

Adverse Effects of some of the Most Widely used Metal Nanoparticles on the Reproductive System

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Abstract

Nanotechnology, which allows the manipulation of molecular dimensions, is used in many aspects of human life, from industrial to medical and therapeutic aspects. Features of nanoparticles and their unique capabilities have attracted a lot of attention. Among nanotechnology structures, metal nanoparticles have been widely used in many aspects of industry and medicine. The unique properties of these nanoparticles make possible to produce and expand them on a large scale, thus making the possibility of exposure to these nanoparticles more likely. Nanotechnology and nanoparticles like a double-edged sword despite its many benefits, it also has a number of disadvantages. One of the most important of these disadvantages is their toxicity. This toxicity may have adverse effects on the environment and humans. One of the most important adverse effects of nanoparticles is adverse effects on the reproductive system. In this paper, the adverse effects of some of the most widely used metal nanoparticles on the reproductive system are described. These adverse effects can be on: sexual behaviors, sexual organs, sperm count, sperm motility, sperm shape, sperm maturity, ovarian and follicle maturation, their fertility rate and also the level of sex hormones in men and women. The adverse effects of these nanoparticles and their toxicity on a variety of tissues and organs lead us to use safer nanoparticles.

Keywords: Nanotechnology, Metal nanoparticles, Toxicity, Reproductive system

1 Introduction

Nanotechnology is defined as the use and manipulation of devices, materials, and systems in nanometer scale, 100 nanometer scale, where the resulting material has new physical and chemical properties that are not seen in its Bulk counterparts. Some scientists believe that Nanotechnology is one of the key technologies in the 21st century. This technology has revolutionized the field of medicine-information technology and materials. In the past 30 years, nanotechnology has become one of the areas where explosive growth has taken place in many dimensions (1-5). Many nanostructures include:fullerenes, nanoparticles, nanopowders, nanotubes, nanowires, nanorods, nano-fibers, quantum dots, dendrimers, nanoclusters, nanocrystals, and nanocomposites are produced on a large scale and are used in many aspects of human life (6). Nanotechnology potential applications in: cancer treatment (7), diagnostics (8), imaging (9), cosmetics(10), anti-aging(11), pollutiosensing (12, 13), hyperthermia (14), textile (15), catalysis (16-19), water and wastewater treatment (20), food industry (21), agriculture fertilizers (22), agriculture (23), drug delivery (24), biosensors and biotechnology (25) and many more have been proven so far. In many of its applications, including pharmacology, this technology has become a challenging innovation (26).

Metal nanoparticles have received a lot of attention due to their electronic and chemical properties, and many scientists are willing to use them in the development of new generation

nanodevices (27). Metal nanoparticles have been widely used in targeted drug delivery, cancer treatment, gene therapy and DNA analysis, antibacterial agents (28, 29), biosensors, enhancing reaction rates, separation science, and magnetic resonance imaging (MRI) (30). Some metal nanoparticles, such as gold and silver nanoparticles, due to their unique and tunable optical properties on account of their surface plasmon resonance (SPR), are widely used in molecular-specific imaging and sensing, photo-diagnostics, and selective photothermal therapy (31). Therefore, although nanotechnology has played a very important role in development and progress in many different aspects: from cell phones to medicines, but also the negative dimensions of this modern technology and its toxic effects must be considered. Due to the widespread use of these nanostructures in various aspects of human life, human exposure to these nanostructures and nanotechnology is inevitable. It is the duty of these nanomaterials to enter and affect the various organs and tissues of the human body in various ways. These nanoparticles may have toxic effects that deformation and inhibition of cell growth. And thus cause various diseases in humans and animal (6, 32). There is a wealth of evidence to support the toxicity of some nanostructures, for example:Titanium oxide nanoparticles, which are widely used in cosmetics and skin care products, reactive oxygen, they create species and cause damage to DNA carbon nanotubes may cause lipide eroxidation, oxidative stress, mitochondrial dys function, and

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changes in cell morphology upon in vitro incubation with keratinocytes and bronchial epithelial cells and thus be dangerous. Silver nanoparticles have been shown to be dose-dependent toxicity and may cause oxidative stress in alveolar macrophages. Quantum dots and fullerenes cause inflammatory reactions and may also cause reactive oxygen species (33-40).

A large number of nanostructures by passing through biological barriers, they can have destructive and toxic effects on many human organs such as have the brain, liver, and kidney. Another important system that is affected by the toxic effects of nanoparticles is reproductive systems. There are many evidences that some nanoparticles can pass from the reproductive barrier systems such as the blood-testis barrier, placental barrier, and epithelial barrier, and then accumulate in the testis, epididymis, ovary, and uterus and eventually cause damage to these organs. The accumulation of nanoparticles in the reproductive system can have adverse effects on sperm and oocytes. These adverse effects include: adverse effects on quantity, quality, motility and sperm morphology, adverse effects on oocytes, detrimental effects on the development of primary and secondary follicles, negative effects on the number of mature oocytes and their reduction, detrimental effects on levels of secreted hormones and changes in sexual behavior. Although the exact mechanism of toxicity of nanoparticles on reproductive organs has not yet been completely elucidated, it is possible that some mechanisms, such as oxidative stress, apoptosis, inflammation, and genotoxicity play a role in the toxicity of nanoparticles and their destructive effects on the reproductive system (41-55).

2 The reproductive system

1.2 The female reproductive system

The female reproductive system has internal and external parts. External sections include labia majora, labia minora, Bartholin's glands, and clitoris. The internal parts also include the vagina, uterus, ovaries and fallopian tubes. The most important functions of the female reproductive system are: oocytes production, which can eventually act as an egg cell and play a role in the reproductive process, participation in the fertilization process, participation in the implantation process, participation in the menstrual cycle And It also produces some female sex hormones to maintain the reproductive cycle (56-58).

2.2 The male reproductive system

The male reproductive system also has internal and external parts. External genitalia include: the penis, scrotum, and testicles and the internal genitalia include: epididymis, vas deferens, ejaculatory ducts, urethra, seminal vesicles, and prostate gland, bulbourethral glands. The most important functions of the male reproductive system are: sperm production, sperm maintenance and protection. In this device, some sex hormones are also produced and secreted to maintain the reproductive system (59-62).

3 Factors affecting on the toxicity of nanoparticles

Size, shape, chemical composition, surface charge, solubility, the type of nanoparticle entry path into the body, the exposure time of nanoparticles, surface chemistry (PEGylation, ligand conjugation), bio distribution, penetration rate, bioavailability and individual characteristics (age, sex) (63, 64).

4 The main ways in which nanoparticles enter the reproductive system

Dermal exposure, pulmonary exposure, and gastrointestinal exposure are the major pathways for nanoparticles to enter the reproductive system.

Dermal: Some nanoparticles used in cosmetics, such as nano-titanium dioxide, can enter the body through skin absorption. Various evidence suggests that the skin absorption rate of nanoparticles is very low. In this way, nanoparticles can be absorbed through the skin without causing significant toxicity (65-70).

Gastrointestinal: This route is one of the main entry and absorption pathways for nanoparticles. Most of the nanoparticles that used in food and the drugs that are taken orally enter the body through this pathway. The nanoparticles mainly enter the bloodstream and secondary organs after entering the gastrointestinal tract. The rate of absorption of different nanoparticles varies. Different nanoparticles have a longer duration in the large intestine and a shorter duration in the stomach. After entering and absorbing, nanoparticles are distributed through this pathway to various organs, including the liver, spleen, and mesenteric lymph nodes (71-74).

Lung: Some nanostructures, such as cerium oxide, enter the body mainly through inhalation and remain in the lungs. Some other nanoparticles enter through inhalation and then enter the central nervous system through olfactory neurons (75, 76). There are many evidences that nanoparticles are absorbed into the bloodstream after entering each of these pathways and eventually enter organs such as the liver, spleen, kidney, brain, ovaries and testes (76).

5 Some of the most widely used metal nanoparticles and their effect on the reproductive system

5.1 Titanium dioxide nanoparticles (TiO₂ NPs)

TiO₂ NPs are widely used in medical, diagnostic and cosmetic fields. The increasing use of these nanoparticles is highly toxic to humans. Some evidence suggests that TiO₂ NPs lead to damage to follicles. These nanoparticles reduce follicular survival and prevent the development and maturation of oocyte. TiO₂ NPs also have adverse effects on sperm. These nanoparticles have an adverse effect on sperm motility. These nanoparticles reduce the number of normal sperm but increases the number of abnormal sperm. Some other evidence suggests that these nanoparticles induce apoptosis in germ cells in the testicular mouse (77-81). The table 1 shows some of the effects of titanium dioxide nanoparticles on the reproductive system.

Table 1: Shows some of the entry routes and adverse effects of TiO₂ NP

The entrance route	Function	Reference
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Orally	Body weight changes, relative changes in testicular weight and genitals.	(82)
-	Some studies have shown that TiO ₂ NPs can be found in cytoplasm and nuclei of ovarian cells accumulate. Nanoparticles accumulated in the cell can induce apoptosis. In addition, the mitochondria and nuclei of ovarian cells were disrupted. Mitochondrial swelling and rupture, nuclear chromatin condensation, and irregularity of the nuclear membrane was also observed.	(83-87)
Intragastric	Spermatogenesis suppression Through alterations of testicular enzymes and oxidative stress in the testes.	(88)
IP	Changes in estrogen and progesterone levels, changes in ovarian tissue, loss of Graafian follicles, destruction of follicles wall, reducing the thickness of Granulosa and Theca layers and decreased corpus luteum.	(89)
Intragastric	The direct effect of TiO ₂ NPs on ovarian function and consequently ovarian damage, as well as these nano particles can cause an imbalance of mineral element distribution and sex hormones, decrease fertility or the pregnancy rate and oxidative stress in mice.	(5)
Orally	This study suggests that oral administration of TiO ₂ NP may alter ovarian tissue. These changes include: destruction of follicles, reduction of their number, disruption of follicle growth, possibility of ovarian cyst formation, decrease in pregnancy rate, decrease in number of births, decrease in oocyte number, decrease in fertilization rate, decrease in fetal growth before implantation and also increase in malondialdehyde hormones and estrogen.	(90)
Intragastric	This study showed that nanosized titanium dioxide reduces body weight, relative ovarian weight, reduced fertility, changes in sex hormone levels, atretic follicle increases, inflammation, and necrosis.	(91)
Gavage	This study shows that TiO ₂ NPs can lead to premature ovarian failure (POF), decreased levels of estradiol hormones, progesterone, increased levels of luteinizing hormone, follicle-stimulating hormone, anti-Müllerian hormone, thyroid-stimulating hormone, free tetraiodothyronine, anti-nuclear antibody and anti-thyroid peroxidase antibody levels in serum. Thus, TiO ₂ nanoparticles can through alterations in hormones and autoimmunity markers lead to POF.	(92)
-	According to studies, the findings indicate adverse effects of Titanium dioxide nanoparticles (TiO ₂ - NPs) on sperm. These nanoparticles are able to cross the blood-testis barrier, inflammation, cytotoxicity, and gene expression changes. In addition, these nanoparticles may cause damage to sperm DNA.	(93)
	This study shows that TiO ₂ -NP has been shown to be dose-dependent toxicity. These nanoparticles at higher doses can induce autophagy and necrosis in Sertoli cells, and consequently negatively affected spermatogenic cells and testicular morphology becomes.	(94)

2.5 Nano-zinc oxide (ZnO)

Zinc oxide nanoparticles have a wide variety of applications in various fields. Numerous studies and evidence have shown that zinc oxide nanoparticles have adverse effects on the reproductive system. These nanoparticles have the ability to cross barriers that protect the reproductive system. These nanoparticles have adverse effects on the female reproductive system and fertility (95-97). Table 2 shows some of the adverse effects of zinc oxide nanoparticles on the reproductive system.

3.5 Silver nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) have been used extensively in areas such as antibiotics, textile, wound dressings, medical devices, antibacterial, antifungal, anti-cancer, and antigenic applications. But along with its diverse development and applications, there are potential risks to human health, especially for reproductive system. (98, 99). Table 3 shows some of these disadvantages and problems.

4.5 Gold nanoparticles

Gold nanoparticles have the wide variety of applications. Some researchers divide the biological applications of these nanoparticles into four main classes: labeling, delivering, heating, and sensing (100). These nanoparticles can be used in: gene delivery (101), PPTT (102), catalyzed (103), chemical

sensing, biological imaging, drug delivery, and cancer treatment (104). Although the unique properties of gold nanoparticles provide a wide range of biological applications, there is evidence that these nanoparticles are toxic at high concentrations (105). Some of these adverse effects are listed in Table 4.

5.5 Iron oxide nanoparticles

Iron oxide NPs are used in many fields including: as contrast agents in imaging Magnetic resonance imaging (MRI), drug delivery, etc. One of the other major applications of these nanoparticles is environmental remediation applications. Thus these nanoparticles are in a greater risk of human exposures (106-115). Table 5 shows some of the risks of this nanoparticle associated with the reproductive system.

6.5 Nickel nanoparticles (Ni NPs)

Nickel nanoparticles (Ni NPs) are used in a variety of fields due to their unique properties. Some of these features include: catalysts, high-density magnetic. These nanoparticles can be used to treat cancer (116), catalytic (117), biosensor (118), nuclear waste, biochemical products, and cells (119, 120). These nanoparticles may cause problems for humans. Some studies and evidence have shown that these nanoparticles may cause apoptosis, oxidative stress, and DNA damage.

Table 2: Shows some of the entry routes and adverse effects of zinc oxide nanoparticles on the reproductive system

The entrance route	Function	Reference
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Intravenously	ZnO has the ability to penetrate fetal ovaries. These nanoparticles may be the amount DNA increase damage and apoptosis in fetal oocyte. Toxic effects of these nanoparticles to their ion - shedding Their ability and low solubility are attributed. Their side depends on the dose. Influence and accumulation of zinc oxide nanoparticles can reduce the number of oocytes, impaired primordial follicle assembly and folliculo genesis dynamics in the ovaries.	(121-123)
Intraperitoneally (IP)	This study showed that oxide nanoparticles have a dose-dependent toxicity. At higher doses, these nanoparticles increase in the corpusluteum, follicular cysts, inflammatory cells infiltration and fibrosis. Histopathological changes in ovary, epithelial destruction, hyperplasia of endometrial glands and changes in estrogen and progesterone levels (decrease in the level of these hormones in high doses and increase in low doses).	(124)
Gastrointestinally	Studies have shown that the use of zinc oxide nanoparticles before and during pregnancy and lactation may increase the risk of health to pregnant women and their fetuses.	(125)
Orally	This study shows that ZNP can induce adverse and toxic dose-dependent effects in testicular germ cells. These nanoparticles may be present in Sertolicell also has adverse effects and The multinucleated giant cell formation and sloughing of immature germ cells from the seminiferoustubules are evidence of this. In addition, these nanoparticles may have the ability to induce apoptosis or autophagy in testicular germ cells.	(126)
Orally	In this study, it was shown that zinc oxide nanoparticles through regulation of specific signaling pathways may have adverse effects on female reproductive systems.	(127)
Intraperitoneal (IP)	ZnO nanoparticles have destructive effects on the cells of the male reproductive system. These effects are as reduction and loss of cells in seminiferous tubules in testicular tissue. In fact, these nanoparticles are able to degenerate and decrease cell types in the seminiferous tubules (such as spermatogonia, primary spermatocyte, spermatid and sperm cells), outer part of the tubules (such as leydig, fibroblast cells and blood vesicles), seminiferous epithelium and tubule are diameters.	(128)
Intravenous	This study showed that these nanoparticles have dose-dependent toxicity. These nanoparticles may cause fetal death and decrease them weigh too.	(129)

Table 3: Shows some of the entry routes and adverse effects of AgNPs on the reproductive system

The entrance route	Function	Reference
Intravenous	AgNPs may interfere with the process of meiosis progression and expression of imprinted genes. Also these nanoparticles reduce the methylation of <i>Zac1</i> gene and increase the methylation of <i>Igf2r</i> . In fact, AgNPs can stop the process of dividing meiosis.	(130-139)
Intravenous	This study shows that AgNPs are transmitted through Ag ⁺ formation in cellsTM ₄ cells and granulosa cells, and germ cells, induce damage. These nanoparticles are also by releasing cytochrome c in to the cytosol induces apoptotic induction.	(135, 140-142)
Orally	Evidence suggests that silver nanoparticles have adverse effects on testicular tissue. These adverse effects include: Histopathology revealed abnormal arrangement, deformity, atrophy, degeneration, and necrosis of epithelial cells of somniferous tubules. These nanoparticles also reduce the concentration of testosterone. Silver nanoparticles also have a negative effect on the number of sperm, leading to a decrease in them.	(140, 143-149)
Subcutaneous	This study suggests that silver nanoparticles may have adverse effects on spermatogenesis. Silver nanoparticles also affect sperm quality.	(150)
Intravenously	This study showed that AgNPs lead to DNA damage in germ cells. These nanoparticles also lead to changes in the seminiferous tubule morphometry. The study also showed that by reducing the size of these nanoparticles, their toxicity increased and also showed that the dose-dependent toxicity nanoparticles.	(151)
	The study found that AgNPs had adverse effects. In pregnant mothers who were injected with these nanoparticles, delayed physical development and impaired cognitive behavior in offspring occurred. The nanoparticles were also found in placenta, breast milk. These nanoparticles can also accumulate in testes and visceral yolk sac.	(152)
Intravenous	This study shows that AgNP has adverse effects on oocyte maturation. This nanoparticle can also have negative effects on arly embryonic development. This nanoparticle is likely to trigger cell apoptosis through the production of ROS and p53-, p21-, and caspase - 3 - dependent regulatory mechanisms.	(153)

Table 4: Shows the Routes of entry of gold nanoparticles and some of their negative effects on the reproductive system

The entrance route	Function	Reference
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-	This study suggests that gold nanoparticles may have toxic and adverse effects on ovarian granulosa cells.	(154)
-	This study shows that gold nanoparticles can have size-dependent toxicity.	(155)
Intraperitoneal	Gold nanoparticles can cause changes in the levels of LH, FSH and testosterone hormones. In fact, increase the amount of these hormones. It is predicted that these nanoparticles may also increase infertility by increasing the levels of these hormones.	(156)
Intravenously	This study shows that gold nanoparticles with smaller sizes are more widely distributed in body tissues and may be distributed in some organs, including the liver, spleen, kidney, testis, thymus, heart, lung, and brain.	(157)

Table 5: shows some of the adverse effects of iron oxide nanoparticles on the reproductive system

The entrance route	Function	Reference
Intraperitoneal	In this study, the effect of surface charge of iron oxide nanoparticles on the passage of placenta and effect on the fetus was studied. Research has shown that both are positively and negatively charged iron oxide nanoparticles have the ability to cross the placenta and accumulate in the fetal body, although nanoparticles with more positive charge accumulate and thus show more toxicity.	(158)
Intraperitoneally	In this study, the effect of iron oxide nanoparticles coated with dimercaptosuccinic acid (DMSA) in pregnant mice was investigated. This study showed that high doses of this nanoparticle reduced spermatogonia, spermatocytes, spermatids and mature sperm. In fact, high doses of this nanoparticle impair fetal growth.	(158)
Intraperitoneally	The results of this study showed that conventional iron oxide particle induced more accumulation and more oxidative stress than nanoparticles. This can negatively effect on the fertility of female rats.	(159)
Intratracheally	This study showed that female mice may show more sensitive response to FeNPs exposure than male mice.	(160)
Intraperitoneally	This study showed that NP Fe ₂ O ₃ has the ability to cross the testicular barrier and enter it. The accumulation of these nanoparticles in the testicles causes oxidative stress and apoptosis. These nanoparticles also caused histopathological lesions such as vacuolization, detachment, and sloughing of germ cells. In addition, testosterone levels increased with exposure to these nanoparticles.	(161)
Orally	In this study, the effects of Fe ₂ O ₃ -NPs on seminal vesicle and prostate gland were studied in mice. These nanoparticles caused food consumption, water intake, and organo-somatic index in mice. These nanoparticles can cause oxidative stress. Therefore, these nanoparticles cause pathological changes in the seminal vesicle and prostate gland.	(162)

Table 6: Shows some of the entrance route of nickel nanoparticles and their negative effects on the reproductive system

The entrance route	Function	Reference
Gavage	This study shows that nickel nanoparticles (Ni NPs) have adverse effects on the reproductive system. These adverse effects are: Ovarian lymphocytosis, vascular dilatation	(163)

	and congestion, inflammatory cell infiltration. Overall weight loss, increased epididymis-to-body weight ratio, altered sperm motility, decreased FSH levels, and testosterone (T).	
Gavage	This study showed that NiNPs caused significant toxicity in rat tests. These nanoparticles create their adverse effects by inducing oxidative stress and apoptosis. Also, this study showed the dose-dependent toxicity of these nanoparticles.	(164)
-	In this study, the effects of nanoparticles (Ni NPs) on gamete quality of marine organisms and on the consequences on fertility potential were investigated. The results showed that these nanoparticles induced oxidative stress, lipid peroxidation and DNA fragmentation, and altered MMP and sperm morphology. These nanoparticles also affect the ability to induce and create anomalies in the offspring.	(165)
Gavage	In this study, the effects of Ni NPs on ovarian cells were investigated. The results showed swelling mitochondrion swelling, disappearance of mitochondrial cristae, and enlargement of the endoplasmic reticulum. The nanoparticles also increased some of the enzymes and proteins associated with apoptosis, including mRNAs associated with caspase 3, caspase 8 and caspase 9, and the proteins Fas, Cyt c, Bax, and Bid in the ovaries.	(166)
Gavage	In this study, the effects of nickel nanoparticles on spermatogenesis were investigated. The results showed various cell apoptosis and disordered arrangement of cells arranged in the seminiferous tubules. The results also showed that these nanoparticles also increased sperm motility.	(167)
	In this study, the effect of Ni NPs on Sertoli-germ co-cultured cells (Sertoli-germ cells) was investigated. The results showed that these nanoparticles can induce apoptosis on Sertoli-germ cells.	(168)

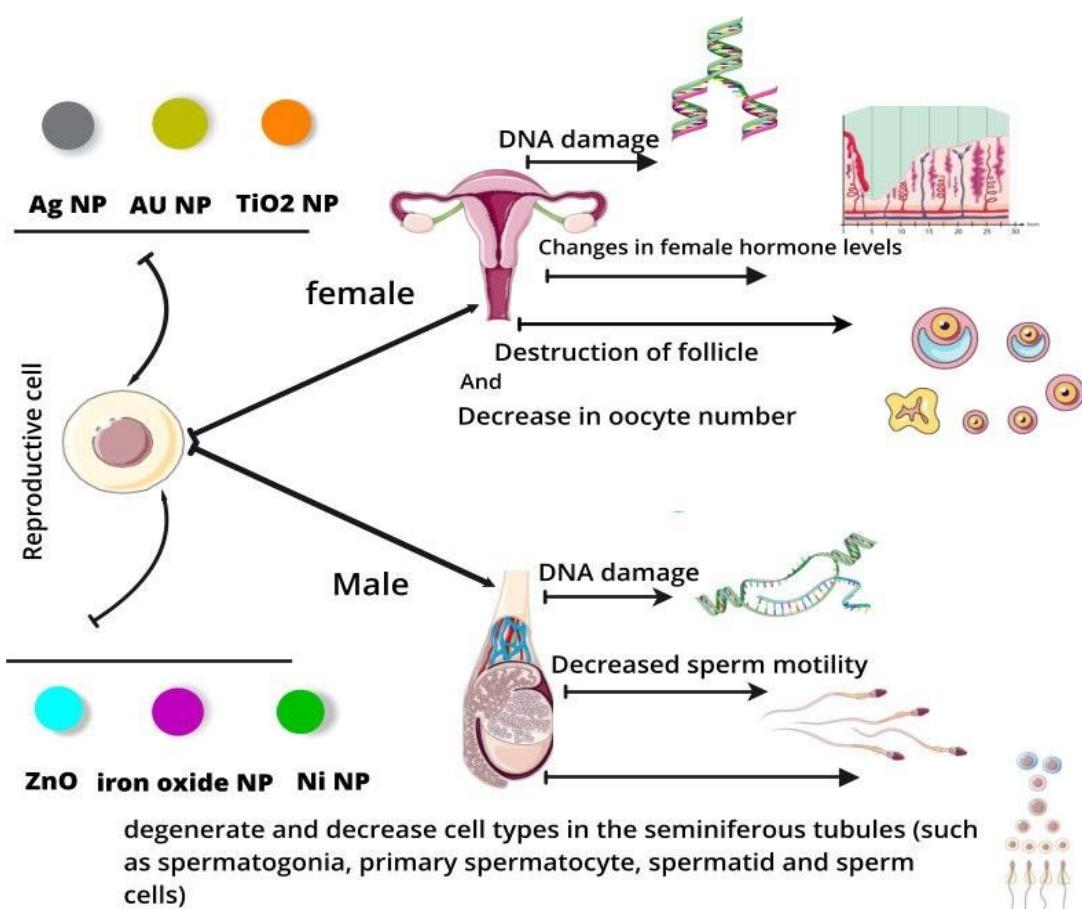


Figure 1: shows some of the adverse effects that metal nanoparticles (titanium oxide, gold, iron, silver, zinc oxide, nickel) have on the reproductive system

Another issue with this nanoparticle is the damage it can cause to the reproductive system (167); That Table 6 lists some of these adverse effects. Figure 1 also shows some of the adverse effects of these nanoparticles on the reproductive system.

6 Conclusion

With the advent of nanotechnology in various fields of medicine and industry, a great change has taken place. A development that led to unique applications that were unlikely to occur before. Nanotechnology, like many other sciences, has a number of disadvantages, despite having many advantages.

One of these disadvantages is the adverse effects that some nanoparticles have on the reproductive system. These adverse effects have so far appeared as adverse effects on sex hormone levels, Adverse effects on the sperm maturation cycle as well as its quality, negative effects on the process of oocyte maturation and inhibition, changes in sexual behavior, adverse effects on the fetus, and so on. All of the above evidence highlights the need for more efficient and safe use of nanoparticles. In such a way that they have less risk. In general, these adverse effects indicate the need to use nanomaterials with greater safety and less hazards.

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