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REVIEW

Is Emerging Nanomedicine a Friend or Foe to Germ Cells?

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Abstract: Nanomaterials are increasingly applied in biomedicine and have significant potential in reproductive medicine. However, because they can impact germ cells, use of nanomaterials could represent a "double-edged sword", whose benefits must be balanced with the possible risks. Because of their excellent physicochemical properties, nanoparticles (NPs) can serve as multi-functional platforms for targeted drug delivery, enhancing outcomes in assisted reproductive technologies, refining in vitro culture systems, and improving the precision of diagnostic imaging. Nevertheless, accumulating evidence indicates that various NPs, including metallic and polymeric forms, can accumulate in reproductive tissues and induce detrimental effects, primarily through increased oxidative stress, DNA damage, and activation of apoptotic pathways. Moreover, NPs can directly compromise gamete quality and function: in oocytes, NP exposure can disrupt key processes, such as meiotic spindle assembly and chromosomal segregation; while in sperm, NPs can impair critical functions, such as histone-to-protamine exchange and mitochondrial integrity. The delicate balance between the benefits and risks of NP use are profoundly influenced by their physicochemical properties. This review critically assesses the "friend or foe" duality of NP use in reproductive medicine, by systematically analyzing their beneficial applications in contrast with their potential for NP-induced toxicity. Mechanistic pathways of NP toxicity are described, and the necessity of a safety-focused approach for the future development of reproductive nanomedicine is emphasised.

Keywords: nanoparticles, reproductive medicine, oxidative stress, gamete quality, nanotoxicology

Introduction

Nanotechnology has emerged as a transformative force in 21st century healthcare, demonstrating significant potential across various biomedical disciplines, with reproductive medicine representing a particularly promising but complex field for the application of nanomaterials.[1–4] The efficacy of reproductive function is fundamentally rooted in the highly orchestrated and sensitive processes of gametogenesis.[5] In males, spermatogenesis requires the mitotic proliferation of spermatogonia, meiosis, and the intricate transformation of haploid spermatids into mature spermatozoa, a process critically dependent on hormonal regulation and Sertoli cell support.[6,7] In females, oogenesis begins with primordial germ cells that develop into prophase I-arrested primary oocytes, which then resume meiosis upon gonadotropin stimulation, complete meiosis I, arrest again at metaphase II, and finish maturation during fertilization.[8] The fidelity of these processes is crucial for successful fertilization and embryonic development.

Nanoparticles (NPs) are characterised by dimensions typically ranging from 1 to 100 nm, a high specific surface area, and easily modifiable surfaces, which can serve as versatile platforms for intervention in fundamental reproductive processes.[9–11] By taking advantage of these unique properties, engineered NPs can be used to precisely modulate specific physiological conditions, and enable targeted delivery of therapeutics designed to treat reproductive disorders or increase the efficacy of

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assisted reproduction.[12–15] Furthermore, NPs can also be applied to create advanced in vitro culture matrices, or enhance the precision of diagnostic imaging of reproductive systems.[16–18] In fact, because of these multi-faceted intervention capabilities, nanotechnology has the potential to revolutionise reproductive medicine. However, because of the physicochemical properties of nanoparticles (NPs), nanotechnology has come to be considered a "double-edged sword", particularly in the context of reproductive health.[19] Unfortunately, the same physicochemical properties that enable therapeutic applications also facilitate unintended interactions with the delicate machinery of gametogenesis.[20] Considerable scientific evidence indicates that various NPs can traverse biological barriers, accumulate in reproductive tissues, and exert toxic effects.[21,22] Reports of interactions between these minute nanoparticles and the reproductive system have prompted inquiries into their impact on sperm and oocyte function, raising concerns about possible fertility disruptions.[4,23]

Consequently, active development of nanomedical applications for reproduction, requires a deeper understanding of their interactions with the fundamental pathways of spermatogenesis and oogenesis. This review systematically evaluates the paradoxical nature of nanoparticles function in the context of reproductive biology, juxtaposing their promising applications against their potential to disrupt gametogenesis, with the goal of establishing a scientific foundation to guide the safe and sustainable advancement of nanomedicine in human reproduction.

Benefits of Nanoparticles for Reproductive Health

In spite of their potential risks, emerging nanoparticles (NPs) have caused a paradigm shift in reproductive medicine, due to their superior and tuneable physicochemical properties.[24–27] The main principal advantage of NPs is that they enable direct, targeted delivery of drugs and other therapeutics. Functionalized nanocarriers can transport pharmaceuticals, genetic material, or antioxidants to specific reproductive cells or pathological sites, thereby augmenting therapeutic efficacy while circumventing systemic toxicity.[28,29] For example, Hao et al developed a self-assembling nanoparticle that precisely delivers siRNA to ovarian tumour sites to achieve targeted silencing of the SMARCE1 gene, affecting the activity of downstream proteases. Ingeniously, the developed NP can also monitor therapeutic response via its surface-conjugated peptide substrates, enabling non-invasive detection of SMARCE1 regulated proteases in urine in vivo.[30] Moreover, by leveraging the physicochemical properties of specific nanoparticles, Ding et al developed an intravenous, non-invasive platform for male contraception, based on iron oxide nanoparticles (IONPs) that can be magnetically guided to accumulate in the testes under external magnetic fields, in order to temporally induce localised hyperthermia and reversible suppression of fertility.[31]

Currently, nanomaterials are increasingly being employed to optimise assisted reproductive technologies (ART), by enhancing gamete quality, supporting cryopreservation, and improving embryo culture systems.[14] For instance, addition of zinc oxide nanoparticles (ZnO NPs) to semen extenders has been shown to significantly improve sperm motility and membrane integrity in boar models.[15,16] For cryopreservation, Galmidi et al applied nanoliter-scale droplet confinement and a fundamental analysis of water diffusion, in order to develop a method that effectively reduces osmotic stress during the cryopreservation of human sperm, leading to a marked increase in post-thaw survival.[15]

Furthermore, NPs can serve as potent contrast agents and biosensors for the early and accurate diagnosis of reproductive disorders.[18,32] Kumar et al constructed silica-coated gold nanorods conjugated with FITC, which allow for non-invasive diagnosis of deep-seated endometriosis via photoacoustic imaging, as well as the fluorescence-guided identification and thermal ablation of lesions.[33] In addition, nanotechnology has been used to develop innovative contraceptive strategies, including sustained-release hormone systems and novel approaches for reversible male contraception.[34,35] Yu et al designed an NIR-activated ferritin nanocage (HFn@BBT) for intravenous male contraception. This noninvasive system provides on-demand fertility control, achieving reversible or permanent infertility through a tuneable photothermal treatment.[36]

These coordinated capabilities, spanning targeted therapy, ART optimisation, diagnostic imaging, and fertility regulation, collectively underscore the transformative potential of nanoscale platforms at addressing diverse reproductive health challenges. However, translation of nanotechnology and nanoparticles for clinical use in reproductive medicine necessitates ongoing rigorous safety evaluations.

Exposure of Reproductive Organs to Emerging Nanomedicine

Research indicates that NPs can infiltrate cellular membranes, engage with intracellular components, and induce immediate structural impairment.[37] This phenomenon has also been observed within the context of the reproductive system. For example, recent research has demonstrated that certain NPs, such as gold nanoparticles, are capable of permeating granulosa cells, and affecting their physiological functions, most notably in the context of their role in hormone secretion.[38] Furthermore, another recent investigation revealed that silica nanoparticles (SiNPs) can enter the luminal space of lysosomes within granulosa cells, and induce cytotoxic effects characterised by diminished cell viability and increased apoptosis in a dose-dependent manner. Similarly, SiNPs can induce perturbations in autophagy-associated proteins, thereby triggering autophagy; while at the same time elevating the BAX/BCL-2 ratio and increasing caspase-3 cleavage, culminating in activation of the mitochondrial-mediated caspase-dependent apoptotic signalling cascade. Also, SiNPs can elevate acidity levels within lysosomes, impairing lysosomal functionality. Through this impairment of lysosomal function, SiNPs indirectly induce dysfunctions in the cellular process of autophagy, which in turn cause follicular atresia by activating apoptotic pathways within granulosa cells.[39] Furthermore, NPs measuring 20 and 40 nm in size were rapidly internalized by epithelial cells within the upper female reproductive tract (FRT): within one hour, these NPs were detectable within the lymphatic ducts responsible for draining the FRT, as well as within the ileac lymph nodes (ILNs) and the mesenteric lymph nodes (MLNs).[40] The blood-testis barrier (BTB) is known for its exceptional tightness compared to other mammalian tissue barriers, and partitions the seminiferous epithelium into two distinct compartments, the basal and the adluminal, playing a pivotal role in facilitating spermatogenesis. Within the blood-testis barrier, tight junctions operate in conjunction with ectoplasmic specialisations, desmosomes and gap junctions, in order to establish a distinct microenvironment that is conducive for the progression of meiosis and subsequent transformation of spermatids into spermatozoa during spermiogenesis. In vitro and in vivo investigations suggest that certain nanoparticles can traverse the blood-testis barrier. Importantly, the ability of specific NPs to penetrate the BTB depends on various physicochemical attributes such as composition, morphology, size and surface coating. Recent research has addressed this issue by examining the process through which titanium dioxide nanoparticles (TiO_2-NPs) traverse the BTB. It was revealed that exposure to TiO_2-NPs resulted in increased oxidative stress, downregulation of TJ proteins (claudin-5, ZO-1, and occludin), disruption of TJ structure and a significant increase in the size of intercellular gaps between TM-4 cells. In fact, in TM-4 cells, the passage of TiO_2-NPs across the BTB is facilitated by interference with actin-mediated adherens junctions.[41] Mechanistic studies revealed that nano-TiO_2 triggers structural impairment within the BTB via activation of MAPK signalling pathways, concomitant with increased levels of key BTB proteins such as F-actin, Claudin-11 and ZO-1, indicative of enhanced reactivity. Significantly, the introduction of nano-TiO_2 resulted in reduced BTB integrity, leading to decreased sperm motility and a greater incidence of sperm morphological abnormalities.[42] In addition, Au NPs undergo retrograde transport from the adluminal compartment to the interstitial compartment of the testes through Sertoli cell-mediated endocytosis and exocytosis. This process can cause damage and has been shown to trigger the release of inflammatory cytokines within mouse testis.[43]

Nanoparticle-Induced Toxicity to the Oocyte

Oxidative Stress: A Critical Mechanism of Nanoparticle-Induced Oocyte Toxicity

Reactive oxygen species (ROS) are oxygen-containing molecules that are characterised by their high reactivity and strong tendency to accept electrons. Primary pro-oxidant agents are reactive oxygen species, which are generated from unstable oxygen derivatives such as hydroxyl radicals ($^{\bullet}OH$), hydrogen peroxide (H_2O_2) and superoxide anion ($^{\bullet}O_2^{-}$). Excessive production of ROS negatively impacts cellular function, potentially causing oxidative stress. This oxidative stress can lead to enzyme inactivation, lipid peroxidation, ATP depletion and disturbances in mitochondrial function. Elevated ROS production is prevented by a range of antioxidant enzymes, including catalase, superoxide dismutase (SOD) and numerous peroxidases. Mitochondria are the primary source of reactive oxygen species within the cellular environment; with the mitochondrial electron transport chain (ETC) serving as the principal site for ROS production within mitochondria. The mammalian mitochondrial system encompasses complexes I through IV. Currently, 11 sites have been identified within mammalian mitochondria that are responsible for generating superoxide (O_2^{-}) and/or

hydrogen peroxide (H_2O_2) during substrate oxidation, and within the Electron Transport Chain (ETC).[44] The complex 2-oxoacid dehydrogenase contains sites O_F, P_F, B_F and A_F, while CI harbours sites I_F and I_Q, CIII hosts site III_{Qo} and the Q-dependent dehydrogenases associated with the QH_2/Q pool contain sites II_F, G_Q, E_F and D_Q. ROS can be produced within the mitochondrial matrix at two distinct locations, namely the I_F (FMN site) and I_Q (CoQ binding site), since electrons are transferred from NADH to CoQ in CI. Additionally, CII generates ROS at the II_F site, which is closely linked to succinate dehydrogenase.[45]

ROS-Induced DNA Damage

ROS have been reported to cause diverse forms of DNA damage, including modifications to bases and/or sugars, sugar-base cyclisation, as well as induction of DNA-protein cross-linking and intra- and inter-strand cross-linking; potentially culminating in the manifestation of DNA strand breaks. In addition to directly damaging DNA molecules, ROS also has the potential to induce DNA damage indirectly. This occurs via interactions between ROS and proteins, lipids and assorted cellular components, resulting in the generation of electrophillic entities capable of interacting with DNA molecules in chemical reactions. In particular, polyunsaturated fatty acids (PUFA) peroxidation may generate a diverse array of reactive aldehydes capable of forming covalent adducts with DNA strands, resulting in the formation of DNA adducts.[46]

ROS-Induced Autophagy

Autophagy is a controlled intracellular degradation mechanism tasked with removal of impaired or unnecessary cytoplasmic components and organelles, including mitochondria and the endoplasmic reticulum (ER). Recent research indicates that ROS may trigger autophagosome formation and subsequent autophagic degradation by functioning as signalling molecules within the cellular environment. In this context, elevated levels of ROS are associated with activation of key nuclear transcription factors, including FOXO3, NRF2, HIF-1 and P53, thereby enhancing their transcriptional activity and increasing expression of downstream associated gene products, such as LC3/BNIP3, p62, BNIP3/NIX and TIGAR/DRAM. In addition, ROS may modulate the activity of PERK, thereby influencing the transcriptional regulation of genes associated with autophagy. Protein products encoded by these genes ultimately trigger the process of autophagy in the cytoplasm. Within the cytoplasmic milieu, ROS exerts a suppressive effect on the enzymatic function of Atg4, during the transition from autophagosomes to autolysosomes, thereby inhibiting deconjugation of Atg8-phosphatidylethanolamine (Atg8-PE) by the Atg4 protease.[47]

ROS-Induced Apoptosis

ROS, and in particular hydrogen peroxide (H_2O_2), play a pivotal role in the induction of apoptosis, in a process that involves the tumour suppressor protein, p53. Induction of apoptosis by the tumour suppressor protein p53 entails the modulation of gene expression for proteins governing pro-apoptotic pathways, alongside direct interactions with mitochondrial proteins, thereby triggering mitochondrial membrane permeabilisation (MOMP) and subsequent release of pro-apoptotic mediators.[48] In addition, apoptosis induced by H_2O_2 is associated with greater levels of both p53 expression and phosphorylation, alongside increased levels of pro-apoptotic elements, such as Noxa and Puma. Caspases are pivotal enzymatic players within the apoptotic pathway, and their functionality is susceptible to regulation via oxidative processes.[49] Moreover, ROS induces the oxidation of cardiolipin, a phospholipid that binds cytochrome c within the inner mitochondrial membrane (IMM). This process consequently triggers release of cytochrome c into the cytosolic environment, where it activates the cascade of events associated with apoptosis.

ROS-Induced Toxicity to Oocytes

Multiple studies have indicated that ROS may influence the developmental progression and viability of oocytes discharged during ovulation. In fact, recent experimental findings have revealed that Methoxychlor (MXC), which has been classified as an organochlorine pesticide, diminishes oocyte maturation rates via induction of aberrant spindle morphologies and DNA double-strand breaks. Furthermore, MXC may potentially influence oocyte quality via induction of superoxide radicals and various ROS, along with perturbations in mitochondrial distribution, reductions in mitochondrial membrane potential and elevations in lipid peroxidation levels. Exposure to MXC has adverse effects on the meiotic maturation of oocytes, primarily by interfering with cellular metabolism associated with ROS.[50] Furthermore, the

biological effects of podophyllotoxin, a lignan derived from podophyllum, have been attributed to increased intracellular ROS levels and enhanced Annexin-V signalling during the MI stage. Through this mechanism, podophyllotoxin disrupts meiotic spindle formation, activating apoptotic processes, and ultimately inhibiting oocyte maturation.[51] In addition, recent experimental findings have found that excess fluoride can detrimentally affect both the structural integrity and functional capacity of ovarian cells, thereby impeding oocyte development. In terms of underlying mechanisms, fluoride induces upregulation of the levels of apoptosis-related factors, concomitant with a reduction in antioxidant enzyme activity. At the same time, excess fluoride is associated with elongation of both the tail length and tailing ratio in ovarian cells. In this manner, ingestion of excess fluoride has been observed to diminish the developmental capacity of oocytes, through initiation of oxidative stress and apoptotic processes within the ovarian tissue of female mice[52] (Figure 1).

The Meiotic Spindle: A Key Regulator of Oocyte Quality and Function

Diploid oocytes must skilfully and accurately divide their chromosome count to haploidy, while simultaneously preserving the optimal quantity of ooplasm essential for sustaining embryonic development. In mammalian oocytes, during the final phase of maturation, termed meiosis, a meiotic spindle emerges within the oocyte that subsequently leads to the separation of bivalent chromosomes and expulsion of the initial polar body. Aberrations in the process of meiosis result in the formation of aneuploid gametes. Such chromosomal anomalies are implicated in adverse outcomes, including congenital anomalies, miscarriages and infertility. Recent experimental findings suggest that appropriate assembly and functionality of the meiotic spindle plays an important role in oocyte maturation, serving as a robust determinant of the quality of human oocytes. In this context, recent studies have investigated the correlation between meiotic spindle size in human metaphase II oocytes and the developmental viability of embryos following intracytoplasmic sperm injection (ICSI). It was determined that MII oocytes displaying spindle dimensions within the range of 90–120 μm^2 yielded embryos demonstrating improved propensity for blastocyst formation and subsequently a heightened pregnancy rate, compared to oocytes characterised by spindle sizes outside of this range. These findings imply that the dimensions of the meiotic spindle could serve as a determinant of the quality of human oocytes.[53] Furthermore, the morphology of the oocyte spindle can also significantly influence oocyte quality, because it is closely associated with critical phenomena such as chromosome alignment and segregation. In fact, a recent investigation revealed that normal spindle morphology is associated with a notably higher propensity for generating euploid embryos, in contrast to oocytes

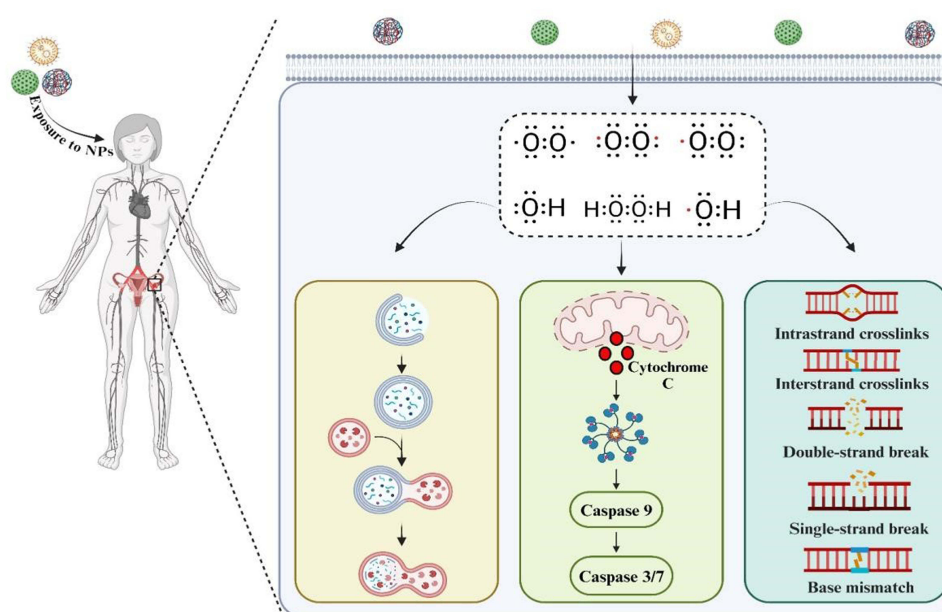

Figure 1 Potential mechanisms by which nanoparticles may induce apoptosis, autophagy, and DNA damage in oocytes via ROS generation, based on data from recent studies.[44,45,47] Created by Figdraw.

with translucent or not clearly visible meiotic spindles.[54] In addition, interactions between oocytes and cumulus cells are also a significant determining factor in the process of meiotic spindle assembly throughout oocyte maturation. Experiments designed to disrupt oocyte-cumulus cell interactions using actin-depolymerising agent latrunculin B resulted in emergence of enlarged meiotic spindles, characterised by dispersed chromosomal arrangements. In contrast, a densely packed chromosomal configuration is typically observed in spindles formed during normal in vivo maturation. This phenomenon implies a potential correlation between cellular contacts and developmental competency. Somatic cell interactions may enhance oocyte quality during meiotic maturation by modulating the spatial arrangement and function of the meiotic spindle via actin-dependent pathways, and improving subsequent developmental outcomes.[55] Thus, within oocytes the meiotic spindle plays a central role in determining both the quality and functionality of oocytes, and significantly influences subsequent pregnancy outcomes.

Nanoparticles with Toxic Implications on Ooocytes

Zinc Oxide Nanoparticles

Zinc oxide (ZnO) is considered the nanoparticle of choice among the spectrum of available nanoparticles. ZnO nanoparticles (ZnO-NPs) have been utilised in a wide variety of applications, including but not limited to personal hygiene products, sensing technologies, antimicrobial formulations and biomedical implements. Consequently, concerns have been raised regarding possible adverse effects associated with ZnO-NPs.[56] Recent investigations show that ZnO NPs can partially interfere with the process of meiosis via induction of oxidative stress, and that the developmental impact of ZnO nanoparticles on oocytes can be ameliorated by antioxidant intervention. This phenomenon induces stress on both the mitochondria and endoplasmic reticulum, subsequently activating autophagy and apoptosis pathways, and leading to oocyte cell death. In addition, perturbations of the architecture of the meiotic cytoskeleton have been observed in ZnO NP exposed populations of oocytes that have completed entry into M-phase. Interestingly, depletion of Grp78, an endoplasmic reticulum chaperone, mimics the meiotic abnormalities and disruption of cytoskeletal structure caused by zinc oxide nanoparticles. Significantly, ZnO NPs induce cytotoxic effects not only through release of Zn^{2+} ions; but also via formation of $ZnCl_2$, which to a notably lesser degree mimics the cytotoxic effects of ZnO nanoparticles. Also, introduction of ZnO NPs resulted in DNA impairment, leading to developmental arrest and oocyte degeneration.[57] Moreover, experimental evidence has demonstrated ZnO NP accumulation in the cytoplasm of oocytes occurs in a dose-dependent manner, eliciting significant DNA damage and induction of apoptosis, and thus leading to a notable reduction in oocyte numbers. In addition, ZnO NPs have been shown to induce DNA damage in pachytene oocytes within foetal ovaries, subsequently disrupting the assembly of primordial follicles and altering folliculogenesis dynamics in the ovaries of the resulting offspring.[58] Moreover, experimental results in zebrafish show that ZnO NPs are cytotoxic to developing oocytes. ZnO-NP cytotoxicity is mediated by caspase-dependent activation of autophagy and apoptosis pathways. Additionally, ZnO NPs induce ROS generation and increased expression of mutated p53 protein in the ovaries. These combined effects culminate in necroptosis, resulting in a necrotic environment that impedes follicular development, disrupts oocyte ovulation and diminishes the reproductive capacity of female zebrafish.[59]

Recent research has investigated possible approaches to reduce the toxicity of ZnO NPs. Notably, Camaioni et al examined the potential reduction of ZnO NP toxicity through silica encapsulation, focusing specifically on the effects of silica coated ZnO NPs on the expansion of cumulus cell-oocyte complexes. The researchers discovered that SiO_2-coated nanoparticles displayed distinct behaviours compared to uncoated nanoparticles; specifically, the coated nanoparticles dissolved more slowly, were not internalised by cells and generally demonstrated lower cytotoxicity. Notably, gene expression analysis revealed that ZnO NPs influenced the expression of genes essential for cumulus-oocyte complex (COC) expansion, whereas SiO_2-coated ZnO NPs did not produce the same effects. In this manner, encapsulation of ZnO NPs within silica matrices diminishes their potential toxicity towards the expansion of cumulus cell-oocyte complexes.[60]

Silver Nanoparticles

Silver nanoparticles (Ag NPs) possess an interesting array of adaptable characteristics, which render them suitable for a broad range of applications within biomedicine and associated fields. Because of this, silver nanoparticles have been the subject of extensive in vitro and in vivo studies aimed at evaluating their potential toxicological effects on biological

tissues and organisms. Recently, the possible deleterious impact of Ag NPs on the process of oocyte maturation was investigated in vitro, specifically focusing on germinal vesicle breakdown (GVBD). Ag NPs mimicked the GVBD-inducing effects of a maturation-inducing hormone (17α, 20β-dihydroxy-4-pregnen-3-one) in zebrafish ovarian follicles. This effect coincided with a decrease in the total concentration of cyclic adenosine monophosphate (cAMP). Moreover, Ag NPs prompted apoptotic cell death in ovarian follicle cells surrounding the oocyte. Similar to Ag NPs, $AgNO_3$ also prompted GVBD, reduced cAMP levels, and triggered apoptosis in ovarian follicle cells. However, gene expression analyses indicated that the levels of transcripts associated with oxidative stress were more sensitive to Ag NPs compared to $AgNO_3$. Notably, zebrafish oocyte maturation is facilitated by H_2O_2, which activates apoptosis in ovarian follicle cells. Taken together, oxidative stress has emerged as a pivotal mechanism behind Ag-NP induced apoptosis in ovarian follicle cells, which subsequently results in GVBD.[61] Similarly, data from additional in vitro and in vivo investigations indicate that Ag NPs can have a detrimental effect on mouse oocyte maturation, reducing IVF rates and negatively affecting subsequent embryonic development. With respect to underlying mechanisms, prior exposure to N-acetylcysteine was effective at preventing ROS generation and apoptosis induced by Ag NPs. This observation strongly suggests the involvement of ROS as a primary modulator of the adverse impacts exerted by Ag NPs on oocyte maturation and subsequent embryonic developmental processes. Furthermore, pre-incubation of oocytes with Ac-DEVD-cho, a specific inhibitor of caspase-3, successfully mitigate adverse outcomes, supporting the direct involvement of caspase-dependent apoptotic signalling pathways in Ag NP-induced effects. Notably, upregulation of p53 and p21 expression levels in blastocysts was observed following preincubation of mouse oocytes with Ag NPs. Thus, cell apoptosis within mouse blastocysts originating from Ag-NP exposed oocytes occurs via induction of intracellular ROS; a process intricately regulated by the involvement of p53, p21 and caspase-3-dependent mechanisms.[62]

Cerium Dioxide Nanoparticles

Cerium oxide (CeO_2) nanoparticles (CeO_2 NPs) are expected to be increasingly utilised in the industrial sector, as integral components employed across diverse applications such as solar energy technology, catalytic processes and gas sensors. Consequently, this will result in a greater risk for occupational exposure to CeO_2 NPs, highlighting the importance of toxicology screenings. Recent research shows that CeO_2 NPs can be taken up by oocytes via endocytosis, resulting in accumulation of CeO_2 NPs aggregates localised in the vicinity of the zona pellucida (ZP). This phenomenon was shown to positively correlate with increased DNA damage in a dose-dependent manner, where significantly increased DNA damage was observed only at the highest concentrations of CeO_2 NPs. Interestingly, treatment with antioxidant compounds was associated with the opposite effect, indicating a promising approach for alleviating the DNA damage induced by CeO_2 NP accumulation in oocytes. Taken together, these results strongly suggest that CeO_2 NPs have toxicological implications on oocyte functionality.[63]

Fullerenol Nanoparticles

Polyhydroxylated fullerenols are water-soluble carbon nanoparticles with notable biocompatibility properties. Recently, an in vitro maturation culture model of oocyte-granulosa cell complexes (OGCs) was used to study the impact of fullerenol on initiation of oocyte meiotic resumption. Fullerenol nanoparticles within adjacent granulosa cells inhibited the extracellular ligand binding domain of the epidermal growth factor receptor (EGFR), leading to reduced binding affinity between EGFR and its physiological ligands. Consequently, EGFR inhibition resulted in decreased downstream activation of extracellular signal-regulated kinase 1 and 2 (ERK1/2), a process directly associated with the modulation of connexin 43 (CX43) expression and internalisation. Furthermore, CX43 reduction, along with transzonal projections (TZPs) retraction, led to disruption of both the gap junction channel and TZP-mediated mass transport. This phenomenon resulted in reduction of cAMP concentrations within the oocyte, facilitating resumption of rat oocyte meiosis. Moreover, the perinuclear localisation of CX43 and EGFR that was observed within granulosa cells may enhance their respective effects. Through the above mechanisms, fullerenol nanoparticles can disrupt the tightly regulated process of oocyte meiotic resumption, potentially leading to a decline in oocyte quality.[64]

Copper Oxide Nanoparticles

The substantial increase in the use of copper oxide nanoparticles (CuO NPs) across a diverse range of applications has prompted concerns regarding their potential toxicity to biological systems. These interactions are associated with ROS generation, resulting in oxidative stress, cytotoxicity, inflammation, genotoxicity and immunotoxicity within living organisms.[65] In the case of reprotoxicity, CuO NP exposure was found to inhibit the oocyte maturation process by disturbing meiotic spindle assembly and chromosomal alignment, as well as the attachment of kinetochore-microtubules. In addition, exposure to CuO NPs influences acetylation of α-tubulin within mouse oocytes, leading to disturbances in both the structural organization of microtubules and microtubule dynamics. Moreover, CuO NP exposure may also result in improper localisation of Ovastacin and Juno, potentially serving as a significant contributory factor to the failure of oocyte maturation. Finally, exposure to CuO NPs disrupts the distribution of mitochondria, resulting in elevated ROS levels, accumulation of DNA damage, and initiation of apoptosis. In summary, CuO NP exposure has been associated with adverse effects on female fertility in mice, primarily by compromising oocyte quality.[66]

Polystyrene Nanoparticles

Polystyrene (PS) is a common plastic synthesised by the polymerisation of styrene monomers.[67] Recent research demonstrated that exogenous polystyrene nanoparticles (PS-NPs) are able to penetrate the zona pellucida, where they are subsequently internalized by oocytes and accumulate within the cytoplasm during the process of meiotic maturation. Although PS-NP exposure did not influence resumption of meiosis in oocytes; it did interfere with meiotic maturation by disrupting spindle assembly and chromosomal alignment. Moreover, PS-NP exposure enhanced oxidative stress and caused mitochondrial aggregation during the process of meiotic maturation. Notably, internalised PS-NPs were observed localised around the endoplasmic reticulum (ER), and disrupted translation in oocytes. Therefore, PS-NPs appear to hinder the progression of meiotic maturation in mouse oocytes through a dual mechanism: first, by elevating oxidative stress levels and inducing mitochondrial dysfunction; and second, by reducing translation efficiency following PS-NP integration into the endoplasmic reticulum during the meiotic maturation process.[68]

Zero-Valent Iron Nanoparticles

Because of their favourable mechanical, physical and chemical characteristics, Zero-Valent Iron nanoparticles (ZVI-NPs) have found extensive applications across diverse industries.[69] Recently, the impact of ZVI-NPs on oocytes and adjacent follicular cells within the context of immune complex-mediated dysfunction has been investigated. Based on these studies, ZVI-NPs appear to inhibit generation of the first polar body (metaphase II) in oocytes, in comparison to a control group.[70]

Perylene Nanoparticles

Perylene nanoparticles also appear to have detrimental effects on oocyte development. Based on a previous study, they have been shown to influence extrusion of the first polar body in oocytes, initially enhancing the number of primordial follicles within ovarian tissue. However, exposure to perylene nanoparticles caused disturbances in the mitochondrial membrane potential, promoting oxidative stress and ultimately triggering autophagy and apoptosis in ovarian tissue.[71]

Nanoparticle-Induced Toxicity on Sperm

Mechanisms of Nanoparticle-Induced Toxic Effects on Sperm Function

In sperm cells, the toxicity induced by nanoparticles is primarily manifested through disruptions of histone-protamine exchange, p53-mediated mitochondrial apoptosis, and increased ROS generation.

Histone-Protamine Exchange

Mammalian spermatogenesis is an intricate developmental procedure in which male germ cells are subjected to a sequence of precisely controlled molecular events, resulting in the formation of mature gametes capable of fertilising an oocyte.[72] During spermatogenesis, a 106-fold condensation of DNA occurs that is crucial for encapsulating the paternal genome within the compact sperm nuclei. In oocytes and somatic cell nuclei, nucleosome-based chromatin packaging involves histone octamers, resulting in a bead-on-a-string configuration. In contrast, the sperm genome is condensed by small, arginine-rich basic proteins called protamines (P1 and P2). This alternative packaging method is

believed to help organise DNA into toroidal structures, achieving a chromatin condensation level 10-fold greater than that found in somatic cell nuclei.[73] Abnormalities in this transition from histones to protamines are associated with irregular chromatin packaging, which may contribute to male infertility by increasing the risk of DNA damage or causing improper epigenetic modifications.[74] Histone removal and degradation are, at least in part, regulated by the ubiquitin-proteasome system. RNF8, an E3 ubiquitin ligase, is involved in DNA damage repair mechanisms through histone ubiquitination. RNF8 is essential for monoubiquitination of histones H2A and H2B, and knockout of RNF8 results in male sterility in mice.[75] Furthermore, Lethal (3) malignant brain tumour like 2 (L3MBTL2) belongs to the family of MBT-domain proteins, which have a significant influence on chromatin remodelling that is crucial for meiosis and spermatogenesis. L3MBTL2 is significantly upregulated in pachytene spermatocytes localised within the testicular environment. Thus, not surprisingly, deletion of L3MBTL2 resulted in increased formation of aberrant sperm cells, a gradual decline in spermatozoa numbers, and premature onset of testicular dysfunction in murine models. Furthermore, the absence of L3MBTL2 also resulted in increased deposition of γH2AX within leptotene spermatocytes, which incorrectly persists on autosomes later in meiosis I. γH2AX is recognized as a highly effective biomarker for assessing DNA damage and repair processes. This phenomenon is associated with impaired crossing-over of chromosomes and synapsis processes during the pachytene phase of meiosis I, coupled with increased germ cell apoptosis. Notably, in GC2 cells, an interaction between L3MBTL2 and the histone ubiquitin ligase RNF8 was observed, and depletion of L3MBTL2 resulted in a decrease in the nuclear levels of both RNF8 and ubH2A. The absence of L3MBTL2 resulted in inhibition of RNF8 and ubH2A pathways, as well as histone acetylation, resulting in elongated spermatids. This, in turn, inhibits protamine 1 deposition and leads to impaired chromatin condensation during spermiogenesis in sperm.[76]

P53-Mediated Mitochondrial Apoptosis

P53 serves as a key regulator that modulates cellular reactions to diverse stress stimuli, by controlling processes such as apoptosis, cell cycle arrest, senescence, DNA repair and the preservation of genetic integrity. Over the years, extensive investigations have elucidated the multi-faceted functions of P53.[77] While traditionally recognised as a transcriptional regulator, p53 has also garnered increasing attention because of its direct involvement in non-transcriptional processes outside of the nucleus; particularly in the context of mitochondria-mediated cell death pathways. This involvement is attributed to the accumulation of p53 protein in both cytosolic and mitochondrial locations, as well as its engagement in protein-protein interactions.[78] For example, p53 interacts with the permeability transition pore complex (PTPC) on the mitochondrial membrane, inducing pore opening. In turn, pore opening in PTPC leads to osmotic swelling in the mitochondria, and subsequently mitochondrial outer membrane permeabilisation (MOMP). Cytosolic p53 can also activate multidomain proapoptotic proteins of the Bcl-2 family, such as Bax and Bak, promoting the formation of multimeric pores that facilitate release of cytotoxic proteins from the mitochondrial intermembrane space (IMS) and/or interactions between Bax/Bak and PTPC components that induce MOMP. Moreover, p53 can inhibit anti-apoptotic Bcl-2-like proteins, such as Bcl-2 and Bcl-XL, which typically regulate their pro-apoptotic counterparts such as Bax, Bak, and Bid.[79] Because of the central role of p53-mediated mitochondrial apoptosis in the elimination of sperm, this pathway has become an important target of infertility treatment. In this regard, recent studies have shown that 4-Nonylphenol (NP) induces apoptosis and hormonal deficiencies, and may impair spermatogenesis and sperm function through p53-independent Fas/FasL-Bax/Bcl-2 pathways.[80]

Oxidative Stress-Induced Damage on Sperm

In sperm, ROS-induced damage is a major factor that contributes to infertility in 30–80% of affected men. Recent experimental evidence suggests that ROS may induce DNA damage in sperm, thereby significantly impacting the pathogenesis of infertility. Therefore, the assessment of oxidative status, antioxidant defence mechanisms, and DNA damage could serve as valuable diagnostic and therapeutic indicators for male infertility.[81] Moreover, ROS levels also significantly influence motility in spermatozoa. In fact, it was observed that elevated ROS levels are associated with an uncoupling of electron transport and adenosine triphosphate synthesis, reducing mitochondrial respiration in sperm, and subsequently causing a decrease in spermatozoa motility.[82] Similarly, Kao et al observed a notable inverse association between sperm motility and the levels of 8-OHdG, as well as between sperm motility and lipid peroxides. In addition, they observed a positive association between sperm motility and the concentrations of ascorbate, α-tocopherol, retinol

and protein thiols within seminal plasma. In support of this, elevated levels of oxidative stress and subsequent oxidative damage were observed in spermatozoa with reduced motility; while diminished antioxidant capacities were found within both the spermatozoa and seminal plasma of males with infertility or subfertility[83] (Figure 2).

Nanoparticles with Toxic Implications on Sperm

Silica Nanoparticles

Nanosilica refers to a nanostructured form (<100 nm) of silicon dioxide, or silica nanoparticles (Si-NPs), that possesses unique physico-chemical properties in contrast to its bulk counterpart: because of its reduced dimensions, Si-NPs have a greater surface-to-volume ratio and enhanced surface reactivity.[84] According to a recent investigation, Si-NPs may impact sperm maturation within the epididymis and have adverse effects on human reproductive function. Si-NPs have been associated with a reduction in sperm count and sperm motility, along with an increase in the rate of sperm abnormalities and structural damage to the testes. Furthermore, Si-NP exposure has led to a decrease in the expression of Protamine 1 (PRM1) protein and an elevation in histone levels, resulting in inhibition of chromatin condensation in sperm. In addition, Si-NP exposure markedly reduced the levels of ubiquitinated histone H2A (ubH2A)/H2B (ubH2B) and RING finger protein 8 (RNF8) within the nucleus of spermatids; while increasing RNF8 levels in the spermatid cytoplasm. Notably, by the 35th day of exposure to Si-NPs, there was a notable increase in the protein expression levels of PIWI-like protein 1 (MIWI) within late spermatids. Also, Si-NPs have the potential to reduce RNF8 levels within the spermatid nucleus, either through upregulation of MIWI expression or by suppressing its degradation. This causes sequestration of RNF8 in the cytoplasm, potentially inhibiting RNF8-mediated ubiquitination of ubH2A and ubH2B. These processes ultimately interfere with removal of H2A and H2B and chromatin condensation, and consequently inhibit the differentiation of round spermatids and chromatin remodelling, resulting in compromised sperm quality and quantity.[85] Also, exposure to Si-NPs resulted in decreased sperm motility, the appearance of histological anomalies in the seminiferous epithelium, and apoptosis of spermatogenic cells, correlating with diminished levels of Lethal (3) malignant brain tumour like 2 (L3MBTL2) and activation of DNA damage-p53-mitochondrial apoptosis pathways. Moreover, the decreased L3MBTL2 levels induced by Si-NP exposure also cause reduced expression of components of the RNF8-ubH2A/ubH2B pathway, leading to incomplete histone-to-protamine exchange. These findings indicate that suppression of Si-NP-induced L3MBTL2 not only triggers the DNA damage-p53-mitochondrial apoptosis pathway, which leads to

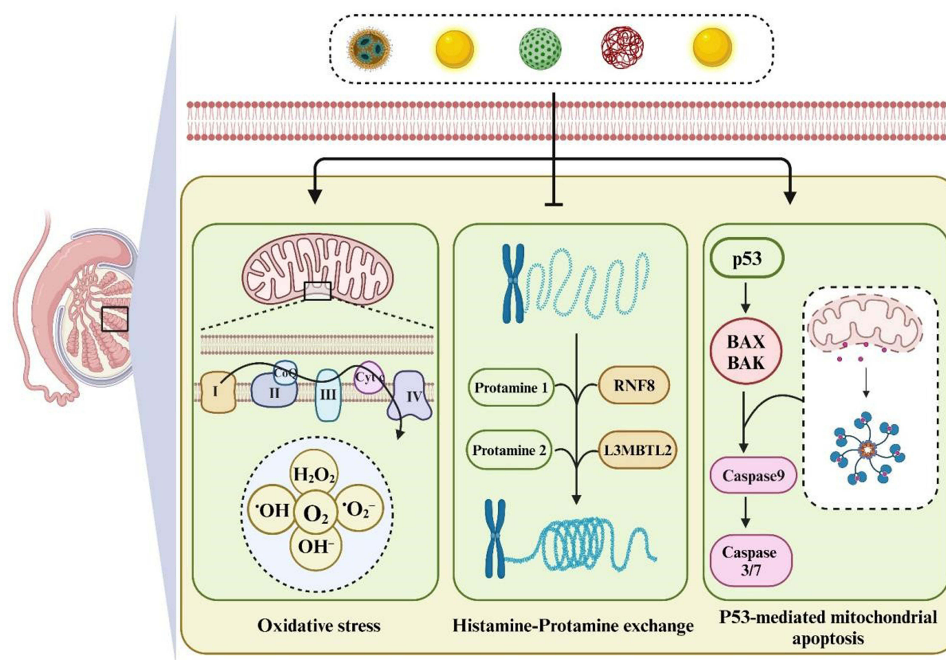

Figure 2 Potential mechanisms of nanoparticle-induced toxic effects on sperm function, based on recent findings.[73,74,77,78,80,81] Created by Figdraw.

apoptosis in spermatogenic cells, but also inhibits the RNF8-ubH2A/ubH2B pathway, resulting in incomplete histone-to-protamine exchange and negatively affecting spermatogenesis. Through the above mechanisms, Si-NPs contribute significantly to reproductive toxicity by downregulating L3MBTL2.[86] Furthermore, recent investigations have examined the impact of Si-NPs on spermatogenic processes over various time intervals. Si-NP exposure resulted in disruption of mitochondrial cristae and a concomitant decrease in ATP levels, leading to a state of oxidative stress within testicular tissues by days 15 and 35 after Si-NP exposure. However, these adverse effects appear to be transient, since complete restoration of testicular structure and function was observed by day 60. Furthermore, silica nanoparticles can induce DNA damage and reduce the quantity and quality of epididymal sperm by days 15 and 35 following exposure; however, these effects are reversed by day 60. In contrast, throughout the 60-day exposure period, no statistically significant alterations in the integrity of epididymal sperm acrosomes, the quantity of testicular spermatogonia and sperm cells, or the levels of the three primary sex hormones were observed. Based on this, Si-NPs can induce reversible damage to sperm in the epididymis without impacting overall fertility; and sperm appear to be more susceptible to silica nanoparticle toxicity than spermatogonia and spermatocytes. Through the above mechanisms, and taking into account the timeline of spermatogenesis, silica nanoparticles predominantly impact sperm maturation in the epididymis by inducing oxidative stress and mitochondrial structural damage, leading to dysfunctions in energy metabolism.[87]

Titanium Dioxide Nanoparticles

Titanium dioxide (TiO_2) NPs are produced globally on a large scale, and used for diverse applications across various industries.[88] TiO_2 NPs can traverse the blood-testis barrier, thereby gaining access to the testes and accumulating within this tissue. Accumulation of TiO_2 NPs is associated with the development of testicular lesions, sperm malformation and disruptions in the homeostasis of serum sex hormone levels. Microarray analysis revealed differential gene expression in testes following TiO_2 NP exposure. Specifically, the expression levels of 70 genes with known functions were increased, while 72 were decreased. Among the genes with altered expression levels, Prm1, Tnp2, Spata19, Tdrd6, Ly6e and Adam3 have been implicated in spermatogenesis; while Cyp2e1, Lep, Srd5a2, Sc4mol, Psmc3ip, and Mvd are linked to steroid and hormone metabolism. In fact, administration of TiO_2 NPs induces testicular toxicity in mice, which is characterised by inhibition of spermatogenesis and perturbations in gene expression.[89] In another investigation, exposure to TiO_2 NPs induced testicular and epididymal lesions, reduced sperm concentrations and sperm motility, and resulted in an increased incidence of abnormal sperm in mice. Furthermore, exposure to TiO_2 nanoparticles resulted in decreased enzymatic activities for glucose-6-phosphate dehydrogenase, succinate dehydrogenase, lactate dehydrogenase, sorbitol dehydrogenase, Ca^{2+}/Mg^{2+}-ATPase, Ca^{2+}-ATPase, and Na^+/K^+-ATPase; while increasing the activities of acid phosphatase, alkaline phosphatase and total nitric oxide synthase in the testicular tissue of mice. In addition, TiO_2 NP exposure also resulted in greater ROS generation, along with elevated levels of malondialdehyde, 8-hydroxydeoxyguanosine and carbonyl, indicative of increased lipid peroxidation, DNA oxidative damage and protein oxidation within the testes, respectively. These findings suggest a potential association between TiO_2 NP-induced suppression of spermatogenesis and alterations in the activity of testicular marker enzymes, coupled with the induction of oxidative stress within the testes.[90] Notably, recent studies have shown that TiO_2 NPs can migrate from the peritoneal cavity to the scrotum, where they accumulate and exert deleterious effects on testicular histology, as well as structural and functional aspects of sperm. These effects are observable within a period of 4–8 days following injection, while the effects are less pronounced beyond a timeframe of 10–38 days post-injection. In addition, sperm motility impairments observed in this study correlated with elevated levels of ROS, implying that oxidative stress could be a causal mechanism underlying the induction of these abnormalities.[91]

Silver Nanoparticles

Human sperm samples were exposed to varying concentrations of silver nanoparticles (Ag NPs) over different durations, after which sperm viability, motility, and the proportion of abnormal to normal sperm were evaluated. These observations revealed a dose- and time-dependent reduction in both sperm viability and motility, with an increase in the ratio of abnormal to normal sperm following Ag NP exposure at a concentration of 200 μg mL^{-1} and 400 μg mL^{-1} for 30 minutes and 60 minutes, respectively. Notably, this analysis also revealed predominantly abnormal sperm morphologies, characterised by disrupted chromatin or the absence of the acrosome in the sperm head, as well as tail bending and mid-piece curvature. Furthermore, the

ultrastructural features of sperm exposed to Ag NPs included disrupted chromatin with swollen, granular and vacuolar abnormalities. In addition, 60 minutes of exposure to Ag NPs at concentrations of 200 μg mL^{-1} and 400 μg mL^{-1}, was associated with increased ROS production and DNA fragmentation. Through the above mechanisms, Ag NPs can induce negative changes in human sperm parameters, emphasising the need for caution regarding the extensive application of Ag NPs.[92] Furthermore, the impact of daily exposure to silver nanoparticles during prepubertal development has also been examined. It was observed that Ag NPs decreased both acrosomal and plasma membrane integrities, decreased mitochondrial activity, and increased the prevalence of sperm abnormalities. Importantly, sperm exhibited heightened susceptibility to the cytotoxic impacts of Ag NPs, with deleterious effects associated with exposure to lower doses during the pre-pubertal stage. These findings indicate that exposure to Ag NPs during the prepubertal period can directly lead to modifications in sperm in adulthood.[93] Notably, a recent study investigated the deleterious impact of Ag NP exposure on sperm parameters and lipid peroxidation of sperm membranes in male rats. It was observed that the presence of Ag NPs led to a notable decrease in both sperm count and motility. Also, Ag NPs substantially elevated malondialdehyde levels in a dose-dependent manner within sperm membranes. Thus, it is possible that Ag NPs diminish the quality of sperm parameters in a dose-dependent fashion by augmenting lipid peroxidation.[94]

Gold Nanoparticles

A recent investigation examined the adverse impact of gold nanoparticles (Au NPs) on sperm function. In initial experiments, the presence of Au NPs was observed to have a detrimental impact on sperm motility, suggesting that they could potentially have negative fertility effects. Moreover, infiltration of Au NPs into sperm cells was observed, potentially resulting in their fragmentation.[95] In another study, M. Nazar et al conducted an investigation into the impact of Au NPs on sperm parameters and chromatin structure in mice. Based on their results, Ag NPs induced a significant reduction in both sperm motility and morphology among the tested experimental groups, particularly in those subjected to Ag nanoparticle-treatment for 35 days, in comparison to the control group. Their findings suggest that Au NPs may have a dual impact: initially affecting sperm motility and interfering with normal sperm morphology, and subsequently influencing sperm chromatin remodelling, resulting in increased chromatin instability and elevated levels of DNA damage in sperm.[96] Expanding upon these discoveries, an independent investigation also found a decrease in sperm motility, which was observed at a dose of 10 μg mL^{-1} of Au NPs, regardless of surface alterations. Importantly, findings from transmission electron microscopy showed the adherence of Ag nanoparticles to the sperm cell membrane, whereas molecular analysis indicated a decline in free thiol residues on the membrane post-exposure, which may explain the observed decline in sperm motility. Notably, exposure to ligand-free nanoparticles resulted in a reduction in sperm fertilization capacity, indicating that disruption of membrane properties in sperm could be detrimental to the fertilization process. These results collectively suggest that Au NPs can disrupt fundamental sperm functions by interacting with the sperm surface membrane.[97] Notably, recent research studied the effects of Ag NP exposure on gametes, which were initially treated with sodium dodecyl sulphate to remove the membrane: exposed to medium containing Au NPs caused a disruption in the chromatin decondensation process and alterations in nuclear structure. Based on these findings, the cytotoxic impact of Au NPs was postulated to be due to interactions with the double-helix of DNA molecules.[98]

Carbon Black Nanoparticles (CBNPs)

Carbon black nanoparticles (CBNPs) have extensive applications in the rubber industry, and are also used in a range of non-rubber products, including pigments and printing inks. During their synthesis and industrial applications, CBNPs can enter an organism via the respiratory system, spreading to critical organs including the gonads, liver, brain, kidneys and blood vessels, and inducing oxidative stress, DNA damage and cytotoxic effects. Hu et al investigated the effects of exposing mice to varying concentrations of CBNPs at distinct life stages (puberty, sexual maturity and adulthood), in order to elucidate the impact of CBNP inhalation on male reproductive physiology and spermatogenesis. After exposure to CBNPs, a notable increase in testicular oxidative stress and inflammation was observed; and these effects varied depending on the duration of the exposure. Also, significant reductions in seminiferous epithelium height (SEH), seminiferous tubule diameter (STD) and the number of Leydig and spermatogenic cells were observed, as well as reductions in sperm motility and speed. These effects varied across the different exposure doses tested. Importantly, the

observed elevated levels of oxidative stress and increased inflammation within the testes adversely affected testicular morphology and impaired spermatogenesis, diminishing testosterone secretion and lowering sperm quality. Also, the observed morphological defects in the testes strongly correlated with a reduction in sperm quantity. Because of the above, CBNPs exposure decreases sperm quality and quantity in a dose-dependent fashion.[99]

Zinc Oxide Nanoparticles

Recent research has investigated the cytotoxic impact of zinc oxide nanoparticles (ZnO NPs) on spermatozoa viability. Various concentrations of ZnO NPs (10, 100, 500 and 1000 µg mL^{-1}) were incubated with semen samples at 37 °C for 45, 90 and 180 minutes. After intervals of 45, 90 and 180 minutes, the highest percentage of cell death observed was 20.8%, 21.2% and 33.2%, respectively. Exposure to the maximal concentration (1000 µg mL^{-1}) of ZnO NPs resulted in the greatest toxicity across all incubation times. Thus, the cytotoxicity induced by ZnO NPs exhibits depended on both the dose and time of exposure.[100] Further experimentation revealed concentration-dependent and time-dependent effects associated with ZnO NPs exposure, which caused an increased incidence of sperm abnormalities within the epididymal tail.[101]

Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONPs) have garnered significant attention because of their distinctive characteristics, including a high surface-to-volume ratio, superparamagnetism, increased surface area, and easy separation techniques. However, they have also been demonstrated to readily accumulate in various tissues and elicit toxicity at different exposure levels.[102] Recent investigations have revealed that administration of IONPs at a dose of 300 mg/kg/day resulted in notable reductions in various sperm-related parameters, including: motility, Leydig cells, Sertoli cells, spermatogonia, primary spermatocytes, spermatids, total length of seminiferous tubules and the volumes of testicular interstitial tissue.[103]

Copper Oxide Nanoparticles

Administration of CuO NPs resulted in a substantial decrease in serum testosterone levels, suppression of sperm concentrations, and a significant increase in the percentage of abnormal and dead sperm. Furthermore, degeneration of germ cells, Leydig cells, Sertoli cells and spermatocytes was observed in testicular tissue, accompanied by vacuolation and inflammatory cell infiltration. In conclusion, CuO NPs have a deleterious and permanent impact on testicular function and the physiological attributes of sperm, with increased detrimental effects associated with the administration of elevated doses of CuO NPs.[104]

Cerium Oxide Nanoparticles

Cerium oxide nanoparticles (CeO_2 NPs) led to a reduction in both sperm motility and sperm count, while also increasing the overall incidence of sperm abnormalities in mice.[105] Furthermore, the impact of CeO_2 NP exposure on the DNA of human spermatozoa has also been recently investigated. It has been revealed that even exposure of human spermatozoa to extremely low concentrations of CeO_2 NP in vitro can lead to notable DNA damage[106] (Figure 3).

The Future Prospective

This review emphasises the dual nature of nanoparticles (NPs). In parallel with their rapid development for applications across biomedical fields, it is imperative to address their associated toxicological effects, especially those impacting reproductive health. As summarised in Table 1, the adverse effects of various NPs, such as zinc oxide (ZnO), silver (Ag), and titanium dioxide (TiO_2), on both sperm and oocyte function have been shown to occur through mechanisms including oxidative stress, DNA damage, and disruption of key cellular processes; and these effects are now well-documented. Building upon this foundational knowledge, future research must pivot to address several critical areas, in order to ensure the safety and sustainable development of nanotechnologies.

A primary objective should be to move beyond phenomenological observations, to facilitate establishment of clear, mechanistic structure-activity relationships that can predict the toxicity of NPs based on their physicochemical properties. This effort should be coupled with the advancement of "safe-by-design" principles, focusing on engineering NPs with enhanced biocompatibility, for instance, through surface modifications, biodegradable materials, or protective coatings, in order to mitigate unintended interactions with germ cells. Furthermore, there is an urgent need to define safe exposure

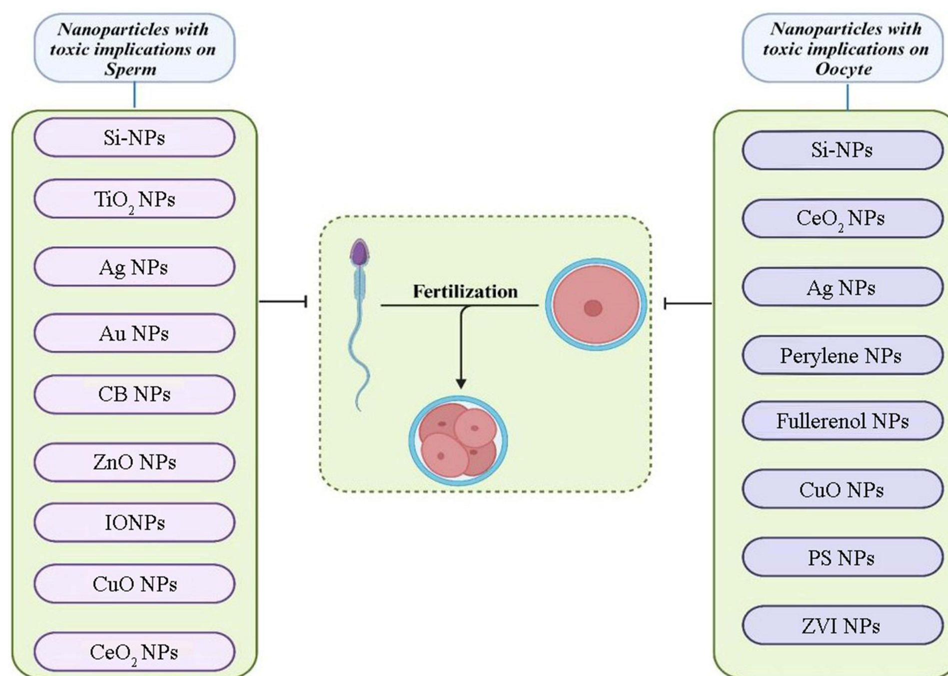

Figure 3 A schematic representation of nanoparticles with toxic implication on sperm and oocytes, based on findings from recent investigations.[59–62,64,66,68,69,83–85,87–99,101–104,107] Created by Figdraw.

thresholds and to develop more physiologically relevant in vitro models, such as reproductive organoids, for improved risk assessment. Investigating the long-term and epigenetic consequences of NP exposure on germ cells and subsequent generational health represents another vital frontier. Finally, exploration of adjuvant strategies, including the application

Table 1 Major Nanoparticles with Toxic Implications on Sperm and Oocytes

Nanoparticles	Species	Reproductive Cells	Biological Implications	Ref.
Zinc oxide nanoparticles	Mouse (in vitro)	Oocytes	Induces oxidative stress and interferes with the process of meiosis	[57]
	Mouse (in vitro and in vivo)	Oocytes	Induces DNA damage and affects pre- and post-natal oogenesis	[58]
	Zebrafish (in vivo)	Oocytes	Activates autophagy and apoptosis, and increases oxidative stress	[59]
	Rat (in vivo)	Sperm	Reduces sperm motility and increases sperm deformities	[108]
	Human (in vitro)	Sperm	Increases cell death	[100]
	Albino mice (in vivo)	Sperm	Decreases the weight of testes in a dose- and time-dependent manner	[101]
Silver nanoparticles	Zebrafish (in vitro)	Oocytes	Induces oxidative stress, promotes apoptotic cell death	[61]
	Mouse (in vitro and in vivo)	Oocytes	Induces oxidative stress, promotes apoptotic cell death	[62]
	Albino rats (in vivo)	Ovarian	Reduces glutathione (GSH) and superoxide dismutase (SOD).	[109]
	Human (in vitro)	Sperm	Increases ROS generation and DNA damage	[92]
	Rat (in vivo)	Sperm	Causes damage to sperm plasma membrane and acrosome integrity	[93]
	Mice (in vivo)	Sperm	Induces germ cell development dysfunction	[110]
Cerium dioxide nanoparticles	Mouse (in vitro)	Oocytes	Increases DNA damage	[63]
	Human (in vitro)	Sperm	Induces marked DNA damage	[106]
	Mice (in vivo)	Sperm	Disrupts the antioxidant/oxidant balance, reducing sperm count and motility	[105]
Fullerenol nanoparticles	Rat (in vitro)	Oocytes	Disrupts the tightly regulated process of meiotic resumption	[64]
Copper oxide nanoparticles	Mice (in vivo)	Oocytes	Elevates ROS, increases DNA damage and causes apoptosis	[66]
	Rat (in vivo)	Oocytes	Damages ovarian ultrastructural features	[111]
	Rat (in vivo)	Sperm	Significantly increases the percentage of abnormal and dead sperm	[104]
	Rat (in vivo)	Sperm	Distorts basement membranes of seminiferous tubules and causes seminiferous cell degeneration	[112]

(*Continued*)

Table 1 (Continued).

Nanoparticles	Species	Reproductive Cells	Biological Implications	Ref.
Polystyrene nanoparticles	Mouse (in vitro)	Oocytes	Elevates oxidative stress and reduces translation efficiency	[68]
	Bovine (in vitro)	Oocytes	Impairs nuclear maturation	[113]
	Mice (in vivo)	Oocytes	Induces apoptosis and autophagy, and disrupts steroidogenesis	[107]
	Mice (in vivo)	Sperm	Induces oxidative stress and damages testicular microstructure and functions	[114]
Zero-valent iron nanoparticles	Mice (in vivo)	Oocytes	Inhibits first polar body generation	[70]
Perylene nanoparticles	Mice (in vivo)	Oocytes	Elevates ROS levels and causes apoptosis	[71]
Silica nanoparticles	Mice (in vivo)	Oocytes	Disrupts meiotic recombination and increases apoptosis in oocytes	[115]
	Mice (in vivo)	Sperm	Decreases RNF8 levels, suppressing histone-to-protamine exchange	[85]
	Mice (in vivo)	Sperm	Inhibits the RNF8-ubH2A/ubH2B pathway resulting in incomplete histone-to-protamine exchange	[86]
	Mice (in vivo)	Sperm	Elevates ROS levels, damaging mitochondrial structure, and DNA	[87]
Titanium dioxide nanoparticles	Mice (in vivo)	Sperm	Capable of crossing the blood–testis barrier, and altering gene expression in testis	[89]
	Mice (in vivo)	Sperm	Elevates ROS levels, inducing biochemical dysfunctions	[90]
	Mice (in vivo)	Sperm	Increases ROS levels, causing DNA damage	[91]
	Human (in vitro)	Sperm	Induces DNA damage	[116]
Gold nanoparticles	Mice (in vivo)	Sperm	Affects sperm chromatin remodelling, increasing the rate of sperm DNA damage	[96]
	Bovine (in vitro)	Sperm	Interacts with the sperm surface membrane, impairing sperm functions	[97]
	Mouse (in vitro)	Sperm	Interacts with the double-helix of DNA, disturbing nuclear chromatin decondensation	[98]
	Mice (in vitro)	Sperm	Spermicidal activity	[117]
Carbon black nanoparticles	Mouse (in vivo)	Sperm	Increases oxidative stress and inflammation, damaging spermatogenesis	[99]
Iron oxide nanoparticles	Boars (in vitro)	Sperm	Increases LPO levels, lowering sperm quality	[118]
	Mouse (in vivo)	Sperm	Significantly decreases sperm motility	[103]
Graphene Oxide Nanosheets	Human (in vitro)	Oocytes	Induces mitochondrial toxicity	[119]
Polylactic Acid Nanoplastic	Mice (in vivo)	Sperm	Disrupts spermatogenesis and mitochondrial dysfunction	[120]

of antioxidants to mitigate oxidative stress induced by NP exposure in germ cells, represents a critical need for mitigating the associated risks. By integrating deep mechanistic toxicology with innovative material science, the field of nanomedicine can find a way to fully harness the benefits of NPs while rigorously safeguarding reproductive health.

Data Sharing Statement

Data will be made available on request. Data is available from the corresponding author.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Liu Y, Lin Z, Wang Y, Chen L, Wang Y, Luo C. Nanotechnology in inflammation: cutting-edge advances in diagnostics, therapeutics and theranostics. *Theranostics*. 2024;14(6):2490–2525. doi:10.7150/thno.91394
2. Guo R, Zhang Z, Zhang S, et al. Innovative nanocarriers: synthetic and biomimetic strategies for enhanced drug delivery. *Mater Today Bio*. 2025;34:102180. doi:10.1016/j.mtbio.2025.102180
3. Herrara V, Tarab-Ravski D, Chauhan SC, et al. Nanotechnology strategies for endometrium health: are we on the right track? *Bioact Mater*. 2025;54:423–449. doi:10.1016/j.bioactmat.2025.08.016
4. Zhu L, Xue H, Hu H, et al. The dual effects of nanomaterials on sperm and seminal fluid oxidative stress. *Mater Today Bio*. 2025;34:102163. doi:10.1016/j.mtbio.2025.102163
5. Hafidh S, Honys D. Reproduction multitasking: the male gametophyte. *Annu Rev Plant Biol*. 2021;72:581–614. doi:10.1146/annurev-arplant-080620-021907
6. Nishimura H, L'Hernault SW. Spermatogenesis. *Current Biol*. 2017;27(18):R988–R994. doi:10.1016/j.cub.2017.07.067
7. Staub C, Johnson L. Review: spermatogenesis in the bull. *Animal*. 2018;12:s27–s35. doi:10.1017/S1751731118000435
8. He M, Zhang T, Yang Y, Wang C. Mechanisms of oocyte maturation and related epigenetic regulation. *Front Cell Dev Biol*. 2021;9:654028. doi:10.3389/fcell.2021.654028
9. Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *J Nanobiotechnol*. 2022;20(1):262. doi:10.1186/s12951-022-01477-8
10. Lin H, Li Z, Zelepukin IV, Deyev SM, Yang X, Li Z. Effects of nanoparticle physicochemical properties on macrophage polarization. *J Control Release*. 2025;387:114215. doi:10.1016/j.jconrel.2025.114215
11. Xu M, Qi Y, Liu G, Song Y, Jiang X, Du B. Size-dependent in vivo transport of nanoparticles: implications for delivery, targeting, and clearance. *ACS Nano*. 2023;17(21):20825–20849. doi:10.1021/acsnano.3c05853
12. Bassey PO, Ilomuanya MO, Oseni BA, et al. Advancements in drug delivery systems for women's reproductive health: vaginal microbiome as a target for innovative drug delivery systems. *Eur J Pharm Biopharm*. 2025;215:114831. doi:10.1016/j.ejpb.2025.114831
13. Swingle KL, Hamilton AG, Safford HC, et al. Placenta-tropic VEGF mRNA lipid nanoparticles ameliorate murine pre-eclampsia. *Nature*. 2025;637(8045):412–421. doi:10.1038/s41586-024-08291-2
14. Silva JRV, Barroso PAA, Nascimento DR, et al. Benefits and challenges of nanomaterials in assisted reproductive technologies. *Mol Reprod Dev*. 2021;88(11):707–717. doi:10.1002/mrd.23536
15. Galmidi BS, Orvieto R, Zurgil N, Deutsch M, Fixler D. Overcoming sperm cell survival challenges cryopreserved in nanoliter volumes. *Int J Mol Sci*. 2025;26(13):6343. doi:10.3390/ijms26136343
16. Laskar SZ, Talukdar D, Ghosh A, Bora PP, Lalrintluanga K, Kalita G. Effect of zinc oxide nanoparticles on quality and fertility of preserved boar semen. *Int J Adv Biochem Res*. 2025;9(2S):270–274. doi:10.33545/26174693.2025.v9.i2Sd.3735
17. Hu Q. The protective effect of zinc oxide nanoparticles on boar sperm during preservation at 17 degrees C. *Anim Reprod*. 2025;22(1):e20230013. doi:10.1590/1984-3143-ar2023-0013
18. Acharya B, Behera A, Moharana S, Behera S. Recent advances in nanotechnology-based drug delivery systems for the diagnosis and treatment of reproductive disorders. *ACS Appl Bio Mater*. 2024;7(3):1336–1361. doi:10.1021/acsabm.3c01064
19. Zare-Zardini H, Hatamizadeh N, Haddadzadegan N, Soltaninejad H, Karimi-Zarchi M. Advantages and disadvantages of using carbon nanostructures in reproductive medicine: two sides of the same coin. *JBRA Assist Reprod*. 2022;26(1):142–144. doi:10.5935/1518-0557.20210070
20. Mohammadi E, Behnam B, Mokhtarzadeh A, et al. Reproductive toxicity of nanoparticles: a comprehensive review. *Curr Med Chem*. 2023. doi:10.2174/0929867331666230815101141
21. Yao Y, Zhang T, Tang M. Toxicity mechanism of engineered nanomaterials: focus on mitochondria. *Environ Pollut*. 2024;343:123231. doi:10.1016/j.envpol.2023.123231
22. Yang M, Wang W-X. Differential cascading cellular and subcellular toxicity induced by two sizes of nanoplastics. *Sci Total Environ*. 2022;829:154593. doi:10.1016/j.scitotenv.2022.154593
23. Xuan L, Ju Z, Skonieczna M, Zhou P-K, Huang R. Nanoparticles-induced potential toxicity on human health: applications, toxicity mechanisms, and evaluation models. *MedComm*. 2023;4(4):e327. doi:10.1002/mco2.327
24. Fraser B, Peters AE, Sutherland JM, et al. Biocompatible nanomaterials as an emerging technology in reproductive health; a focus on the male. *Front Physiol*. 2021;12:753686. doi:10.3389/fphys.2021.753686
25. Davis EH, Jones C, Coward K. Rethinking the application of nanoparticles in women's reproductive health and assisted reproduction. *Nanomedicine*. 2024;19(14):1231–1251. doi:10.2217/nnm-2023-0346
26. Fu Q, Fu L. Engineering nanosystems for regulating reproductive health in women. *Theranostics*. 2025;15(2):439–459. doi:10.7150/thno.102626
27. Zhao F, Fan M, Jing Z, et al. Engineered nanoparticles potentials in male reproduction. *Andrology*. 2025;13(4):694–705. doi:10.1111/andr.13729
28. Salaheldin TA, Bharali DJ, Mousa SA. Functionalized nano-targeted moieties in management of prostate cancer. *Fut Oncol*. 2020;16(13):869–883. doi:10.2217/fon-2019-0635
29. Nayak R, Kar B, Ghosh G, Rath G. Current trends in chitosan based nanopharmaceuticals for topical vaginal therapies. *Int J Biol Macromol*. 2021;193(Pt B):2140–2152. doi:10.1016/j.ijbiomac.2021.11.045
30. Hao L, Boehnke N, Elledge SK, et al. Targeting and monitoring ovarian cancer invasion with an RNAi and peptide delivery system. *Proc Natl Acad Sci U S A*. 2024;121(11):e2307802121. doi:10.1073/pnas.2307802121
31. Ding W, Chen Z, Gu Y, Chen Z, Zheng Y, Sun F. Magnetic testis targeting and magnetic hyperthermia for noninvasive, controllable male contraception via intravenous administration. *Nano Letters*. 2021;21(14):6289–6297. doi:10.1021/acs.nanolett.1c02181

32. Luo L, Zhou H, Wang S, et al. The application of nanoparticle-based imaging and phototherapy for female reproductive organs diseases. *Small*. 2024;20(41):e2207694. doi:10.1002/smll.202207694
33. Kumar PPP, Chung SJ, Hadrick K, et al. Noninvasive detection and thermal ablation therapy of endometriosis using silica-coated gold nanorods. *Adv NanoBiomed Res*. 2025. doi:10.1002/anbr.202500101
34. Su Z, Diao T, McGuire H, et al. Nanomaterials solutions for contraception: concerns, advances, and prospects. *ACS Nano*. 2023;17(21):20753–20775. doi:10.1021/acsnano.3c04366
35. Su Z, Yao C, Tipper J, et al. Nanostrategy of targeting at embryonic trophoblast cells using CuO nanoparticles for female contraception. *ACS Nano*. 2023;17(24):25185–25204. doi:10.1021/acsnano.3c08267
36. Yu X, Shuai J, Meng G, et al. Ferritin-nanocaged aggregation-induced emission nanoaggregates for NIR-II fluorescence-guided noninvasive, controllable male contraception. *Mater Today Bio*. 2024;25:100995. doi:10.1016/j.mtbio.2024.100995
37. Huang J, Zou L, Bao M, Feng Q, Xia W, Zhu C. Toxicity of polystyrene nanoparticles for mouse ovary and cultured human granulosa cells. *Ecotoxicol Environ Safety*. 2023;249:114371. doi:10.1016/j.ecoenv.2022.114371
38. Stelzer R, Hutz RJ. Gold nanoparticles enter rat ovarian granulosa cells and subcellular organelles, and alter in-vitro estrogen accumulation. *J Reprod Dev*. 2009;55(6):685–690. doi:10.1262/jrd.20241
39. Zheng Z, Zuo W, Ye R, et al. Silica nanoparticles promote apoptosis in ovarian granulosa cells via autophagy dysfunction. *Int J Mol Sci*. 2023;24(6):5189. doi:10.3390/ijms24065189
40. Howe SE, Konjufca VH. Protein-coated nanoparticles are internalized by the epithelial cells of the female reproductive tract and induce systemic and mucosal immune responses. *PLoS One*. 2014;9(12):e114601. doi:10.1371/journal.pone.0114601
41. Ni D-Q, Ma -D-D, Hao S-L, Yang W-X, Kovacs T, Tan F-Q. Titanium dioxide nanoparticles perturb the blood-testis barrier via disruption of actin-based cell adhesive function. *Aging*. 2021;13(23):25440. doi:10.18632/aging.203763
42. Lu T, Ling C, Hu M, et al. Effect of nano-titanium dioxide on blood-testis barrier and MAPK signaling pathway in male mice. *Biol Trace Element Res*. 2021;199:2961–2971. doi:10.1007/s12011-020-02404-4
43. Yu J, Xu J, Li H, et al. Gold nanoparticles retrogradely penetrate through testicular barriers via Sertoli-cells mediated endocytosis/exocytosis and induce immune response in mouse. *Ecotoxicol Environ Safety*. 2023;255:114827. doi:10.1016/j.ecoenv.2023.114827
44. Brand MD. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. *Free Radical Biol Med*. 2016;100:14–31. doi:10.1016/j.freeradbiomed.2016.04.001
45. Hernansanz-Agustín P, Ramos E, Navarro E, et al. Mitochondrial complex I deactivation is related to superoxide production in acute hypoxia. *Redox Biol*. 2017;12:1040–1051. doi:10.1016/j.redox.2017.04.025
46. Yu Y, Cui Y, Niedernhofer LJ, Wang Y. Occurrence, biological consequences, and human health relevance of oxidative stress-induced DNA damage. *Chem Res Toxicol*. 2016;29(12):2008–2039. doi:10.1021/acs.chemrestox.6b00265
47. Li L, Tan J, Miao Y, Lei P, Zhang Q. ROS and autophagy: interactions and molecular regulatory mechanisms. *Cell Mol Neurobiol*. 2015;35:615–621. doi:10.1007/s10571-015-0166-x
48. Luna-Vargas MP, Chipuk JE. The deadly landscape of pro-apoptotic BCL-2 proteins in the outer mitochondrial membrane. *FEBS J*. 2016;283(14):2676–2689. doi:10.1111/febs.13624
49. Circu ML, Aw TY. Glutathione and modulation of cell apoptosis. *Biochimica Et Biophysica Acta*. 2012;1823(10):1767–1777. doi:10.1016/j.bbamcr.2012.06.019
50. Liu Y, Wang YL, Chen MH, et al. Methoxychlor exposure induces oxidative stress and affects mouse oocyte meiotic maturation. *Mol Reprod Dev*. 2016;83(9):768–779. doi:10.1002/mrd.22683
51. Jiang W-J, Hu -L-L, Ren Y-P, et al. Podophyllotoxin affects porcine oocyte maturation by inducing oxidative stress-mediated early apoptosis. *Toxicon*. 2020;176:15–20. doi:10.1016/j.toxicon.2020.01.006
52. Song WY, Meng H, Wang XG, et al. Reduced micro RNA-188-3p expression contributes to apoptosis of spermatogenic cells in patients with azoospermia. *Cell proliferation*. 2017;50(1):e12297. doi:10.1111/cpr.12297
53. Tomari H, Honjo K, Kunitake K, et al. Meiotic spindle size is a strong indicator of human oocyte quality. *Reprod Med Biol*. 2018;17(3):268–274. doi:10.1002/rmb2.12100
54. Tilia L, Venetis C, Kilani S, Cooke S, Chapman M. Is oocyte meiotic spindle morphology associated with embryo ploidy? A prospective cohort study. *Fertility Sterility*. 2016;105(4):1085–1092.e1087. doi:10.1016/j.fertnstert.2015.12.018
55. Barrett SL, Albertini DF. Cumulus cell contact during oocyte maturation in mice regulates meiotic spindle positioning and enhances developmental competence. *J Assisted Reprod Genet*. 2010;27:29–39. doi:10.1007/s10815-009-9376-9
56. Hou J, Wu Y, Li X, Wei B, Li S, Wang X. Toxic effects of different types of zinc oxide nanoparticles on algae, plants, invertebrates, vertebrates and microorganisms. *Chemosphere*. 2018;193:852–860. doi:10.1016/j.chemosphere.2017.11.077
57. Huang C, Wu D, Khan FA, et al. Zinc oxide nanoparticle causes toxicity to the development of mouse oocyte and early embryo. *Toxicol Lett*. 2022;358:48–58. doi:10.1016/j.toxlet.2022.01.010
58. Zhai Q-Y, Ge W, Wang -J-J, et al. Exposure to Zinc oxide nanoparticles during pregnancy induces oocyte DNA damage and affects ovarian reserve of mouse offspring. *Aging*. 2018;10(8):2170. doi:10.18632/aging.101539
59. Mawed SA, Marini C, Alagawany M, et al. Zinc oxide nanoparticles (ZnO-NPs) suppress fertility by activating autophagy, apoptosis, and oxidative stress in the developing oocytes of female zebrafish. *Antioxidants*. 2022;11(8):1567. doi:10.3390/antiox11081567
60. Camaioni A, Massimiani M, Lacconi V, et al. Silica encapsulation of ZnO nanoparticles reduces their toxicity for cumulus cell-oocyte-complex expansion. *Particle Fibre Toxicol*. 2021;18:1–15. doi:10.1186/s12989-021-00424-z
61. Chen SX, Yang XZ, Deng Y, et al. Silver nanoparticles induce oocyte maturation in zebrafish (Danio rerio). *Chemosphere*. 2017;170:51–60. doi:10.1016/j.chemosphere.2016.12.016
62. Huang CH, Yeh JM, Chan WH. Hazardous impacts of silver nanoparticles on mouse oocyte maturation and fertilization and fetal development through induction of apoptotic processes. *Environ Toxicol*. 2018;33(10):1039–1049. doi:10.1002/tox.22590
63. Courbiere B, Auffan M, Rollais R, et al. Ultrastructural interactions and genotoxicity assay of cerium dioxide nanoparticles on mouse oocytes. *Int J Mol Sci*. 2013;14(11):21613–21628. doi:10.3390/ijms141121613
64. Lei R, Bai X, Chang Y, et al. Effects of fullerenol nanoparticles on rat oocyte meiosis resumption. *Int J Mol Sci*. 2018;19(3):699. doi:10.3390/ijms19030699

65. Naz S, Gul A, Zia M. Toxicity of copper oxide nanoparticles: a review study. *IET Nanobiotechnol*. 2020;14(1):1–13. doi:10.1049/iet-nbt.2019.0176
66. Zhang M, Wang W, Zhang D, et al. Copper oxide nanoparticles impairs oocyte meiosis maturation by inducing mitochondrial dysfunction and oxidative stress. *Food Chem Toxicol*. 2024;185:114441. doi:10.1016/j.fct.2024.114441
67. Kik K, Bukowska B, Sicińska P. Polystyrene nanoparticles: sources, occurrence in the environment, distribution in tissues, accumulation and toxicity to various organisms. *Environ Pollution*. 2020;262:114297. doi:10.1016/j.envpol.2020.114297
68. Park S, Jeon H-J, Choi DY, Oh JS. Polystyrene nanoparticles incorporate into the endoplasmic reticulum and disturb translation during meiotic maturation in mouse oocytes. *Toxicology Vitro*. 2022;82:105380. doi:10.1016/j.tiv.2022.105380
69. Xue W, Huang D, Zeng G, et al. Performance and toxicity assessment of nanoscale zero valent iron particles in the remediation of contaminated soil: a review. *Chemosphere*. 2018;210:1145–1156. doi:10.1016/j.chemosphere.2018.07.118
70. Sribna VO, Voznesenska TY, Blashkiv T. The influence of zero-valent iron nanoparticles on oocytes and surrounding follicular cells in mice. *Appl Nanosci*. 2019;9:1395–1403. doi:10.1007/s13204-019-00978-7
71. Wang H, Zhang J, Feng D, Feng X. Effects of mPEG-DSPE/corannulene or perylene nanoparticles on the ovary and oocyte. *RSC Adv*. 2020;10(29):16972–16981. doi:10.1039/D0RA02129F
72. Hale DW. Mammalian spermatogenesis. In: *Advances in Genome Biology*. Vol. 4. Elsevier; 1996:249–304.
73. Wykes SM, Krawetz SA. The structural organization of sperm chromatin. *J Biol Chem*. 2003;278(32):29471–29477. doi:10.1074/jbc.M304545200
74. Barrachina F, Soler-Ventura A, Oliva R, Jodar M. Sperm nucleoproteins (histones and protamines). *A Clinician's Guide to Sperm DNA and Chromatin Damage*. 2018;31–51.
75. Song Y, Guo Y, Guo Z, et al. Function of RAD6B and RNF8 in spermatogenesis. *Cell Cycle*. 2018;17(2):162–173. doi:10.1080/15384101.2017.1361066
76. Meng C, Liao J, Zhao D, et al. L3MBTL2 regulates chromatin remodeling during spermatogenesis. *Cell Death Different*. 2019;26(11):2194–2207. doi:10.1038/s41418-019-0283-z
77. Vaseva AV, Moll UM. The mitochondrial p53 pathway. *Biochimica et Biophysica Acta*. 2009;1787(5):414–420. doi:10.1016/j.bbabio.2008.10.005
78. Estaquier J, Vallette F, Vayssiere J-L, Mignotte B. The mitochondrial pathways of apoptosis. *Adv Mitochondrial Med*. 2012;2012:157–183.
79. Morselli E, Galluzzi L, Kroemer G. Mechanisms of p53-mediated mitochondrial membrane permeabilization. *Cell Res*. 2008;18(7):708–710. doi:10.1038/cr.2008.77
80. Gao Y, Hong J, Guo Y, et al. Assessment spermatogenic cell apoptosis and the transcript levels of metallothionein and p53 in Meretrix meretrix induced by cadmium. *Ecotoxicol Environ Safety*. 2021;217:112230. doi:10.1016/j.ecoenv.2021.112230
81. Hosen MB, Islam MR, Begum F, Kabir Y, Howlader MZH. Oxidative stress induced sperm DNA damage, a possible reason for male infertility. *Iran J Reprod Med*. 2015;13(9):525.
82. Ferramosca A, Provenzano SP, Montagna DD, Coppola L, Zara V. Oxidative stress negatively affects human sperm mitochondrial respiration. *Urology*. 2013;82(1):78–83. doi:10.1016/j.urology.2013.03.058
83. Kao S-H, Chao H-T, Chen H-W, Hwang TI, Liao T-L, Wei Y-H. Increase of oxidative stress in human sperm with lower motility. *Fertil Steril*. 2008;89(5):1183–1190. doi:10.1016/j.fertnstert.2007.05.029
84. Napierska D, Thomassen LC, Lison D, Martens JA, Hoet PH. The nanosilica hazard: another variable entity. *Particle Fibre Toxicol*. 2010;7:1–32. doi:10.1186/1743-8977-7-39
85. Liu J, Li X, Zhou G, et al. Silica nanoparticles inhibiting the differentiation of round spermatid and chromatin remodeling of haploid period via MIWI in mice. *Environ Poll*. 2021;284:117446. doi:10.1016/j.envpol.2021.117446
86. Liu J, Li X, Zhou G, et al. Silica nanoparticles induce spermatogenesis disorders via L3MBTL2-DNA damage-p53 apoptosis and RNF8-ubH2A/ubH2B pathway in mice. *Environ Pollution*. 2020;265:114974. doi:10.1016/j.envpol.2020.114974
87. Xu Y, Wang N, Yu Y, et al. Exposure to silica nanoparticles causes reversible damage of the spermatogenic process in mice. *PLoS One*. 2014;9(7):e101572. doi:10.1371/journal.pone.0101572
88. Chen T, Yan J, Li Y. Genotoxicity of titanium dioxide nanoparticles. *J Food Drug Anal*. 2014;22(1):95–104. doi:10.1016/j.jfda.2014.01.008
89. Gao G, Ze Y, Zhao X, et al. Titanium dioxide nanoparticle-induced testicular damage, spermatogenesis suppression, and gene expression alterations in male mice. *J Hazardous Mat*. 2013;258:133–143. doi:10.1016/j.jhazmat.2013.04.046
90. Hong F, Si W, Zhao X, et al. TiO2 nanoparticle exposure decreases spermatogenesis via biochemical dysfunctions in the testis of male mice. *J Agri Food Chem*. 2015;63(31):7084–7092. doi:10.1021/acs.jafc.5b02652
91. Smith MA, Michael R, Aravindan RG, et al. Anatase titanium dioxide nanoparticles in mice: evidence for induced structural and functional sperm defects after short-, but not long-, term exposure. *Asian J Androl*. 2015;17(2):261–268. doi:10.4103/1008-682X.143247
92. Wang E, Huang Y, Du Q, Sun Y. Silver nanoparticle induced toxicity to human sperm by increasing ROS (reactive oxygen species) production and DNA damage. *Environ Toxicol Pharmacol*. 2017;52:193–199. doi:10.1016/j.etap.2017.04.010
93. Mathias FT, Romano RM, Kizys MM, et al. Daily exposure to silver nanoparticles during prepubertal development decreases adult sperm and reproductive parameters. *Nanotoxicology*. 2015;9(1):64–70. doi:10.3109/17435390.2014.889237
94. Layali E, Tahmasbpour E, Jorsaraei S. Effects of silver nanoparticles on lipid peroxidation and quality of sperm parameters in male rats. 2016.
95. Wiwanitkit V, Sereemaspun A, Rojanathanes R. Effect of gold nanoparticles on spermatozoa: the first world report. *Fertil Steril*. 2009;91(1):e7–e8. doi:10.1016/j.fertnstert.2007.08.021
96. Nazar M, Talebi AR, Sharifabad MH, Abbasi A, Khoradmehr A, Danafar AH. Acute and chronic effects of gold nanoparticles on sperm parameters and chromatin structure in Mice. *Int J Reprod BioMed*. 2016;14(10):637.
97. Taylor U, Barchanski A, Petersen S, et al. Gold nanoparticles interfere with sperm functionality by membrane adsorption without penetration. *Nanotoxicology*. 2014;8(sup1):118–127. doi:10.3109/17435390.2013.859321
98. Zakhidov S, Marshak T, Malolina E, et al. Gold nanoparticles disturb nuclear chromatin decondensation in mouse sperm in vitro. *Biochemistry Supplement Series A*. 2010;4:293–296. doi:10.1134/S1990747810030074
99. Hu Z, Zhang Y, Zhang L, Tian Y. Respiratory exposure to carbon black nanoparticles may induce testicular structure damage and lead to decreased sperm quality in mice. *Reprod Toxicol*. 2021;106:32–41. doi:10.1016/j.reprotox.2021.10.001

100. Barkhordari A, Hekmatimoghaddam S, Jebali A, Khalili MA, Talebi A, Noorani M. Effect of zinc oxide nanoparticles on viability of human spermatozoa. *Iran J Reprod Med*. 2013;11(9):767.
101. Radhi MJ, Al-Bairuty GAAL. Effect of Zinc oxide nanoparticles (ZnO-NPs) on weights of some reproductive organs and sperm abnormalities in the tail of epididymis of albino mice. *J Pharmaceut Sci Res*. 2019;11(1):243–246.
102. Liu G, Gao J, Ai H, Chen X. Applications and potential toxicity of magnetic iron oxide nanoparticles. *Small*. 2013;9(9-10):1533–1545. doi:10.1002/smll.201201531
103. Mirzaei varzeghani S, Parivar K, Abdollahifar M-A, Karamian A. Effects of iron oxide nanoparticles on mouse sperm parameters and testicular tissue. *Iran J Toxicol*. 2018;12(6):39–44. doi:10.32598/IJT.12.6.490.1
104. Hassan L, Hasan IM, Al-Amgad Z, Ahmed H. Acute exposure to copper oxide nanoparticles impairs testicular function and sperm quality in adult male albino rats. *SVU-Int J Vet Sci*. 2024;7(1):1–21. doi:10.21608/svu.2023.226884.1288
105. Adebayo O, Akinloye O, Adaramoye O. Cerium oxide nanoparticle elicits oxidative stress, endocrine imbalance and lowers sperm characteristics in testes of balb/c mice. *Andrologia*. 2018;50(3):e12920. doi:10.1111/and.12920
106. Préaubert L, Tassistro V, Auffan M, et al. Very low concentration of cerium dioxide nanoparticles induce DNA damage, but no loss of vitality, in human spermatozoa. *Toxicol Vitro*. 2018;50:236–241. doi:10.1016/j.tiv.2018.03.013
107. Xue Y, Cheng X, Ma Z-Q, et al. Polystyrene nanoplastics induce apoptosis, autophagy, and steroidogenesis disruption in granulosa cells to reduce oocyte quality and fertility by inhibiting the PI3K/AKT pathway in female mice. *J Nanobiotechnol*. 2024;22(1):460. doi:10.1186/s12951-024-02735-7
108. Ahmed DH, El-Beih NM, El-Hussieny EA, El-Sayed WM. Zinc oxide nanoparticles induced testicular toxicity through inflammation and reducing testosterone and cell viability in adult male rats. *Biol Trace Element Res*. 2025;203(4):1934–1948. doi:10.1007/s12011-024-04330-1
109. Shalaby OE, Ahmed YH, Mekkawy AM, Mahmoud MY, Elbargeesy GA. The ameliorative effect of selenium-loaded chitosan nanoparticles against silver nanoparticles-induced ovarian toxicity in female albino rats. *J Ovarian Res*. 2025;18(1):4. doi:10.1186/s13048-024-01577-z
110. Yokota S, Kawakami T, Yoshioka H, et al. In utero impacts of intratracheal administration of silver nanoparticles on spermatogenesis in two generations of mice. *Environ Sci Pollution Res*. 2025;32(25):15304–15320. doi:10.1007/s11356-025-36607-w
111. Shalaby AMA, Abdel-Aziz Abul-Ela ES, Mohamed Moustafa A, Hafez Mohamed S. The ultrastructural changes in the adult rat ovary after administration of copper oxide nanoparticles and the possible ameliorative influence of selenium. *Ultrastruct Pathol*. 2025;49(2):109–129. doi:10.1080/01913123.2024.2449091
112. Mohamed AF, Hanafy SM, Abdelgalil RM, Abo-Ouf AM. Effect of copper oxide nanoparticles (CuONPs) on the testes of adult male albino rats and the possible protective role of extra virgin olive oil (EVOO). *Ultrastruct Pathol*. 2025;49(2):130–147. doi:10.1080/01913123.2025.2462534
113. Merlo B, Volsa AM, Tovar L, et al. Effects of polystyrene nanoparticles on bovine oocyte in vitro maturation. *Theriogenology*. 2025;244:117482. doi:10.1016/j.theriogenology.2025.117482
114. Xu W, Yuan Y, Tian Y, et al. Oral exposure to polystyrene nanoplastics reduced male fertility and even caused male infertility by inducing testicular and sperm toxicities in mice. *J Hazardous Mat*. 2023;454:131470. doi:10.1016/j.jhazmat.2023.131470
115. Lei M, Zhu Z, Wei C, et al. Prenatal silicon dioxide nanoparticles exposure reduces female offspring fertility without affecting males. *Adv Sci*. 2025;12(3):2410353. doi:10.1002/advs.202410353
116. Santonastaso M, Mottola F, Iovine C, et al. Protective effects of anthocyanin and α-tocopherol against titanium dioxide nanoparticle-induced DNA damage in human sperm cells. *Exposure Health*. 2025;17(2):523–535. doi:10.1007/s12403-024-00675-z
117. Salih HA, Al-Bayati MA. Spermicidal activity of gold nanoparticles on male mice in vitro. *Adv Animal Vet Sci*. 2024;13(1). doi:10.17582/journal.aavs/2025/13.176.188
118. Kalita MK, Baruah PM, Ahmed K, et al. Supplemental effect of metallic nanoparticles on cryopreserved semen quality, lipid peroxidation, sperm head ultrastructure and field fertility levels in crossbred (Hampshire x Niang Megha) boars. *Cryobiology*. 2025;120:105277. doi:10.1016/j.cryobiol.2025.105277
119. Li M, Lu H, Ye C, et al. Graphene oxide nanosheets induce mitochondrial toxicity in human ovarian granulosa cells: implications for female reproductive health. *Int J Nanomed*. 2025;20(null):4461–4479. doi:10.2147/IJN.S495259
120. Zhao Q, Fang Z, Wang P, et al. Polylactic acid micro/nanoplastic exposure induces male reproductive toxicity by disrupting spermatogenesis and mitochondrial dysfunction in mice. *ACS Nano*. 2025;19(5):5589–5603. doi:10.1021/acsnano.4c15112

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