Review Paper: Effect of Titanium Dioxide Nanoparticles on Male and Female Reproductive Systems

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ABSTRACT

Titanium Dioxide (TiO_2) nanoparticle has a wide range of application in industrial and consumer products especially in cosmetics such as high sun protection factor creams in order to protect the skin from UV light. In spite of its increased production and use there is not enough epidemiological data regarding TiO_2 nanoparticle toxicity. Toxic effects of TiO_2 nanoparticles on human reproductive systems have been investigated by many studies mostly by employing animal models, but results are extremely conflicted and inconsistent. In this review we summarized published data about the effects of TiO_2 nanoparticle on male and female reproductive systems to clarify its possible toxic effects on reproduction and fertility.

1. Introduction

Today nanotechnology is a growing research field, with many potential application in pharmaceuticals, cosmetics, medicine, engineering, biology, biotechnology, agriculture and industry [1]. Nanoparticles are commercially produced from metal and non-metal, polymeric materials and bioceramics have widespread application in all aspects of modern life. These particles have unique features such as small size, high surface area, special physicochemical and electrical properties and high reactivity [2]. Naturally, humans are exposed to various nanoscale materials which may impose toxic effects on organs and tissues [3]. Many studies have investigated the toxicity, immunotoxicity, reproductoxicity and genotoxicity of nanoparticles [4]. Since nanoparticles are very small, they can easily enter the human body and then tissues [5]. According to FDA guidance about the toxic potential of nanoproducts, the need of the hour is to determine the toxicological effects of nanoparticles [6].

Some nanoparticles produce detrimental effects on reproductive tissues as well as in fetal development. These adverse effects are related to nanoparticle composition, surface modification, dose, exposure route and animal species [7-9]. In addition, emergent studies are available, regarding application of nanoparticles in reproductive technologies for inducing oocyte maturation, improving the survival and development of oocytes after cryopreservation, gene knockdown in oocytes, delivering antibodies into oocytes, sustained surge of

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gonadotropins and enhanced reproductive output, and nanoparticle-based semen purification [10-15].

TiO_2 are widely used in paints, plastics, inks, food colorants, toothpastes, papers, and cosmetic and skin care products. In addition TiO_2 nanoparticles are produced abundantly and used extensively because of their high stability, anticorrosive and photocatalytic properties [16]. It is particularly used in sunblock creams in order to protect the skin from UV light and are under investigation as a novel treatments for acne vulgaris, recurrent condyloma accuminata, atopic dermatitis, hyperpigmented skin lesions, and other non-dermatologic diseases [17]. Furthermore TiO_2 nanaoparticles are potential photosensitizers and in nanotherapeutics they can be used for advanced imaging and photodynamic therapy [18]. Therefore, its wide use has raised concerns about its potential toxicity as it is demonstrated that the TiO_2 nanoparticle has cytotoxic, genotoxic and embryotoxic effects [19-23].

In a meta-analysis carried out from 1994 to 2011 on the different endpoints in cell and animal models, more than 50% of the reports showed positive statistical significance in cytotoxicity of TiO_2 nanoparticle in a dose-dependent approach, and demonstrated its accumulation in tissues, liver, spleen, kidney, brain and reproductive tissues [24]. Toxic effects of TiO_2 nanoparticles on human reproductive systems have been investigated by many studies with conflicting and inconsistent results [25-27]. This review paper will focus on current knowledge on the reproductive toxicity of TiO_2 nanoparticle.

2. Effects of TiO_2 Nanoparticle on Male Reproductive System

Studies on the effects of TiO_2 nanoparticles on male reproductive system have used different concentrations of nanoparticle and variable route and duration of administration which resulted to inconsistent results.

Dehghani et al. demonstrated that intraperitoneal injection of TiO_2 nanoparticles at a dose of 50, 100 and 150 mg/kg for five days did not alter FSH hormone level and the number of spermatogonial cells, but the mean number of spermatocytes and spermatid cells decreased significantly in experimental groups. In addition at the highest dose, LH and testosterone level decreased significantly [28].

Gao et al. administered 2.5, 5, and 10 mg/kg of TiO_2 nanoparticles intragastrically to mice for 90 days, which led to its accumulation in testis, resulting in testicular lesions, sperm malformations, and alterations in serum sex hormone levels. Furthermore, the expression of genes related to spermatogenesis and steroid and hormone metabolism was altered [29].

Intraperitoneal injection of 500 mg/kg nanosized TiO_2 significantly increased sperm abnormality and germ cell apoptosis, and reduced sperm density and motility without any obvious pathological changes in testis and epididymis [30].

In another study, intraperitoneal injection of TiO_2 nanoparticles in 30 and 50 mg/kg doses for 21 days resulted in significant increase and decrease in the level of LH and testosterone, respectively, without any changes in the levels of FSH hormone and structure of testis tissue [31].

Hong et al. (2015) demonstrated that intragastric administration of TiO_2 nannoparticles in doses of 2.5, 5, 10 and 30 mg/kg to male mice for 60 consecutive days resulted in lesions of testis and epididymis, decreases of sperm concentration and sperm motility, and an increase in the number of abnormal sperm. Decreased activities of lactate dehydrogenase, sorbitol 31 dehydrogenase, succinate dehydrogenase, glucose-6-phosphate dehydrogenase, Na^+/K^+, Ca^{2+}-ATPase and Ca^{2+}/Mg^{2+}-ATPase, and elevated activities of acid phosphatase, alkaline phosphatase and total nitric oxide synthase in the testes of mice was observed. In addition, production of reactive oxygen species, level of lipid peroxidation and 8-hydroxy deoxyguanosine as a DNA oxidative product increased in the testes. It implied that spermatogenesis suppression caused by TiO_2 nanoparticles exposure may be associated with alterations of testicular-marked enzymes and oxidative stress in the testes [32].

Bakare et al. investigated the effects of five concentrations of 9.38, 18.75, 37.50, 75.00 and 150.00 mg/kg TiO_2 nanoparticles, which were administered intraperitoneally for five consecutive days. A significant increase in abnormal sperm cells at tested concentrations was observed after 5 and 10 weeks from the first day of exposure. In addition, disrupted cellular architecture, vacuolation and necrosis of testicular tissues were observed [33].

Ye et al. cultured primary rat Sertoli cells in media containing 5, 15, or 30 μg/mL TiO_2 nanoparticles for 24 h. Their findings showed that TiO_2 nanoparticles cross the Sertoli cell membrane into the cytoplasm or nucleus, and significantly suppressed their viability in a concentration-dependent manner. Increased expression of NF-κB, TNF-α, and IL-1β, and decreased IκB expression was observed too [34].

After administration of TiO_2 nanoparticle at 100 mg/kg/day orally for 8 weeks to adult male rats, histopathological alterations and marked reduction in the weight of testis, epididymis, seminal vesicle and prostate gland were observed with a decrease in serum testosterone level, sperm motility, sperm concentration and viability and increase of incidence of sperm morphological abnormalities [35].

3. Effects of TiO_2 Nanoparticle on Female Reproductive System

The female population is particularly vulnerable and deserves special attention, because toxicity in this group may impact both female reproductively and fetal development but there are limited studies regarding the possible toxic effects of TiO_2 nanoparticles on female reproductive system.

Zhao et al. exposed female mice to 2.5, 5 and 10 mg/kg TiO_2 nanoparticle by intragastric administration for 90 consecutive days. After the experiment's duration, it was observed that nano-TiO_2 resulted in significant reduction of body weight, relative weight of ovary and a decline in fertility. TiO_2 was deposited in the ovary, altering hematological parameters. Additionally, serum parameters, sex hormone levels and atretic follicle count increased, and inflammation and necrosis were observed. In addition, inflammation-related or follicular atresia–related cytokine expressions were altered, which shows that fertility reduction and ovary injury of mice is associated with inflammatory factors [36].

In one study, by using scanning electron microscopy, transmission electron microscopy, single-particle inductively coupled plasma mass spectrometry and SEM/energy-dispersive X-ray, it was observed that short-term (5 days) oral exposure to anatase TiO_2 nanoparticles (0, 1, 2 mg/kgbw/day) in rat can lead significantly to their accumulation in ovarian tissue. Furthermore, histological modifications were observed at both dose levels in ovarian granulosa cells without general toxicity. No morphological effects were seen in uterus and estradiol levels, indicating that direct effects on gametogenesis or estrogen homeostasis did not occur under the present experimental conditions. Additionally, TiO_2 aggregated in spleen, which shows that immune function, e.g. the cytokine network, is revealed as a potentially critical issue in toxicology of TiO_2 [37].

Gao et al. observed that TiO_2 nanoparticle accumulate in the ovary of mice after its intragastric administration at the dose of 10 mg/kg for 90 consecutive days, causing damage to ovary, such as alterations in functional gene expression levels, imbalance of mineral element distribution, upregulation of CYP17A1 gene expression related to estradiol synthesis, as well as decrease of progesterone, fertility and pregnancy rate and increased oxidative stress. Microarray analysis also showed upregulation of 223 genes and downregulation of 65 genes of known function in the ovaries [38].

Yoosefi et al. showed that administering 10 and 100 ppm of TiO_2 nanoparticles to mice in water for 14 days significantly reduced the amounts of FSH and LH in both male and female mice, with reductions in estradiol and progesterone in females and in testosterone in males [39, 40].

The intravenous injection of TiO_2 nanoparticles at a dose of 0.8 mg/mouse in pregnant mice was shown to result in decreased uterine weight and an increased fetal reabsorption rate [41], because it can penetrate the placental barrier [42].

Inhalation of TiO_2 nanoparticles by pregnant C57BL/6 mice from gestational day 8 to 18 resulted in abnormal expression of genes of the retinoic acid signaling pathway in the liver of newborn female mice [43]. Alteration in the expression of genes related to brain development has been demonstrated after injection of TiO_2 nanoparticles to pregnant mice [23].

In another study, after culture of rat ovarian preantral follicle in media containing 12.5 µg/ml, 25 µg/ml and 50 µg/ml TiO_2 nanoparticles, and with the increase of TiO_2 concentration, the survival rate of follicles, formation rate of antral follicles and mature oocytes decreased significantly; however, micron TiO_2 at the same dose had no obvious influence on follicle development and oocyte maturation [44].

4. Conclusion

According to the literature, TiO_2 nanoparticle can impose adverse effects on male and female reproductive system especially in high doses but its effects are strongly related to duration and routes of administration. After entering the body, TiO_2 nanoparticles circulates in the blood and accumulate in reproductive tissues such as testis and ovary. TiO_2 nanoparticle comes into close contact with different cells of testis and causes apoptosis and necrosis of testicular tissue leading to disturbance of spermatogenesis, reduces sperm's motility, morphology. Also in the ovary, it increase the number of atretic follicles, and cause inflammation and necrosis.

Since TiO_2 nanoparticles enhance production of reactive oxygen species, its adverse effects on reproductive tissue may be related to lipid peroxidation of cell membrane. In addition to reproductive tissues, the endocrine system appears to be a target of TiO_2 nanoparticles in both sexes because its administration decreases the expression of genes related to sex hormone metabolism. In addition, since TiO_2 nanoparticles aggregate in spleen, fertility reduction and reproductive tissue injury after administration of TiO_2 nanoparticle may be associated with alteration of cytokines and inflammatory factors. However, more studies are needed to examine the effects of TiO_2 nanoparticles on oocyte and sperm's genome and its possible incorporation this into gamete's chromatin because parental genomic disorder contributed to a variety of developmental disorders in embryos.

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Conflict of Interest

The authors declared no conflict of interests.

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