4]. Furthermore, reproductive health is fundamental to maintaining demographic stability and optimizing population-level health outcomes [5].

Male Reproductive System: Male reproductive function is fundamental to spermatogenesis and the production of functional spermatozoa, which are requisite for oocyte fertilization and the maintenance of generational homeostasis. The system consists of the testes, epididymis, vas deferens, prostate, and seminal vesicles. In addition to being crucial for reproduction, these organs play a major role in the male hormonal environment and in healthy bodily function. In addition, adverse male reproductive health is a critical issue due to certain conditions: prostate cancer, testicular cancer, erectile dysfunction, and infertility [6]. Testicular cancer is the most prevalent malignancy observed in younger men, whereas prostate carcinoma is the second most frequent cancer globally [7]. Infertility is an important problem in some men as it is associated with lifestyle and disease (*e.g.*, varicocele). These challenges can significantly affect a effect on a man's fertility, emotional well-being, and relationships.

Reproductive health disorders, which can affect the reproductive systems of both men and women, are on the rise. For instance, these disorders are increasing and also occurring in younger people, frequently with serious implications like infertility, organ damage, and reduced fertility. Since these issues not only involve relevant aspects of physical health but also emotional state and inter-familial processes, their solutions have become constantly more urgent. Diagnostic tools are vital in determining and managing reproductive health issues. Conventional contrast agents cannot usually provide adequate information in clinical diagnostics due to their low specificity and sensitivity, and the risk of causing allergic reactions. They create clearer contrast, are more compatible with the body, and have a shorter circulation time, showing promising alternatives for accurate and reliable imaging. This invention is especially timely as reproductive health receives new scrutiny. In particular, there is a growing interest in using nano-imaging to detect diseases or morbidities in the male and female reproductive systems. These advances are potentially paving the way toward early detection and better monitoring of diseases affecting the reproductive system, such as cancer, inflammation, and other disorders.

Nanotechnology has opened up new directions for the development of novel therapeutic modalities over the last few years, which may be advantageous in overcoming these limitations. Polymeric micelles, liposomes, dendrimers, and inorganic nanoparticles are examples of nanoparticle-based drug delivery systems that have been engineered to improve the bioavailability, stability, and targeted delivery of chemotherapeutics, resulting in reduced systemic toxicity as well as

CHAPTER 8

Nanomaterials as Endocrine-Disrupting Compounds and Their Effects on Male and Female Neuroendocrine Axes

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Abstract: Nanomaterials (NM) possess unique characteristics such as very low size (nm), high conductivity, strength, durability, and chemical reactivity, making them suitable for their use in fields such as aerospace engineering, material science, cosmetics, electronics, medicine, biotechnology, and clothing. This has caused an increased human exposure to these NM in the last decades, generating public concern regarding human well-being, especially reproductive toxicity. In this chapter, reproductive disruption in the male and female hypothalamus-pituitary-gonad axis regulation, at all levels, induced by different types of nanoparticles (NPs) is revised. NPs can cross practically all biological barriers, especially the Blood-Brain Barrier (BBB), allowing them to enter neurons in the hypothalamus. Their ability to cross the Blood-Testis-Barrier (BTB) and Blood-Follicle-Barrier (BFB) allows them to enter endocrine cells, disturbing neuroendocrine regulation of reproduction. NPs' size, physicochemical properties, exposure time, administration pathway, and experimental design are important for their effects on reproduction. The solubility factor of NPs also plays a major role in nanotoxicity. Therefore, it is essential to determine the precise risk and management strategies to protect the reproductive health of the general and especially occupational populations exposed to NM.

Keywords: Endocrine disruptors, Epididymis, Female reproductive system, Granulosa cells, Hypothalamus, Leydig cells, Male reproductive system, Nanomaterials, Nanoparticles, Neuroendocrine axis, Oxidative stress, Ovaries, Reproduction, Sertoli cells, Spermatozoa, Testis.

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INTRODUCTION

In the last decades, the concern and study of the toxicological effects of Endocrine-Disrupting Chemicals (EDCs) has increased, because these compounds can interfere with hormone biosynthesis, secretion, transport, metabolism, binding to receptors, or elimination of endogenous hormones, affecting the regulation processes in female and male reproduction, causing reproductive disruption [1, 2].

Types of Endocrine-Disrupting Chemicals

According to their origin, EDCs are classified as natural (N-EDCs) and synthetic (S-EDCs). N-EDCs include heavy metals, such as cadmium (Cd), lead (Pb), copper (Cu), mercury (Hg), zinc (Zn), nickel (Ni), arsenic (A), manganese Mn [3], as well as plant molecules, as are phytoestrogens, which are compounds content in many plants, with a structure similar to the endogenous steroid hormone estradiol (E_2). They can bind to membrane or cytosolic alpha and beta-receptors for E_2, thus altering gene transcription and cellular processes such as proliferation, apoptosis, and migration [2, 4]. S-EDCs are of great global concern due to chemical production (about 200 million tons), increasing pollution, thus impacting human health [5].

These include man-made compounds, such as pharmaceutical agents (diethylstilbestrol, DES), pesticides (organochlorine (OCPs), polyfuoroalkyl octane sulfonate, PFOS), (perfluorocompounds dioxins), plastics (Bisphenol A), plasticizers (Phthalates), synthetic chemicals as solvents, lubricants, their byproducts (polychlorinated biphenyls, PCBs), polybrominated biphenyls (PBBs) [1, 5], fungicides, herbicides, pesticides, dioxines, synthetic organofluoride chemicals, Per- and polyfluoroalkyl substances (PFAS), food and beverage packaging, textiles, and, of interest for this chapter, nanomaterials (NM) [2, 3].

Nanomaterials: Properties and Exposure Pathways

The National Institute of Environmental Health Sciences defines nanomaterials as nano-sized particles, with external dimensions in the size range of approximately 1-100 nanometers [6, 7]. Due to their unique physicochemical properties, such as high conductivity, strength, durability, and chemical reactivity [8], NM are used in the fields of medicine, cosmetics, biotechnology, aerospace engineering, material science, electronics, and clothing, due to their physicochemical, thermal, and electrical properties [8 - 10]. Human exposure to anthropogenic sources of NM has increased exponentially in the last few decades, generating public concern regarding human well-being [11]. Engineered NM, such as nanoparticles (NPs), nanofibers, and nanosheets, have been increasingly used in food, cosmetics, and nanomedicine industries [12], increasing the exposure of humans

to those NM. NPs can enter the body through inhalation, ingestion, skin uptake, injection, or implantation [13]. Due to their small size, NPs can penetrate the skin barrier and enter the bloodstream [14], and reach vital organs such as the liver and spleen, where they are caught by the reticuloendothelial system, for deactivation and elimination [15]. Also, NPs have the potential to cross biological barriers, such as the Blood-Brain Barrier (BBB), reaching the brain and other important organs [16]. Although NPs are useful for delivering drugs directly to the organs, this is also a disadvantage, because NPs used to carry drugs may be toxic to the brain or other organs [17]. NPs can also reach the testis [18, 19] and fetus, which are also protected by blood barriers [20]. However, the size, shape, aggregation, surface, and charge of NPs allow them to penetrate the biological barriers [11, 21, 22]. The capacity of positively charged NPs to cross the cell membrane resides in the negative charge of phospholipids. Once inside the cell, cationic polystyrene NPs are capable of inducing ROS production, GSH depletion and oxidative stress due to mitochondrial injury by increased calcium uptake and mitochondrial and cell membrane damage, leading to cell death without inflammation. Therefore, ROS generation and oxidative stress are useful tests to evaluate NPs toxicity [24]. Carbon nanotubes (CNT) and metal-based NPs have a great commercial interest due to their properties [25].

Diagnostic, Therapeutic, and Commercial Applications

NPs are used as new tools for the diagnosis and treatment of diseases, such as cancer, also for efficient water purification, stronger and lighter building materials, increased computing power and speed, enhanced generation and conservation of energy; these are some of the industrial applications of NPs [26]. Consequently, the widespread use of NPs has raised the concern about human exposure and consequent deleterious effects on health [27]. Due to their very small size, NPs can enter the cell and interfere with important cell functions. They can interact with proteins, membranes, DNA, and organelles, establishing NPs-biological interfaces that depend on colloidal and dynamic biophysicochemical interactions, allowing the formation of protein coronas, particle wrapping, intracellular uptake, and biocatalytic processes, leading to bioadverse consequences [28]. There are four ways for NPs to enter the cell: clathrin/caveola-mediated endocytosis, phagocytosis, macropinocytosis, and pinocytosis. NPs uptake by clathrin/caveola-mediated endocytosis occurs by specific (ligand-receptor) or nonspecific (hydrophobic, Coulombic) binding interactions [28]. They can exit the cell *via* lysosome secretion, vesicle-related secretion, and non-vesicle-related secretion [29, 30]. NPs-mediated toxicity is a major focus of many studies regarding their utilization [11].

CHAPTER 9

Nanomaterials and Placental Barrier: Implications for Reproductive Health

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Abstract: The wide application of nanomaterials in medicine, industry, and consumer products has also raised some concerns regarding the potential impact of nanomaterials on reproductive health. The placenta barrier forms a significant area of maternal and fetal circulation that has been preserved as a way of regulating the transport of nutrients as well as protecting the fetus against harmful factors. However, engineered nanoparticles (ENMs) may overcome this obstacle due to their nanoscale sizes, physicochemical properties, and pose a threat due to their developmental toxicity. This chapter tells us about the interaction of nanomaterials with the placental barrier, considering translocation processes, toxicity pathways, and potential implications on fetal development. The area of nanoparticles, their surface charge, composition, and functionalization play a significant role in their resistance to the placental clearance. Besides, nanomaterials are capable of oxidative stress, inflammation, and DNA damage, leading to long-term reproductive and developmental impacts. The chapter

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also stands to investigate the mathematical models that forecast the transport of nanoparticles across the placenta, and the amounts of current regulations that govern the safety of nanoparticles. The future research should focus on more sophisticated *in vivo* research, physiologically relevant models, and AI-guided predictive models to determine the behavior of nanoparticles during pregnancy. This research undertaken will provide a contribution towards the safe and ethical application of nanotechnology and alleviate the potential reproductive risks. This chapter does not concern applications of nanotechnology in contraceptives but gives broader implications of nanomaterials' interactions with the placental barrier as far as the general reproductive toxicity is concerned. It focuses not on fertility control or contraceptive technologies, but on maternal and fetal safety during pregnancy, with a special focus on the possibility of developmental toxicity caused by exposure to nanoparticles.

Keywords: Fetal development, Nanomaterials, Nanoparticle toxicity, Placental barrier, Reproductive health.

INTRODUCTION

Background and Significance

Nanotechnology has transformed multiple industries, including medicine, pharmaceuticals, and consumer products, by enabling the manipulation of materials at the atomic and molecular levels [1]. ENMs are engineered to have special features of physicochemical properties, including, but not limited to, a high surface area, tunable reactivity, and greater bioavailability, which makes them useful in drug delivery, imaging, and therapeutic uses [2]. They have, however, raised concern over their possible toxicity, especially the interactions with their biological barriers, like the placenta.

The placenta acts as a selective barrier, which is used in the passage of important nutrients and serves as a safeguard of the developing fetus against unfavorable substances. Despite this protective action, research has shown that some of the nanoparticles may circumvent the placental barrier, exposing the fetus to possible developmental toxicity [3]. There is growing evidence of the possibility of induction of oxidative stress, inflammation, and epigenetic changes by such exposure, which could affect the outcomes of pregnancy and offspring health [4].

The issue of placental activity and fetal growth that would be under the impact of nanomaterials is of great significance due to the increasing tendency to use them in real life. This chapter has a description of the association between nanomaterials and the placenta barrier and the potential mechanisms through which nanomaterials are transported to fetal circulation, and the health and reproductive implications of such an association. It addresses important physicochemical aspects that affect the transportation of nanoparticles,

toxicological aspects, and regulatory issues. Moreover, mathematical modeling techniques are also included to explain the diffusion process and clearance of nanoparticles in the placental environment. This work will help to justify the safe use of nanotechnology in healthcare by the synthesis of the present findings in research and pointing to the directions where further research will take place.

THE PLACENTAL BARRIER: STRUCTURE AND FUNCTION

Anatomy and Physiology of the Placenta

The placenta is a non-permanent, but necessary organ during pregnancy, which promotes the exchange of nutrients and gases between the mother and the growing fetus and acts as a selective barrier to dangerous substances. It has structural elements both fetal and maternal, such as the chorionic villi, where maternal-fetal exchange takes place, and the maternal decidua, where immunological support prevails [5].

Placental development is a complicated process of trophoblast differentiation, which results in the creation of layers that divide maternal and fetal blood circulation. The layers are the syncytiotrophoblast, cytotrophoblast, and endothelial cells of fetal capillaries, and each of them plays a role in the placental barrier activity [6]. The multinucleated structure with no intercellular junctions is called the syncytiotrophoblast, which is the key to the regulation of molecular transport. It allows oxygen, glucose, amino acids, and micronutrients to enter, and certain drugs and pathogens to be restricted from entering. However, emerging studies indicate that engineered nanomaterials (ENMs), because of their nano-level size and novel physicochemical characteristics, could bypass this barrier, potentially exposing the fetus to toxic substances [4].

Mechanisms of Molecular Transport

The placenta regulates molecular transport to ensure fetal development while preventing harmful substance entry. Yet, Engineered Nanomaterials (ENMs) can escape these defense processes, and this depends on their size, charge, and surface characteristics [7].

Diffusion is passive, which means small molecules that are not polar, such as oxygen and carbon dioxide, enter the placenta without any energy. This size-dependent exploitation by some lipophilic nanoparticles is possible [8]. The process of facilitated diffusion involves the use of transport proteins like GLUT1, which can be imitated by some surface-modified nanoparticles and can be transferred to the fetal circulation [9].

CHAPTER 10

Nanotechnology in Contraception: Progress and Challenges

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Abstract: Nanotechnology has significantly revolutionized all the fields of medicine, such as drug delivery, medicine, and regenerative medicine. Its application as a means of contraception is one of the emerging frontiers of this technology, providing novel answers to persisting problems concerning traditional contraceptive methods. However, current options such as hormonal pills, intrauterine devices (IUDs), and barriers tend to have disadvantages such as side effects, unreliable effectiveness, and user noncompliance. Given these challenges, nanotechnology based on contraception aims to offer more effective, targeted, and user-friendly alternatives. To increase the controlled release of contraceptive agents with a reduction in systemic side effects, nano-carriers such as liposomes, polymeric nanoparticles, and microspheres have been developed. Also, strategies to develop nano-based non-hormonal contraception are being developed based on smart polymers and toxic sperm immobilizing agents for safe and reversible contraception. This also promises to find suitable applications in the emerging nanotechnology-based technology in the field of male contraception, where sperm motility will be reduced temporarily without affecting the sperm count or overall reproductive risk. According to him, nano-sensors and wearable gadgets are now monitoring fertility, keeping individuals in control of their hormonal fluctuations with high accuracy. Although promising in these innovations, many obstacles exist to facilitate the use of nanotechnology in contraception. Despite these concerns, legal

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market access to nanoformulations, regulatory hurdles in clinical approval, the long-term safety and biocompatibility of nanoformulations, ethical considerations, and affordability in low-resource settings remain sizeable barriers. Furthermore, the application of Artificial Intelligence (AI) on nanotechnology for personalized contraception is also an area for more investigation. An in-depth analysis of the progress in the field of nanotechnology-based contraception is developed in this chapter, emphasizing recent developments, challenges, and future directions. Given the existing limitations and improved design of nano-based contraceptives, the field has great potential in modifying reproductive healthcare and providing safer, more reliable, and easily accessible contraceptive options for individuals globally.

Keywords: Contraception, Drug delivery, Nanocarriers, Nanomedicine, Nanotechnology, Reproductive health.

INTRODUCTION

Nanotechnology deals with the use of materials in the 1 to 100 nm range to develop such advanced systems as having unique physical, chemical, and biological properties. From this microscopic level, materials behave in distinctive ways for the benefit of uses such as, for example, in medicine [1]. Nanomedicine is the field of nanotechnology that tries to enhance disease diagnosis, drug delivery, tissue engineering, and personalized medicine. Targeted delivery of drugs is one of the major contributions of medicine in its nanotechnology. Liposomes, polymeric nanoparticles, dendrimers, and micelles are nanocarriers that are engineered to transport the drug to the cells or the specific tissues, reducing the systemic side effects and also enhancing the therapeutic efficacy [2].

It is also changing diagnosis in diagnostic medicine through highly sensitive nanosensors and imaging. This includes enhancement of imaging precision of modalities of MRI, CT scans, and fluorescence-based diagnostics through quantum dots and gold nanoparticles [3]. Furthermore, nanotechnology-based biosensors provide real-time monitoring of biomarkers, and this facility proves to be of great value in early detection and treatment of disease. In regenerative medicine, nanomaterials are being explored for tissue engineering, wound healing, and the development of bioactive scaffolds that promote cell regeneration [4]. Their application in artificial organs and prosthetics is also gaining momentum. Beyond these areas, reproductive medicine is increasingly benefiting from nanotechnology. Innovations in fertility treatments, hormonal therapy, and contraception are emerging, offering more efficient, safe, and reversible reproductive health solutions. One of the most promising applications is nanotechnology-based contraception, which aims to improve the effectiveness and convenience of birth control methods while minimizing adverse effects [5, 6].

Contraception plays a fundamental role in reproductive health, enabling individuals and couples to plan pregnancies, space births, and prevent unintended pregnancies. It also contributes to maternal and child health, population control, and gender equality by allowing women greater autonomy over their reproductive choices [7]. Globally, an estimated 1.1 billion women of reproductive age need family planning, yet about 270 million women have an unmet need for modern contraceptives. Barriers to contraceptive access include lack of awareness, cultural and religious beliefs, health concerns, cost, and inadequate healthcare infrastructure [8].

Effective contraception offers numerous health, economic, and social benefits. By preventing high-risk pregnancies and unsafe abortions, it significantly reduces maternal mortality rates [9]. Additionally, contraceptive methods, particularly barrier methods like condoms, help prevent the transmission of Sexually Transmitted Infections (STIs), including HIV [10]. Birth spacing, facilitated by contraception, allows for better maternal recovery and improves child health outcomes, reducing neonatal and infant mortality rates [10]. Beyond health advantages, family planning plays a crucial role in empowering women by enabling them to pursue education and career opportunities, ultimately contributing to economic growth and poverty reduction [11]. Despite these advantages, conventional contraceptive methods often present challenges such as side effects, lack of compliance, and failure rates. Hormonal contraceptives, for instance, may cause weight gain, mood swings, and increased risk of cardiovascular conditions [12]. IUDs, though highly effective, may lead to discomfort and complications in some users. Male contraception remains largely limited to condoms and vasectomy, with few reversible options available. These challenges necessitate novel approaches to contraception, where nanotechnology holds immense promise [13].

Nanotechnology-based contraception is revolutionizing birth control by addressing the limitations of traditional methods, offering improved efficacy, safety, and user convenience. Researchers are exploring nanoformulations for controlled drug delivery and smart contraceptive devices that provide long-term yet reversible options [14]. Nanocarriers such as liposomes, polymeric nanoparticles, and micelles enhance the sustained release and bioavailability of hormonal and non-hormonal contraceptive agents, reducing side effects and the need for frequent administration. Additionally, implantable nanoformulations serve as Long-Acting Reversible Contraceptives (LARC), minimizing user intervention. For those preferring non-hormonal alternatives, sperm-immobilizing nanoparticles and smart polymer barriers provide localized and reversible contraception without the side effects associated with hormonal methods [15].

CHAPTER 11

Ethical Considerations in Reproductive Nanotechnology

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Abstract: Nanotechnology has revolutionized the field of nanomedicine, which continues to expand with the development of new nanoparticles (NPs), nanomaterials (NMs), nanodevices (NDs), and nanobiochips (NChs). These technologies are utilized in the prevention, diagnosis, and treatment of diseases, including several types of cancer affecting reproductive organs. Additionally, nanotechnology plays a crucial role in Assisted Reproductive Technologies (ART), particularly in infertility treatments. Even though the use and application of nanotechnology have a significant impact on reproductive medicine and ART, guidelines and ethical standards to regulate its implementation have not yet been established. This has generated concern and uncertainty due to the unknown toxic effects that NPs may have on reproductive organs. Although countries such as Canada, the United States, China, and the European Union are actively working to determine the toxicity of different types of NMs and are establishing norms and ethical principles to regulate their use in research, as well as in conventional and reproductive medicine, there is still no international legislation or ethical and legal framework to regulate the use and application of NPs and NMs for the diagnosis and treatment of reproductive diseases, nor for infertility treatments. Therefore, the objective of the present study is to review and identify the ethical principles and considerations applied in reproductive medicine and biology, as well as in ART.

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Keywords: Ethics in nanomedicine, Nanoparticles, Nanomaterials, Nanotechnology, Reproductive medicine, Reproductive system toxicity.

INTRODUCTION

Nanotechnology is a multidisciplinary field that has revolutionized its applications in research and medical care and promotes the development of nanomedicine, which plays a key role in the prevention and diagnosis of various diseases using diverse methods, devices, and structures at the nanometric scale [1, 2], including gastrointestinal, cardiovascular, infectious, and reproductive diseases [3], aiming to provide cellular or molecular treatments molecular. The advances in nanotechnology are driven by the development of new nanoparticles (NPs), nanomaterials (NMs), and nanobiochips (NChs) [2]. These technologies are used in the prevention, diagnosis, and treatment of diseases, including various types of cancer affecting humans [3]. In recent years, the use of nanotechnology and its application in reproductive medicine have become increasingly valuable tools for studying the structure and function of reproductive organs, as well as gametes [4]. Moreover, nanotechnology has been recognized as a valuable tool in Assisted Reproductive Technologies (ART), such as *In Vitro* Fertilization (IVF), sperm transfer, intracytoplasmic sperm injection (ICSI), and zygote intrafallopian transfer (ZIFT) [5], which are utilized as infertility treatments. Even though the use of nanotechnology in reproductive medicine and in ART represents significant growth and scientific advancement [6], specific guidelines for regulating the use and application of these NMs have not yet been established. International organizations are looking for the implementation of norms and regulations to determine the toxicity of NPs and to regulate their applications in humans [7]. Indeed, norms and principles in reproductive medicine and biology are guided by the four pillars of medical ethics: non-maleficence, beneficence, autonomy, and justice [8, 9]. Compliance with these principles relies on doctors and researchers, who are obliged to act for the benefit of people. The four principles are focused on not causing harm, pain, or suffering to individuals during medical or scientific practice (non-maleficence); acting for the benefit of patients and promoting their well-being (beneficence); informing the patient about their health status and offering the necessary treatment options so that they can decide about their own life. In addition, the doctor is obliged to always maintain privacy in the management of medical information (autonomy); and finally, ensuring dignified and equitable treatment and a fair distribution of resources and benefits, regardless of gender, race, or age (justice) [9]. Nevertheless, ethical principles in reproductive nanomedicine are more complex than those in conventional medicine, as nanomedicine raises ethical concerns regarding the toxicity and long-term effects of NPs [3, 10] in reproductive organs. While the use and application of nanotechnology have a significant impact on this field, the

uncertainty generated by nature and the potential toxic effects of NPs on reproductive organs create an ethical concern for individuals exposed to these NMs [1]. Despite this, juridical and ethical-specific norms do not exist to regulate the use of nanotechnology in reproductive medicine.

Nanoethical Considerations in Reproductive Medicine and Biology

The use of nanotechnology has increased in reproductive medicine and ART, where it is applied to cancer detection and treatment, non-cancerous pathologies, and infertility treatments. However, the use of NPs and NMs raises ethical concerns and challenges related to their toxicity, as the side effects of NPs in reproductive organs remain unknown [3]. In medical practice, various ethical, social, legal, and even religious concerns have been established regarding justice, human rights, autonomy, the physician-patient relationship, and confidentiality, among others. Nevertheless, ethical concerns in reproductive nanomedicine go beyond these principles, as various studies have demonstrated that different types of NMs cause toxic effects in reproductive organs [11] and gametes [12].

In nanomedicine, it is controversial to establish specific codes or norms concerning the use of nanotechnology in research, diagnosis, and treatment of reproductive diseases and infertility. It is necessary to carefully consider these ethical concerns regarding the use of specific NMs and their long-term effects on organisms. In addition, patient privacy and clinical data protection must be ensured [2], as well as respect for human rights and dignity. Multiple international organizations from developed countries, such as Canada, the United States, China, and the European Union, are conducting research to determine the toxicity of different types of NMs and the risk they pose to human health and the environment; furthermore, they are working to establish strategies and norms to regulate their use [7]. Countries such as Australia, Canada, and the United States are characterized by their interest in bioethics and significant investments in nanotechnology research; therefore, they are considered pioneers in establishing ethical principles and norms for nanomedicine in public health. These countries have proposed the following ethical considerations, norms, and codes that must be incorporated into research and nanomedicine [2].

Toxicity and Unforeseen Side Effects of Nanoparticles

The use of nanotechnology in the field of nanomedicine has raised several ethical concerns regarding the size, stability, and diversity of NPs and NMs within living organisms [13]. The mechanism of action of NPs is determined by their physical and chemical properties, including size, shape, surface area, resistance, conductivity, charge, solubility, toxicity, and others. Nevertheless, NMs do not share all these properties, except for the size (1-100 nm) [14]; therefore, their

CHAPTER 12

Future Horizons: Nanotechnology and the Next Generation of Reproductive Medicine

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Abstract: This chapter focuses on the potential role of nanotechnology for transforming reproductive medicine, particularly in enhancing diagnosis and treatment within Assisted Reproductive Technologies (ART). Although there are advancements in the field that have significantly enhanced fertility treatments, numerous challenges persist throughout the various stages of assisted reproduction, from gamete collection and analysis to oocyte fertilization and embryo transfer. A deeper understanding of the factors influencing male and female fertility is crucial before exploring potential solutions using nanotechnology. For women, key considerations include tubal health, endometrial status, and hormonal regulation, while men's assessments should focus on seminal fluid quality and sperm parameters. It is also important to recognize other health conditions that can impact fertility, such as gynecological infections, cancer, and urinary system disorders (in men). This chapter is dedicated to the discussion of various processes in assisted reproduction, showcasing the capabilities of nanomaterials in infertility diagnosis, gamete and embryo manipulation, imaging, and drug delivery. Additionally, it will consider the potential of nanotechnology to address other health issues affecting fertility, paving the way for the next generation of reproductive medicine.

Keywords: Bioimaging, Cryopreservation, DNA integrity, Fertility treatments, Gamete collection, Nanotechnology, Nanomaterials, Nanocarriers, Nanodiamonds, Non-invasive genetic screening, Oxidative stress, Ovulation detection, Quantum dots, Reproductive medicine, Sperm motility, Surface-enhanced Raman scattering (SERS).

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INTRODUCTION

Nanotechnology has demonstrated significant potential across various fields, and in this discussion, we will explore its applications within reproductive medicine. By manipulating materials at the nanoscale, researchers are developing innovative solutions to address long-standing challenges in Assisted Reproductive Technologies (ARTs). These challenges include gamete collection, preparation, and analysis; embryo culture and cryopreservation; and embryo transfer (Fig. **1**). Additionally, nanotechnology holds promise in dealing with other health conditions that impact fertility, such as gynecological cancer, infections, and male and female reproductive disorders.

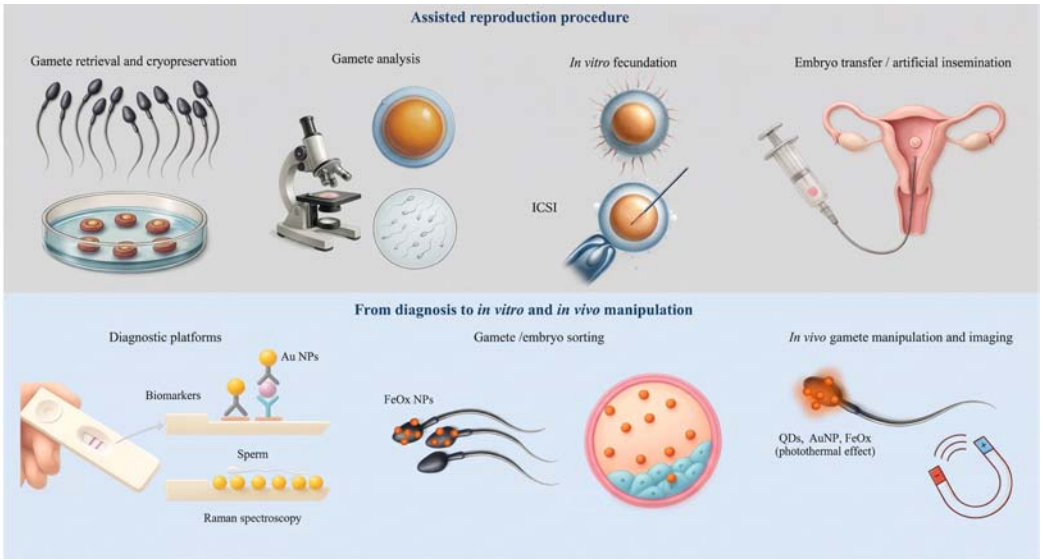

Fig. (1). Schematic representation of the key steps in assisted reproduction treatment, including gamete retrieval, analysis and sorting, cryopreservation, *in vitro* fertilization, embryo culture, and intrauterine transfer. The figure highlights examples of nanotechnology integration within these steps, showcasing advantages such as enhanced sensitivity, multifunctionality, potential for *in vivo* applications, and improved imaging capabilities. Image partially created with Ilustrae.co (CC BY-NC 4.0) and modified with PowerPoint.

Nanomaterials are being studied for their ability to improve diagnostic accuracy, enhance imaging techniques, and deliver targeted treatments in reproductive medicine (Fig. **1**). For instance, nanoparticles conjugated with specific antibodies to target hormone levels have demonstrated improvement in the prediction of ovulation, offering a sensitive and cost-effective solution for fertility assessment [1]. Similarly, Quantum Dots (QDs) have shown promise in non-invasive imaging of mammalian gametes, reducing phototoxicity while enabling sperm and oocyte

tracking in real time [2]. Surface-enhanced Raman scattering spectroscopy (SERS), which uses nanostructured metal surfaces, has improved sperm analysis by identifying molecular markers associated with sperm health, increasing diagnostic accuracy [3, 4].

Apart from improving diagnostic methods, nanoparticles have been used to support gamete preparation, sperm cryopreservation, and targeted drug delivery. For instance, by employing magnetic nanoparticles for sperm motility enhancement [5, 6], nanoparticle-based cryoprotectants to improve post-thaw sperm viability [7, 8], and drug- or enzyme-loaded polymerosomes, decorating sperm cells for targeted gynecological cancer and infertility therapies [9, 10].

This chapter will explore the potential benefits of using nanotechnology in ARTs. However, it is important to note that several challenges remain before these technologies can be translated into clinical applications, including issues related to biocompatibility, long-term effects, and regulatory approval.

NANOTECHNOLOGY FOR INITIAL FERTILITY ASSESMENT

When a couple is dealing with infertility, the first step before treatment is an assessment of the reproductive health of both men and women. Women typically undergo serological testing for infections such as Hepatitis B, Hepatitis C, HIV, syphilis, and others, along with hormonal profiling (TSH, T4, prolactin, FSH, LH, estradiol), vitamin D levels, and ovarian reserve markers like AMH [11, 12]. In men, standard assessments include serologies, blood type, and a detailed semen analysis. It is also suggested that both partners undergo karyotyping to detect possible genetic anomalies [13].

In the case of women, the traditional methods for hormone profiling are often invasive, since they require blood sampling. Recently, some non-invasive alternatives have been introduced. A notable example is a skin-interfaced wearable aptamer nanobiosensor designed for real-time monitoring of estradiol levels through sweat analysis [14]. This device employs a gold nanoparticle-MXene-based detection electrode, achieving an ultra-low detection limit of 0.14 pM, thereby facilitating reproductive hormone tracking at home without the need for bulky and expensive laboratory equipment.

Another promising biosensor is a micropyramidal electrode-based electrochemical immunosensor, designed for ultrasensitive detection of both progesterone (P4) and estradiol (E2) in saliva [15]. This device operates on a low-cost, disposable, and flexible platform that significantly improves the detection limits compared to conventional planar electrodes. This biosensor can detect levels as low as sub-

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Mohammad Mehdi Ommati

Dr. Mohammad Mehdi Ommati is an internationally recognized expert in Physiology and Toxicology. With over 250 peer-reviewed journal articles, more than 25 book chapters, and the authorship of several influential books, his pioneering research in reproductive toxicology and physiology has earned him global acclaim. Dr. Ommati's work has significantly advanced the understanding of xenobiotic-induced toxicity in both reproductive and non-reproductive tissues, with a particular focus on sex-differentiated responses. His research investigates a broad range of intracellular mechanisms, including oxidative stress, mitochondrial dysfunction, endocrine disruption, and cellular pathways such as autophagy, apoptosis, notch, necroptosis, and IL-17 signaling. Dr. Ommati has served as a Distinguished Associate Professor (Talent-Type A) at Henan University of Science and Technology (HAUST) and Shanxi Agricultural University (SXAU), China. He is currently transitioning to the School of Medicine at Linyi University (Shandong, China), where he will continue his pioneering work in environmental health and reproductive toxicology. Dr. Ommati has been recognized as one of the world's leading scientists, as evidenced by his inclusion in Elsevier's 2021-2025 ranking of the Top 2% Most-Cited Scientists. His contributions have earned him numerous accolades, including Global Academic Awards - Research Excellence Award (2025-6), the Outstanding Scientist Award at the 12th International Scientist Awards on Engineering, Science, and Medicine (2020), and the Outstanding Teacher Award at Henan University of Science and Technology (2023–2024). He also received a diploma from Universidad Autónoma Metropolitana in Mexico in recognition of his exceptional collaboration within their Master's program in Animal Reproductive Biology. As a dedicated mentor and academic leader, Dr. Ommati has supervised over 50 undergraduate and postgraduate students, including Ph.D. candidates. His research collaborations span national and international boundaries, as exemplified by his involvement with the Natural Science Foundation of Shanxi. In addition to his research, Dr. Ommati serves on the editorial boards of several prestigious journals. Through these roles, he actively shapes the future directions of research in reproductive health and toxicology. Dr. Ommati also holds a visiting professorship at Shiraz University of Medicine, further enhancing his global academic impact. In summary, Dr. Ommati's groundbreaking contributions to reproductive physiology and toxicology, combined with his commitment to mentorship and international collaboration, have solidified his reputation as a trailblazer in his field. His ongoing research continues to drive innovation and provide actionable insights that aim to improve reproductive health worldwide.