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Impact of nanoparticles and nanoplastics on female reproductive health†

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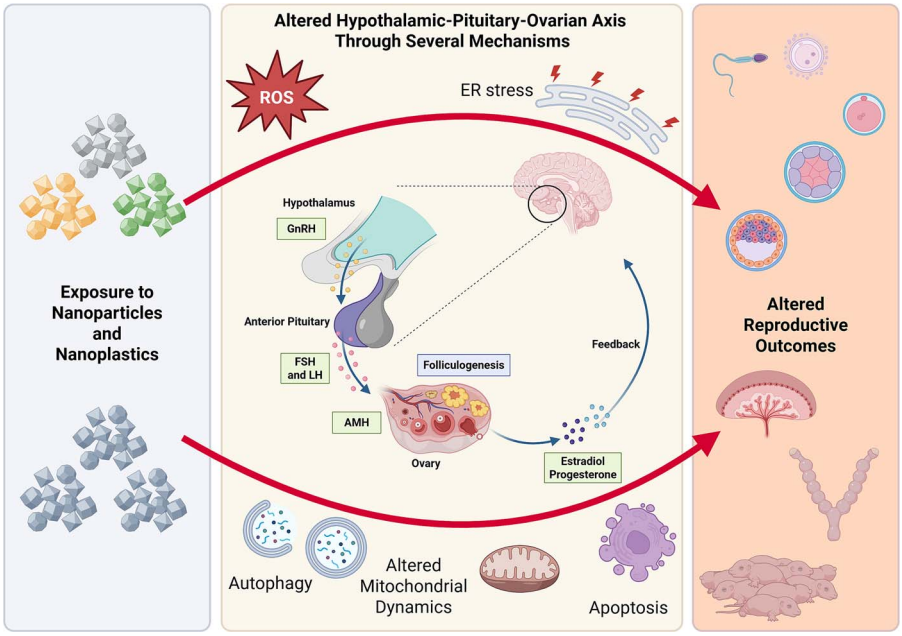
Abstract

Nanomaterials including nanoparticles and nanoplastics are deposited in the environment, resulting in human exposure to nanoparticles and nanoplastics through dermal, oral, and inhalation routes. After exposure, nanoparticles and nanoplastics are absorbed and distributed to many organs in wildlife, animal models, and humans. As a consequence, nanoparticles and nanoplastics have been found in several human tissues including the ovary and brain, raising concern regarding their potential effects on female reproduction. The physicochemical characteristics of nanoparticles and nanoplastics influence their behavior and their toxicity. One of the main challenges in understanding the toxic effects of nanoparticle and nanoplastic exposure is identifying the underlying molecular pathways. This review integrates available data on the effects of nanoparticles and nanoplastics on female reproductive health. Specifically, this review describes recent published data on the effects of nanomaterials on the hypothalamic–pituitary–gonadal axis, folliculogenesis, steroidogenesis, estrous cyclicity, placental function, embryo development, and fertility. This review also highlights the known mechanisms by which nanomaterials exert toxic effects in the female reproductive tract, and it emphasizes the gaps in the literature that need to be addressed to better understand the effects of nanoparticle and nanoplastic exposure on female reproduction and their underlying mechanisms of toxicity.

Graphical Abstract



Summary Sentence

Nanoparticles and nanoplastics reach female reproductive organs, affecting ovarian health and reproductive parameters through several mechanisms.

Key words: nanoparticles, nanoplastics, female reproduction, ovary, toxicity.

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Introduction

Humans and animals are routinely exposed to nanomaterials such as nanoparticles and nanoplastics that can adversely affect reproductive health [1, 2]. Nanoparticles are nanomaterials with dimensions between 1 and 100 nm [3, 4], which have unique surface and quantum properties and behaviors compared to the same materials at larger dimensions [4]. By changing nanoparticle properties such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity, the functions of nanoparticles can change, leading to a variety of nanoparticle applications [3]. Specifically, nanoparticles are used in environmental applications for: (1) bioremediation and catalysis; (2) drug delivery systems; (3) delivery of pesticides, herbicides, fertilizers, and regulators of plant growth; (4) food preservation, fortification, and nutrient sensors; (5) diagnostic tools; (6) tissue engineering; and (7) antimicrobials [3–5].

Nanomaterials are unintentionally produced when plastics in the environment undergo degradation and result in the formation of persistent and harmful microplastics (<5 mm) and nanoplastics (≤100 nm) [5]. These micro- and nanoplastics pose an expanding threat to ecosystems, affecting multiple trophic levels and exhibiting the ability to transfer and accumulate across food chains. Microparticles have been detected in multiple human organs including the reproductive organs [6–8]. Importantly, conventional detection methods often fail to capture particles smaller than 5 μm, leading to significant underestimation of nanoplastic exposure, despite their expected abundance and biological reactivity [9, 10].

Humans and animals are exposed to nanoparticles and nanoplastics through dermal, oral, and inhalation routes [1, 11, 12]. Experimental studies indicate that nanoparticles and nanoplastics induce inflammation, oxidative stress, and cellular damage across multiple biological systems [13, 14]. Further, studies indicate that nanomaterials can alter the female reproductive system [15, 16], raising concern about the repercussions of nanomaterial exposures on female reproductive health.

The female reproductive system is regulated by the hypothalamic–pituitary–gonadal (HPG) axis [17, 18]. Briefly, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which travels through the hypophyseal portal circulation to stimulate GnRH receptors in the anterior pituitary, inducing the release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH act on specific cell populations in the ovaries to regulate folliculogenesis, steroidogenesis, and ovulation. During folliculogenesis, primordial ovarian follicles mature into primary, preantral, and antral follicles [19]. The antral follicles either undergo atresia (death) or grow into preovulatory follicles, which ovulate an egg for fertilization after a cyclic LH surge stimulus [20]. During steroidogenesis, LH binds to its receptors on theca cells in the ovary, promoting androgen production through the regulation of proteins involved in mitochondrial cholesterol transport (i.e., steroid acute regulatory protein; STAR) and steroid biosynthesis. LH also stimulates progesterone secretion in granulosa cells, contributing to negative feedback on GnRH release. FSH binds to its receptors on granulosa cells to support follicular growth and to promote conversion of theca-derived androgens into 17β-estradiol via enzymes such as hydroxysteroid 17-beta dehydrogenase 1 (HSD17B1) and cytochrome P450 19A1 (CYP19A1) [17]. Sex steroid hormones and inhibin produced by the ovary regulate the estrous and menstrual cycles and subsequently provide negative feedback to the hypothalamus and anterior pituitary to regulate GnRH and gonadotropin secretion, respectively [18].

If an egg released by pre-ovulatory follicles is fertilized, a zygote will form and eventually develop into an embryo. Embryo development is supported by the placenta. The placenta is a crucial organ for maternal and fetal health, supporting pregnancy through multidirectional interactions between the mother, fetus, and placental tissues. As a transient organ unique to mammals, the placenta anchors the conceptus to the uterine wall, enables physiological exchange between the mother and fetus, and produces hormones that regulate maternal adaptations to pregnancy [21, 22]. The placenta plays a vital role in fetal development by expressing steroid receptors and glucose transporters, and it provides immunological protection by facilitating the transfer of maternal antibodies and regulating the passage of xenobiotics, including nanomaterials [23, 24]. Female reproduction processes are tightly controlled; thus, any disruption of the female reproductive system by nanomaterials can adversely affect female reproduction.

Increasing evidence has demonstrated that exposure to nanoparticles and nanoplastics affects the HPG axis and ovarian function [1, 2, 25]. This review integrates available data on the effects of nanoparticles and nanoplastics on female reproductive health. Specifically, this review describes published data on the effects of nanomaterials on the HPG axis, folliculogenesis, steroidogenesis, estrous cyclicity, placental function, embryo development, and fertility. This review also highlights the known mechanisms by which nanomaterials exert toxic effects in the female reproductive system, and it emphasizes the gaps in the literature that need to be addressed to better understand the effects and mechanisms underlying the toxic effects of nanoparticle and nanoplastic exposure on female reproduction.

Literature search methods

An online search using PubMed (www.pubmed.ncbi.nlm.nih.gov/) was performed on October 1, 2025 to identify publications on the effects of nanoparticles and nanoplastics on female reproductive health. The search included the keywords: "toxicity" in combination with the words "nanoplastics," "nanoparticles," "female reproduction," and "ovary." The initial search found a total of 261 potentially relevant studies. We included manuscripts in this review evaluating the effects of nanoparticles and nanoplastics on female reproduction regardless of the concentrations tested in the cited studies. This is because very few studies have assessed human exposure levels to nanomaterials, even though humans can be exposed to a wide variety of nanoparticles and nanoplastics. After the initial search, the following exclusion criteria were used to refine the search and remove the following types of manuscripts from the pool of manuscripts included in the review: duplicated papers, papers older than 4 years, language other than English, and review articles. Next, titles, abstracts, or whole manuscripts were screened to remove papers focused on non-mammalian species. The remaining papers were used as the basis for the present review.

Nanoparticles and nanoplastics in the environment, wildlife, animal models, and humans

The global nanoparticle contract manufacturing services market is projected to increase from 3.42 billion US dollars (USD) in 2025 to 5.17 billion USD by 2031 [26], suggesting a potential for increased exposure to nanomaterials over time. In recent years, research has shown that nanoparticles and nanoplastics are deposited in the environment [27], increasing the potential for human exposure through dermal, inhalation, oral, and medical routes, often resulting in nanoparticle and nanoplastic internalization and distribution in the body [12, 28, 29]. Nanoparticles and nanoplastics have also been shown to accumulate in wildlife species [30–32]. Plastic fragments have been found in the gastrointestinal tract of the great shearwater, with fragments having a mean length and width 7×5 mm [32]. Plastic fragments have also been found in fecal samples from European hedgehogs (*Erinaceus europaeus*), wood mice (*Apodemus sylvaticus*), field voles (*Microtus agrestis*), and brown rats (*Rattus norvegicus*) [30]. Interestingly, up to 70% of the plastic fragments were smaller than 1 mm [30]. The most abundant plastics were polyester (26%), polyethylene (13%), and polynorbornene (10%). Similarly, carbon nanotubes have been found in the livers of domestic ducks living near polluted areas such as those close to oil fields and brick factory areas [31].

Nanomaterials can cross several biological barriers in animal models including the blood–brain barrier [33, 34]. For example, one study showed that gestational exposure to zirconia nanoparticles (ZrO_2NPs) used in wastewater remediation and drinking water purification leads to the presence of ZrO_2NPs in the mouse fetal brain [33]. Interestingly, translocation of ZrO_2NPs into the fetal brain was 55% higher after blood–placental barrier formation, but before formation of the fetal blood–brain barrier, and it was 96% higher before maternal blood–placental barrier formation compared to exposure after the full development of the maternal blood–placental barrier and the fetal blood–brain barrier [33]. Similarly, in another study, short-term exposure to microplastics and nanoplastics through gavage led to nanomaterials crossing the blood–brain barrier in mice and reaching the brain as soon as 2 h after exposure [34].

In addition to nanomaterials reaching the brain, several studies indicate that nanoparticles and nanoplastics are absorbed and distributed to several other organs in animal models [35–37]. For example, oral exposure to silver nanoparticles (AgNPs), widely used as antibacterial agents, for 13 weeks led to the distribution of AgNPs in the gastrointestinal tract, kidney, liver, and spleen in Sprague–Dawley rats [35]. Topical exposure of pig ears to titanium dioxide nanoparticles (TiO_2NPs), used as food additives and in the cosmetic industry, for 30 days resulted in TiO_2NP penetration in pig ears [36]. Dermal exposure to TiO_2NPs for 60 days led to TiO_2NP penetration and distribution to several tissues including the lungs, kidneys, liver, spleen, and brain in hairless mice [36]. Intravenous administration of gold nanoparticles (AuNPs) used in medicine diagnostics and electronics led to biodistribution of nanoparticles of all sizes in organs including the liver, spleen, lung, and brain in mice [37]. Gestational and early lactational exposure to zinc oxide nanoparticles (ZnONPs), used in the cosmetic and food industries, led to the distribution of ZnONPs in the mammary tissue of dams and to the livers and kidneys of the pups in rats [38], suggesting maternal–fetal transfer of ZnONPs. Oral administration of TiO_2NPs and ZnONPs every day for 13 weeks resulted in absorption and distribution of both nanoparticles in Sprague–Dawley rats, with significantly higher absorption of ZnONPs than TiO_2NPs [39]. Further, oral exposure to AgNPs for 28 days resulted in AgNP distribution to several organs such as the brain, ovary, testes, and liver in Sprague–Dawley rats [40]. Interestingly, the brain and testes showed a low clearance rate, suggesting that the brain and testes may have reduced abilities to clear AgNPs compared to other tissues [40]. Similarly, polystyrene microplastics and polystyrene nanoplastics reach the spleen, liver, brain, urinary bladder, and ovary after intratracheal instillation in mice [41]. Further, studies indicate that polystyrene nanoplastics are cleared rapidly compared to polystyrene microplastics in lungs, with polystyrene nanoplastics accumulating twice as much as polystyrene microplastics in the spleen, liver, brain, urinary bladder, and ovary in mice [41].

Several recent studies indicate that nanoparticles accumulate in human tissues [42–44]. Magnetite nanoparticles have been detected in human brain samples, with concentrations ranging from 0.2 to 12 μg/g dry tissue, demonstrating the ability of magnetite, most probably coming from airborne particulate matter pollution, to reach the brain [42]. In a health surveillance study in a workplace that manufactures silver nanomaterials, AgNP exposure was estimated at silver concentrations of 0.35 and 1.35 $\mu g/m^3$ and AgNPs were found in the blood of two workers [43]. TiO_2NPs present in foods have been found in the synovial fluid from ankles [45, 46]. Specifically, 4.3% of synovial fluid samples were found to contain TiO_2NPs. Interestingly, the prevalence of TiO_2NPs in synovial fluid samples decreased after the use of TiO_2NPs in consumer products was banned in Europe [46], suggesting a possible relationship between the European Union ban of TiO_2NPs and the identified decrease in prevalence of TiO_2NP exposure. In addition, polystyrene nanoplastics have been detected in several human organs including the liver, kidney, and brain [8].

Nanoparticles have been found in tissues from the female reproductive system [44, 47]. Intravenous exposure to gadolinium-loaded PEGylated liposomes (nanomaterials used in imaging and drug delivery systems) resulted in a two-fold greater accumulation of nanomaterials in the ovaries and uterus during ovulation compared to during the non-ovulatory stage in mice [47], demonstrating that the biodistribution pattern of nanomaterials is influenced by cyclicity due to increased angiogenesis at the ovulation stage. Ambient black carbon nanoparticles have been found in follicular fluid and ovarian tissue from women undergoing assisted reproductive technology treatments in Sweden [44]. Black carbon particles have been detected in follicular fluid samples, with an average mean particle count of $5.8 \times 10^5 \pm 5.3 \times 10^5$ black carbon particles per milliliter of fluid [44]. Further, the black carbon particle load in the medulla was 3.8-fold higher on average compared to the ovarian cortex and the particles were observed in both non-growing follicles and growing antral follicles [44], demonstrating that nanomaterials can reach the ovaries, distribute to several follicle types, and come into contact with the female germ cells in humans.

Microplastics have also been detected in follicular fluid from women undergoing assisted reproductive treatment

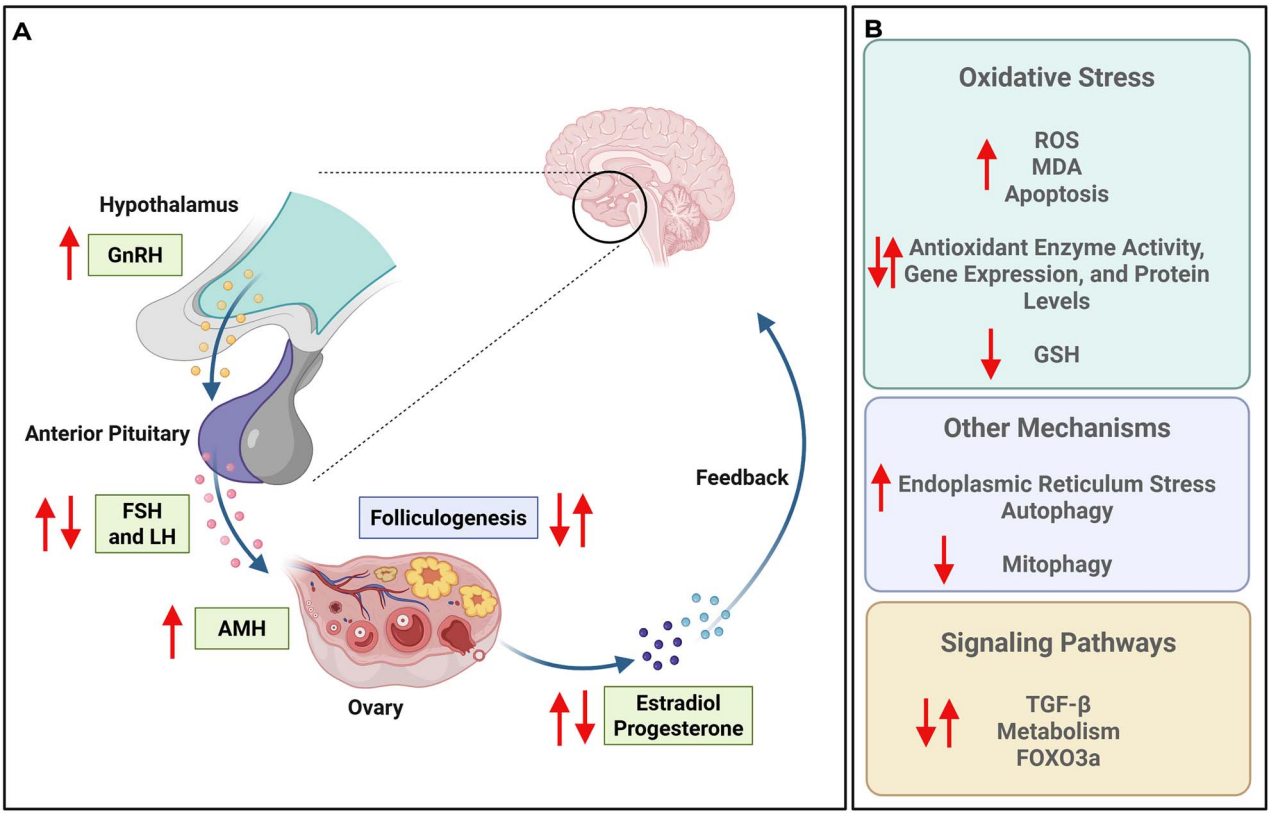

Figure 1. Effects and mechanisms of toxicity of nanoparticles and nanoplastics on the hypothalamic–pituitary–ovarian (HPO) axis. (A) Nanoparticles and nanoplastics alter the HPO axis by affecting gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, the pituitary hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the ovarian-synthesized hormones anti-Müllerian hormone (AMH), estradiol, progesterone, and testosterone. In addition, nanomaterials affect folliculogenesis by decreasing the number of follicles and corpora lutea and altering follicular morphology. (B) Oxidative stress is the main mechanism described for how nanomaterials affect female reproductive function. However, other mechanisms have been described and include disruption of signaling pathways important for reproduction. ROS, reactive oxygen species; MDA, malondialdehyde; GSH, glutathione.

in Italy [6]. The presence of microplastics was detected in 14 out of 18 samples of follicular fluid, with an average concentration of 2191 particles/mL (0–7181 particles/mL) and a mean diameter of 4.48 μm (3.18–5.54 μm) [6]. Further, microplastics have been detected in follicular fluid from women undergoing assisted reproductive technology in China [7]. Interestingly, all of the samples in the study contained variable amounts of microparticles with chlorinated polyethylene, fluorosilicone rubber, and polyvinyl chloride being the most abundant [7]. Further, when a subset of samples was randomly selected for pyrolysis gas chromatography–mass spectrometry, polyethylene (22.284 mg/kg), polypropylene (0.837 mg/kg), polystyrene (0.600 mg/kg), and polyvinyl chloride (1.061 mg/kg) were detected in the samples [7].

Collectively, multiple studies demonstrate the environmental presence of nano-sized particles and their ability to cross physiological barriers through multiple exposure routes, ultimately accumulating in several organs, including reproductive tissues in animals and humans. These findings raise growing concern regarding the potential effects of internalization of nanomaterials in the female reproductive system.

Effects of nanoparticles and nanoplastics on female reproduction

Nanoparticles and nanoplastics adversely influence female reproductive physiology by perturbing regulatory processes along multiple levels of the HPG axis (Figure 1). Nanoparticles and nanoplastics can impair neuroendocrine signaling in the hypothalamus and anterior pituitary; disrupt ovarian development and function; and consequently alter steroidogenesis, cyclicity, and fertility (Figure 1 and Table 1). The sections below highlight recent studies on the impact of nanomaterials on the hypothalamus, anterior pituitary, ovary, cyclicity, placental function, embryo development, and fertility.

Effects of nanoparticles and nanoplastics on the hypothalamus and anterior pituitary

Several studies have shown that nanoparticles and nanoplastics can alter hypothalamic and anterior pituitary function [48, 49] (Table 1). Carbon black nanoparticle exposure via intratracheal administration at an occupationally relevant dose increased circulating FSH levels and pituitary *Fshb* subunit gene expression compared to controls in female mice [49]. Magnesium oxide nanoparticles (MgONPs), used in the medical and therapeutic fields, for 4 weeks decreased circulating FSH and LH levels in a dose-dependent manner in female and male Wistar rats [25]. AgNP exposure for 35 days reduced LH and FSH levels compared to control in mice [16]. TiO_2NP exposure for 60 days increased serum FSH and LH levels compared to control in mice [50]. TiO_2NP exposure for 10 weeks increased GnRH levels, decreased

Table 1. Effects of nanoparticles and nanoplastics on the female reproductive system

Nanomaterial	Dose	Model	Effects	Reference
Effects on the hypothalamus and anterior pituitary				
Carbon black	10 mg/mL/week	Mouse	Increased FSH; Increased *Fshb*	[49]
MgONPs	131.5 and 263 mg/kg	Rat	Decreased FSH and LH	[25]
AgNPs	20 nm; 500 mg/kg/day	Mouse	Decreased FSH and LH	[16]
TiO_2NPs	2.5, 5, or 10 mg/kg	Mouse	Increased FSH and LH	[50]
TiO_2NPs	10 and 100 mg/kg	Rat	Increased GnRH; Decreased LH; Increased FSH	[48]
Polystyrene microplastics	5–5.9 μm; 0.1 mg/day	Mouse	Increased FSH and LH	[51]
Polystyrene nanoplastics	70–80 nm; 100 mg/kg/day	Mouse	Decreased FSH and LH	[52]
Polystyrene nanoplastics	50–90 nm; 0.5 and 1 mg/kg	Mouse	Decreased FSH and LH	[53]
Effects on the ovary				
MgONPs	131.5 and 263 mg/kg	Rat	Decreased total follicle number; Increased atretic follicles	[25]
AgNPs	20 nm; 500 mg/kg/day	Mouse	Decreased primordial, primary, preantral, and antral follicles	[16]
AgNPs	200 nm, 100 mg/kg	Rat	Deformed follicles, areas of necrosis, hyalinization, and dilated congested blood vessels in the ovary	[55]
NiONPs	<30 nm; 5 mg/kg	Rat	Constriction of primordial and primary follicles; Enlargement of secondary follicles; Hyperplasia in antral and atretic follicles	[56]
ZnONPs	27.5 nm; 100, 200, and 400 mg/kg	Mouse	Decreased ovarian coefficient; Increased atretic follicles; Altered organization of granulosa cells, zona pellucida, and corona radiata	[54]
SiNPs	110 nm; 25 mg/kg	Mouse	Increased ovarian follicular atresia	[57]
TiO_2NPs	20–30 nm; 100, 300, and 500 mg/kg	Mouse	Decreased ovarian index; Reduced number of primordial and growing follicles; Increased follicular atresia	[58]
TiO_2NPs	2.5, 5, or 10 mg/kg	Mouse	Reduced ovarian weight; Increased atretic follicles; Inflammatory cell infiltration in the ovary	[50]
TiO_2NPs	10 and 100 mg/kg	Rat	Decreased corpora lutea and antral follicle numbers; Increased atretic follicle numbers	[48]
Carbon black	1064 mg/m^3 for 6 h/day	Rat	Decreased number of preantral and antral follicles	[59]
Polystyrene microplastics	5–5.9 μm; 0.1 mg	Mouse	Decreased total follicle number	[51]
Polystyrene nanoplastics	70–80 nm; 100 mg/kg	Mouse	Decreased number of growing follicles; Increased atretic follicle numbers	[52]
Polystyrene nanoplastics	100 and 1000 μg/L	Mouse	Increased atretic follicle density; Decreased follicle diameter and corpora lutea density	[60]
Polystyrene nanoplastics	50–90 nm; 0.5 and 1 mg/kg	Mouse	Decreased follicle numbers	[53]
Polystyrene nanoplastics	0.1, 1, and 10 μg/mL	Mouse	Reduced ovarian weight and follicle numbers	[61]
Nanoplastics	0.5, 1, 10, and 50 μg/mL	Mouse	Altered oocyte maturation	[7]
Polystyrene nanoplastics	25 nm; 1 mg	Mouse	Decreased ovarian size; Reduced secondary and antral follicles	[62]
Polystyrene nanoplastics	25 nm; 1 mg	Mouse	Decreased growing follicles; Decreased AMH	[63]
Polystyrene nanoplastics	50 nm; 5 and 25 mg/kg	Mouse	Reduced primordial, primary, and secondary follicles; Increased atretic follicles; Decreased AMH	[64]
Effects on sex steroid hormone synthesis				
MgONPs	131.5 and 263 mg/kg	Rat	Decreased estrogen and progesterone	[25]
NiONPs	<30 nm; 5 mg/kg	Rat	Increased estradiol and progesterone	[56]
ZnONPs	27.5 nm; 100, 200, and 400 mg/kg	Mice	Decreased estradiol and progesterone	[54]
ZnONPs	37 nm; 5 μg/mL	Mouse antral follicles in vitro	Increased ovarian *Cyp19a1;* Increased estradiol; Decreased ovarian *Esr1*	[65]

(continued)

Table 1. Continued.

Nanomaterial	Dose	Model	Effects	Reference
CuNPs	54 nm; 60, 120, and 180 mg/kg	Rat	Increased 19-hydroxiandrostenedione and estradiol; Decreased progesterone and testosterone; Increased CYP11A1, CYP17, and CYP19; Decreased CYP1A2, CYP1B1, and CYP3A4	[66]
TiO_2NPs	20–30 nm; 100, 300, and 500 mg/kg	Mouse	Decreased estradiol and progesterone levels	[58]
TiO_2NPs	10 and 100 mg/kg	Rat	Decreased testosterone and progesterone; Increased estradiol	[48]
TiO_2NP	17 nm; 2, 25, and 50 μg/mL	Mouse antral follicles in vitro	Increased levels of androstenedione and testosterone; Altered the expression of *Hsd3b1*, *Ar*, and *Esr1*	[67]
Polystyrene microplastics	5–5.9 μm; 0.1 mg	Mouse	Decreased estradiol; Increased testosterone	[51]
Polystyrene nanoplastics	70–80 nm; 100 mg/kg	Mouse	Decreased estradiol	[52]
Polystyrene nanoparticles	100 and 1000 μg/L	Mouse	Decreased progesterone	[60]
Polystyrene nanoplastics	50–90 nm; 0.5 and 1 mg/kg	Mouse	Increased estradiol and progesterone	[53]
Polystyrene nanoplastics	25 nm; 1 mg/day	Mouse	Decreased estradiol levels and expression of *Cyp11, Cyp19, Star, Stard5, Ldlr, Lhcgr, and Scarb1* genes	[62]
Polystyrene nanoplastics	50 nm; 5 and 25 mg/kg	Mouse	Decreased estradiol	[64]

FSH, follicle-stimulating hormone; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; *Fshb*, follicle-stimulating hormone beta subunit; AMH, anti-Müllerian hormone; *Cyp19a1*, cytochrome P450, family 19, subfamily a, polypeptide 1; *Esr1*, estrogen receptor alpha; CYP11A1, cytochrome P450, family 11, subfamily A, member 1; CYP17, cytochrome P450, family 17, subfamily A, polypeptide 1; CYP1A2, cytochrome P450, family 1, subfamily A, member 2; CYP1B1, cytochrome P450, family 1, subfamily B, member 1; CYP3A4, cytochrome P450, family 3, subfamily A, member 4; *Hsd3b1*, hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1; *Ar*, androgen receptor; *Star*, steroidogenic acute regulatory protein; *Stard5*, Star-related lipid transfer domain containing 5; *Ldlr*, low-density lipoprotein receptor; *Lhcgr*, luteinizing hormone receptor; *Scarb1*, scavenger receptor class B, member 1.

LH levels, and increased FSH levels compared to control in rats [48]. Further, polystyrene microplastic exposure via oral gavage for 30–44 days increased serum FSH and LH levels compared to control in female mice [51]. Polystyrene nanoplastic exposure for 35 days decreased serum levels of FSH and LH compared to control in mice [52]. Polystyrene nanoplastic exposure for 90 days decreased FSH and LH levels compared to control in mice [53]. Collectively, these studies demonstrate that nanomaterials alter hypothalamic and pituitary function. However, future studies are needed to identify the underlying mechanisms of nanomaterial-induced changes in hypothalamic and pituitary function.

Effects of nanoparticles and nanoplastics on the ovary

In addition to affecting hypothalamic and/or pituitary function, exposure to nanoparticles affects ovarian structure and function [16, 50, 54] (Table 1). For example, MgONP exposure for 4 weeks decreased the numbers of all follicle types and increased the number of atretic follicles in the ovary compared to control in female rats [25], suggesting that MgONP induces apoptosis in ovarian follicles. AgNP exposure for 35 days decreased the numbers of primordial, primary, preantral, and antral follicles compared to control in mice [16]. Further, AgNP exposure led to the presence of deformed follicles, areas of necrosis, hyalinization, and dilated congested blood vessels in the ovary compared to control in rats [55]. Exposure to nickel (II) oxide nanoparticles (NiONP), used in electronic coating, plastics, and textiles, for 15 and 30 days altered ovarian follicle morphology as evidenced by constriction of primordial and primary follicles, enlargement of secondary follicles, and hyperplasia in antral and atretic follicles compared to control in rats [56]. ZnONP exposure for 7 days decreased ovarian coefficient (ovarian weight [mg]/body weight [g]), increased atretic follicle numbers, and altered the organization of the granulosa cells, zona pellucida, and corona radiata compared to control in female mice [54]. Intratracheal exposure to silica nanoparticles (SiNPs), one of the main components in particulate matter in the environment, every third day for a total of 15 days induced ovarian follicular atresia through apoptosis in granulosa cells in Institute of Cancer Research (ICR) mice [57]. TiO_2NP exposure for 10 days significantly decreased ovarian index (ovary weight/body weight) compared to controls in ICR mice [58]. TiO_2NP also caused disorganized granulosa cell layers, loss of structural integrity, and marked reduction in the number of primordial and growing follicles, accompanied by increased follicular atresia compared to controls in ICR mice [58]. TiO_2NP exposure for 60 days reduced ovarian weight, increased atretic follicles, and caused inflammatory cell infiltration in the ovary compared to control in mice [50]. TiO_2NP exposure for 10 weeks decreased corpora lutea and antral follicle numbers, whereas it increased atretic follicle numbers compared to control in rats [48]. Exposure to carbon black nanoparticles for 30 days decreased the number of preantral and antral follicles compared to control in rat ovaries [59]. Collectively, these studies demonstrate that nanoparticles alter ovarian structure and function. However, future studies are needed to identify the underlying mechanisms of nanoparticle-induced changes in ovarian structure and function.

Exposure to nanoplastics also affects ovarian structure and function [52, 60]. Polystyrene microplastic exposure via oral gavage for 30–44 days decreased total follicle number compared to control in female mice [51]. Polystyrene nanoplastic exposure for 35 days decreased the number of growing follicles while increasing atretic follicle numbers compared to control in mice [52]. Oral exposure to polystyrene nanoplastics for 29 days increased atretic follicle density and decreased

follicle diameter and corpora lutea density compared to control in mice [60]. Polystyrene nanoplastic exposure for 90 days decreased follicle numbers compared to control in mice [53]. Polystyrene nanoplastic exposure for 11 weeks over the premating, mating, pregnancy, and lactation periods reduced ovarian weight and follicle numbers in the offspring compared to control in mice [61].

Microplastics found in human follicular fluid have been shown to affect ovarian structure and function as well as mouse oocyte maturation in vitro [7]. Specifically, smaller microplastics were more likely to cross the zona pellucida and get into the oocyte than larger microplastics and all tested microplastics decreased oocyte maturation compared to controls [7]. Polystyrene nanoplastic exposure for 42 days decreased ovarian size compared to control in mice [62]. Interestingly, histological examination showed that polystyrene nanoplastic exposure caused abnormal ovarian structure and reduced the numbers of secondary and antral follicles compared to control [62]. Polystyrene nanoplastic exposure for 5 weeks decreased the number of growing follicles and reduced anti-Müllerian hormone (AMH) levels compared to control in mice [63]. Further, polystyrene nanoplastic exposure for 8 weeks reduced the numbers of primordial, primary, and secondary follicles and increased the number of atretic follicles compared to control in mice [64]. Moreover, polystyrene nanoplastic exposure decreased AMH levels compared to control in mice [64]. Taken together, these studies indicate that nanoplastics, like nanoparticles, can alter ovarian structure and function. However, further studies are needed to understand the mechanisms underlying the effects of nanoplastics on the ovary.

Effects of nanoparticles and nanoplastics on sex steroid hormone synthesis

Nanoparticles can affect sex steroid hormone levels [65, 66] (Table 1). MgONP exposure for 4 weeks decreased circulating estrogen and progesterone levels in a dose-dependent manner compared to control in female and male Wistar rats [25]. NiONP exposure for 15 and 30 days increased plasma estradiol and progesterone levels compared to control in rats [56]. ZnONP exposure for 7 days decreased serum estradiol and serum progesterone levels in a dose-dependent manner compared to control in female mice [54]. ZnONP exposure for 96 h increased ovarian expression of cytochrome P450, family 19, subfamily a, polypeptide 1 (CYP19A1), leading to increased estradiol levels and decreased estrogen receptor alpha (*Esr1*) expression compared to control in cultured mouse antral follicles [65]. Exposure to copper nanoparticles (CuNP), widely used in industrial and commercial products, for 17 days increased the levels of sex steroid hormones including 19-hydroxyandrostenedione and estradiol, and it decreased the levels of progesterone and testosterone compared to controls in pregnant rats [66]. Interestingly, CuNP-induced changes in hormone levels were accompanied by increased levels of cytochrome P450, family 11, subfamily A, member 1 (CYP11A1), cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17A1), and CYP19A1 and decreased levels of cytochrome P450, family 1, subfamily A, member 2 (CYP1A2), cytochrome P450, family 1, subfamily B, member 1 (CYP1B1), and cytochrome P450, family 3, subfamily A, member 4 (CYP3A4) compared to controls [66]. TiO_2NP exposure for 10 days altered hormone levels immediately after exposure, reducing estradiol and progesterone levels compared to control in mice [58]. TiO_2NP exposure for 10 weeks decreased testosterone and progesterone and increased estradiol levels in serum in rats [48]. TiO_2NP increased the levels of androstenedione and testosterone and altered the expression of hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (*Hsd3b1*), androgen receptor (*Ar*), and *Esr1* compared to control in cultured mouse antral follicles [67], suggesting that nanoparticles have differential effects on hormones, which depend on exposure length and system/animal model.

Similar to nanoparticle exposure, microplastic and nanoplastic exposure can affect sex steroid hormone levels. Polystyrene microplastic exposure via oral gavage for 30–44 days decreased serum estradiol levels, whereas it increased serum testosterone levels compared to control in female mice [51]. Polystyrene nanoplastic exposure for 35 days decreased estradiol levels compared to control in female mice [52]. Oral exposure to polystyrene nanoparticles for 29 days decreased serum progesterone levels compared to control in mice [60]. Polystyrene nanoplastic exposure for 90 days increased estradiol and progesterone levels compared to control in mice [53]. Polystyrene nanoplastic exposure for 42 days decreased estradiol levels and the expression of genes involved in steroidogenesis (i.e., *Cyp11a1, Cyp19a1,* StAR-related lipid transfer domain containing 5(*Stard5),* low-density lipoprotein receptor *(Ldlr),* luteinizing hormone/choriogonadotropin receptor (*Lhcgr*), and scavenger receptor class B, member 1 (*Scarb1*)) compared to control in mice [62]. Further, polystyrene nanoplastic exposure for 8 weeks decreased serum estradiol levels compared to control in mice [64]. Collectively, these studies indicate that nanomaterials interfere with ovarian steroidogenesis. However, further studies are needed to understand the mechanisms underlying the effects of nanomaterials on ovarian steroidogenesis and to elucidate the downstream impacts of nanomaterial-induced abnormal ovarian steroidogenesis on reproductive outcomes.

Effects of nanoparticles and nanoplastics on cyclicity

Both nanoparticles and nanoplastics have been shown to affect estrous cyclicity [48, 60]. For example, TiO_2NP exposure for 10 weeks altered estrous cyclicity as evidenced by decreased time spent in proestrus and increased time spent in estrus in exposed rats compared to control rats [48]. Oral exposure to polystyrene nanoplastics for 29 days significantly increased estrous cycle length compared to control in mice [60]. Gestational and lactational exposure to polystyrene nanoplastics led to a longer time spent in estrus and a shorter time spent in diestrus compared to control in female mouse offspring [68]. Polystyrene nanoplastic exposure for 42 days led to a prolonged estrous cycle compared to control in mice [62]. Polystyrene nanoplastic exposure for 8 weeks reduced the time spent in estrus, whereas it increased time spent in metestrus/diestrus compared to control in mice [64]. Taken together, these studies indicate that nanoparticles and nanoplastics can alter estrous cyclicity. However, further studies are needed to understand the mechanisms underlying the effects of nanoparticles and nanoplastics on reproductive cyclicity.

Effects of nanoparticles and nanoplastics on placental function and embryo development

Limited information is available on the effects of nanomaterials on placental function and embryo development (Figure 2 and Table 2). However, one study showed that AgNP

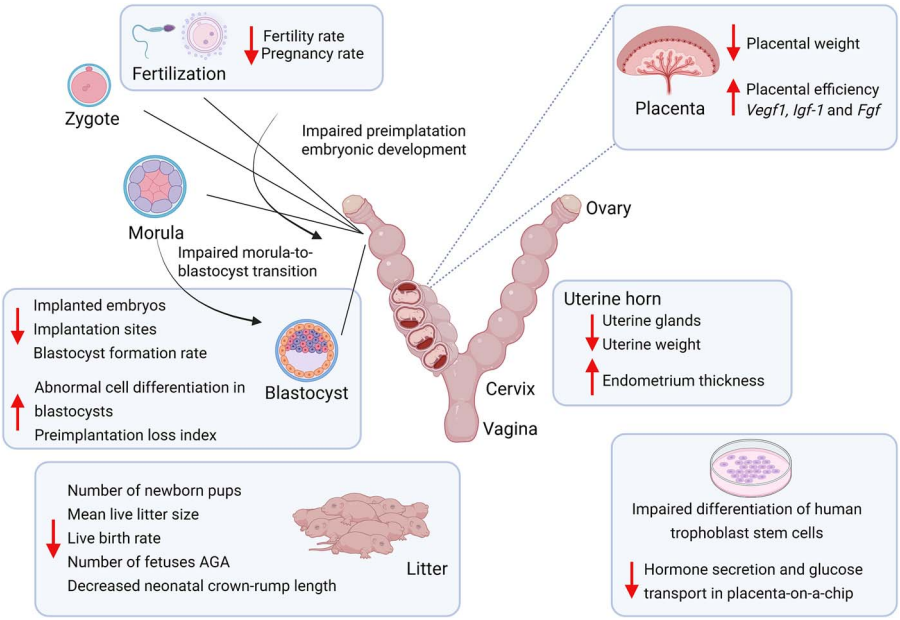

Figure 2. Reproductive outcomes of nanoparticles and nanoplastics. Exposure to nanoparticles and nanoplastics affects several female reproductive tissues and outcomes including placental function, embryo development, and fertility. AGA, appropriate for gestational age; *Vegf1*, vascular endothelial growth factor; *Igf1*, insulin-like growth factor 1; *Fgf*, fibroblast growth factor.

Table 2. Nanoparticles, nanoplastics, and reproductive outcomes.

Nanomaterial	Dose	Model	Reproductive outcome	Reference
AgNPs	0.15–0.6 μg/mL	*In vitro* mouse blastocysts	Decreased blastocyst formation rate; Increased abnormal cell differentiation by increased Oct-4 levels	[69]
AgNPs	~22 nm; 300 mg/kg	Rat	Altered fetal liver and kidney function	[73]
CuNPs	40 nm; 20 μg/mL	Human placenta-on-a-chip model	Impaired human trophoblast stem cell differentiation; Reduced hormone secretion and glucose transport	[70]
CuONPs	50 nm; 1, 5, 10, 20 μg/mL	Mouse	Impaired preimplantation and embryonic development	[71]
Polystyrene nanoplastics	100 nm; 1 mg/kg;	Rat	Increased preimplantation loss rate and placental efficiency; Decreased placental weight and *Vegf*, *Igf-1*, and *Fgf* expression	[72]
Polystyrene nanoplastics	70–80 nm; 100 mg/kg	Mouse	Decreased uterine gland number; Increased endometrium thickness	[52]
Polystyrene nanoplastics	25 nm; 1 mg/day	Mouse	Decreased the number of implantation sites	[62]
Polystyrene nanoplastics	0.5 or 1 mg/kg	Mouse	Decreased neonatal crown-rump length, embryo implantation sites, and uterine wet weight	[53]
AgNPs	2–30 nm; 1000 μg/mL or 350 μg/mL	Mouse	Decreased number of newborn pups	[69]
AgNPs	22 nm; 300 mg/kg	Rat	Increased preimplantation loss index	[73]
CuNPs	60, 120, and 180 mg/kg/d	Rat	Decreased pregnancy rate and mean live litter size	[66]
CuONPs	50 nm; 1, 5, 10, and 20 μg/mL	Mouse	Decreased live birth rate	[71]
Polystyrene nanoplastics	100 nm; 1 mg/kg	Rat	Decreased number of fetuses appropriate for gestational age	[72]
Polystyrene nanoplastics	25 nm; 1 mg/day	Mouse	Decreased litter size	[62]
Polystyrene nanoplastics	50 nm; 5 and 25 mg/kg	Mouse	Decreased the number of implanted embryos and newborn pups	[64]
Polystyrene nanoplastics	25 nm; 1 mg/d	Mouse	Decreased fertility rate	[63]
Polystyrene nanoplastics	0.5 or 1 mg/kg	Mouse	Decreased live birth rate	[53]
Polystyrene nanoplastics	30 mg/kg	Mouse	Increased miscarriage rate and premature delivery; Reduced litter size	[68]

Oct-4, octamer-binding transcription factor 4; *Vegf*, vascular endothelial growth factor precursor; *Igf-1*, insulin-like growth factor 1; *Fgf*, fibroblast growth factor.

exposure decreased blastocyst formation rate and increased abnormal cell differentiation in blastocysts as evidenced by increased levels of the inner cell mass marker POU domain, class 5, transcription factor 1 (OCT-4) compared to controls in mouse blastocysts in vitro [69]. Copper nanoparticle exposure impaired the differentiation of human trophoblast stem cells, resulting in reduced hormone secretion and decreased glucose transport in a placenta-on-a-chip model [70]. Copper oxide nanoparticles (CuONPs) impaired preimplantation embryonic development by affecting the morula-to-blastocyst transition and by reducing the pluripotency of the inner cell mass and mouse embryonic stem cells [71]. Exposure to polystyrene nanoplastics from gestational day 5 to 20 increased preimplantation loss rate, decreased the placental weight of male offspring, and it increased placental expression of vascular endothelial growth factor precursor (*Vegf*), insulin-like growth factor 1 (*Igf-1*), and fibroblast growth factor (*Fgf*) compared to control in rats [72]. Oral exposure to polystyrene nanoplastics for 42 days decreased the number of implantation sites compared to control in mice [62]. Polystyrene nanoplastic exposure for 90 days decreased neonatal crown-rump length (a key indicator of developmental status), decreased embryo implantation sites, and decreased uterine wet weight compared to control in mice [53]. Although still limited, the existing studies suggest that exposure to nanoparticles and nanoplastics adversely affects implantation, placental quality, and blastocyst formation and cell differentiation. However, more research is needed to address the mechanisms through which nanoparticles and nanoplastics affect implantation, placenta, and blastocyst quality.

Effects of nanoparticles and nanoplastics on fertility

Nanoparticles have been shown to reduce fertility [66, 73] (Figure 2 and Table 2). Exposure to vaginal gels containing AgNPs for 8 weeks prior to mating decreased the number of newborn pups compared to control in mice [69]. Exposure to green biosynthesized AgNPs from gestational day 1 to 19 increased the preimplantation loss index compared to control in rats [73]. Copper nanoparticle exposure for 17 days decreased pregnancy rate and mean live litter size compared to control in rats [66]. Copper oxide nanoparticles decreased live birth rate compared to control in mice [71].

Exposure to nanoplastics can also affect fertility [62, 72]. Exposure to polystyrene nanoplastics from gestational day 5 to 20 decreased the number of fetuses classified as appropriate for gestational age compared to control in rats [72]. Oral exposure to polystyrene nanoplastics for 42 days decreased litter size compared to control in mice [62]. Polystyrene nanoplastic exposure for 8 weeks decreased the number of implanted embryos and the number of newborn pups compared to control in mice [64], suggesting that direct exposure to nanoplastics impairs fertility and negatively affects gestational outcomes. Polystyrene nanoplastic exposure for 5 weeks decreased the fertility rate in mice [63] and polystyrene nanoplastic exposure for 90 days decreased live birth rate compared to control in mice [53]. Exposure to polystyrene nanoplastics from gestation day 0.5 to postnatal day 21 increased miscarriage rate and premature delivery, and it reduced litter size compared to control in mice [68]. Collectively, these data indicate that exposure to nanoparticles and nanoplastics alters several measures of subfertility/infertility, including decreased pregnancy rate, decreased number of newborns, and decreased birth rate. Future studies should address the causes underlying female subfertility/infertility due to nanoparticle and nanoplastic exposure.

Mechanisms of nanoparticles and nanoplastics underlying toxicity in the female reproductive system

One of the main challenges in understanding the toxic effects of nanoparticle exposure is identifying the underlying molecular pathways. Below, we briefly mention some of the most widely described mechanisms by which nanoparticles and nanoplastics cause female reproductive toxicity (Figure 1 and Table 3).

Oxidative stress

Nanoparticle exposure can induce oxidative stress in the female reproductive system, which often leads to cell death in female reproductive organs such as the ovary [1]. Copper oxide nanoparticle exposure for 30 days induced oxidative stress in the mouse ovary [74]. Specifically, CuONP induced reactive oxygen species (ROS) formation, impaired mitochondrial dynamics, and altered oocyte maturation as evidenced by disrupted meiotic spindle assembly, chromosome alignment, and kinetochore microtubule attachment compared to control in mouse oocytes [74]. MgONP exposure for 4 weeks increased the levels of the lipid peroxidation product malondialdehyde (MDA) and decreased activity of the antioxidant enzymes known as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in the ovary compared to control in rats [25], demonstrating the ability of MgONPs to alter oxidative stress pathways in the ovaries. Oral exposure to NiONPs for 15 and 30 days increased the levels of MDA, hydrogen peroxide (H_2O_2), and nitric oxide and increased the activity of CAT and GPx compared to control in rats [56]. Curcumin nanoparticles, well-known antioxidants, protected rat ovaries from toxicity induced by carbon black nanoparticle exposure [59]. Silver nanoparticle exposure decreased ovarian glutathione (GSH) levels and SOD activity compared to control in rats [55].

Titanium dioxide nanoparticle exposure for 10 days decreased the ovarian expression of the antioxidant enzymes superoxide dismutase 2 (*Sod2*), catalase (*Cat*), and glutathione peroxidase (*Gpx*) compared to control in mice [58]. Interestingly, TiO_2NP exposure for 24 h induced formation of ROS, altering the mitochondrial membrane and increasing apoptosis in KK1 granulosa cells in vitro [58]. TiO_2NP exposure also increased the BCL2-associated X protein to B cell leukemia/lymphoma 2 (*Bax/Bcl2*) ratio at the highest nanoparticle internalization rate concentration compared to control [67], suggesting induction of apoptosis due to increased internalization into antral follicles.

Oral exposure to ZnONPs for 7 days increased ovarian MDA levels and expression of the antioxidant-associated genes nuclear factor erythroid 2-related factor 2 (*Nrf2*), c-jun N-terminal kinase (*Jnk*), and NAD(P)H dehydrogenase, quinone 1 [54], suggesting an initial attempt to protect the ovary from oxidative stress. However, ZnONPs also decreased the levels of SOD activity and kelch-like ECH-associated protein 1 *(Keap1)* expression and it increased the expression of apoptotic factors (i.e., caspase 9, caspase 3, and caspase

Table 3. Mechanisms underlying nanoparticle and nanoplastic toxicity.

Nanomaterial	Dose	Model	Marker	Reference
Oxidative stress				
CuONPs	<50 nm; 1.25, 2.5, 5 mg/kg	Mouse	Increased ROS levels on oocytes; Impaired mitochondrial dynamics in oocytes	[74]
MgONPs	263 mg/kg	Rat	Increased MDA; Decreased activity of SOD, CAT, and GPx	[25]
NiONPs	<30 nm; 5 mg/kg	Rat	Increased ovarian MDA levels; Increased ovarian H_2O_2, and nitric oxide; Increased ovarian activity of CAT and GPx	[56]
AgNPs	200 nm, 100 mg/kg	Rat	Decreased ovarian GSH levels and SOD activity	[55]
TiO_2NPs	100, 300, and 500 mg/kg	Mouse	Decreased ovarian expression of *Sod2*, *Cat*, and *Gpx*	[58]
TiO_2NPs	20–30 nm; 100, 200 mM	KK1 cells	Increased ROS; Altered mitochondrial membrane; Increased apoptosis	[58]
TiO_2NPs	17 nm; 2, 25, and 50 μg/mL	Mouse antral follicles in vitro	Increased Bax/Bcl2	[73]
ZnONPs	27.5 nm; 100, 200, and 400 mg/kg	Mouse	Increased ovarian MDA; Increased ovarian expression of *Nrf2*, *Jnk, Nqo-1, Casp9*, *Casp3*, and *Casp12;* Decreased ovarian expression of *Keap1;* Decreased activity of SOD; Antioxidant NAC protects ovaries from ZnONP-induced toxicity	[54]
ZnONPs	37 nm; 15 μg/mL	Mouse antral follicles in vitro	Increased expression of *Nrf2*, *Cat*, *Sod1*, *Gsr*, and *Gpx;* Decreased ROS	[65]
Pristine TiO_2NPs, TiO_2NPs (salicylic acid (SA-TiO_2NPs), and 5-aminosalicylic acid (5SA-TiO_2NPs)	20–30 nm for all three types of NPs	Rat	Pristine TiO_2NPs and 5SA-TiO_2NPs decreased ovarian GSH/GSSG; Pristine and SA-TiO_2NPs decreased GSH/GSSG in uteri; Pristine TiO_2NPs and SA-TiO_2NPs decreased activity of CuZnSOD in oviducts	[75]
Polystyrene nanoplastics	25 nm, 1 mg/day	Mouse	Decreased serum GSH and CAT activity and total antioxidant capacity; Increased serum MDA; Decreased ovarian NRF2; Increased ovarian apoptosis	[64]
Polystyrene nanoplastics	150 μg/mL	COV434 cells	Increased NRF2 after 24 h of exposure; Decreased NRF2 levels after 48 h of exposure	[64]
Polystyrene nanoplastics	25 nm; 100 μg/mL	KGN cells	Increased ROS; Increased apoptosis; Disrupted Hippo pathway, MST1, LATS1, and YAP1	[63]
Polystyrene nanoplastics	100 nm; 5, 25, 75 μg/mL	Porcine luteal cells in vitro	Increased superoxide and nitric oxide levels; Decreased SOD activity	[76]
Polystyrene nanoplastics	70–80 nm; 100 mg/kg/d	Mouse	Increased serum CAT and GPx activity	[52]
Polystyrene nanoplastics	0.1, 1, and 10 μg/mL	Mouse	Decreased ovarian expression of *Sod1* and *Gpx*	[61]
Other mechanisms				
SiNPs	200–800 μg/mL	Mouse granulosa cells	Endoplasmic reticulum stress: activation of the inositol 1,4,5-trisphosphate receptor type 1 (IP3R1)–mediated calcium mobilization; Apoptosis through the PERK-ATF4-CHOP-ERO1α pathway	[57]
ZnONPs	27.5 nm; 100, 200, and 400 mg/kg	Mouse	Endoplasmic reticulum stress: increased ovarian expression of *Eif2a*, *CHOP*, *JNK*, and *Atf4*	[54]
CuONPs	50 nm; 10 μg/mL	Mouse blastocysts	Mitophagy: blocked autophagic flux and impaired mitophagy; Accumulation of damaged mitochondria	[71]
Polystyrene nanoplastics	25 nm, 1 mg/day	Mouse	Autophagy: increased levels of autophagy protein 5 (ATG5) and beclin-1	[62]

(continued)

Table 3. Continued.

Nanomaterial	Dose	Model	Marker	Reference
TiO_2NPs	2.5, 5, or 10 mg/kg	Mouse	Altered TGF-β pathway: increased ovarian activin A, follistatin, BMP2, BMP4, TGF-β1, Smad2, Smad3, and Smad4; Decreased levels of inhibin α	[50]
Polystyrene nanoplastics	0–400 μg/mL	KGN human granulosa cells	Altered metabolism: increased cytoplasmic vacuoles, total lysosomal area, and lipid droplet number	[78]
Polystyrene nanoplastics	30 mg/kg	Mouse	Activation of the AKT-FOXO3a signaling pathway	[68]

ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; *Sod2*, superoxide dismutase 2; Bax, BCL2-associated X protein; Bcl2, B-cell leukemia/lymphoma 2; *Nrf2*, nuclear factor erythroid 2-related factor 2; *Jnk*, c-jun N-terminal kinase; *Nqo-1*, NAD(P)H dehydrogenase, quinone 1; *Casp9*, caspase 9; *Casp3*, caspase 3; *Casp12*, caspase 12; NAC, N-acetylcysteine; *Sod1*, Superoxide dismutase 1; *Gsr*, Glutathione disulfide reductase; GSH, glutathione; GSSG, glutathione disulfide; MST1, macrophage stimulating 1; LATS1, large tumor suppressor kinase; YAP1, yes-associated protein 1; PERK, protein kinase R-like ER kinase; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; ERO1α, endoplasmic reticulum oxidoreductase 1 alpha; *Eif2a*, eukaryotic translation initiation factor 2A; *Atf4*, activating transcription factor 4; TGF-β1, Transforming growth factor beta 1.

12) compared to control in mice [54]. Addition of the antioxidant N-acetylcysteine (NAC) protected ovaries from ZnONP-induced effects on ovarian coefficient, estrogen and progesterone levels, and gene expression changes in antioxidant and apoptotic molecules in mice [54], suggesting that ovarian toxicity of ZnONPs is induced by oxidative stress. Zinc oxide nanoparticle exposure for 96 h increased expression of the antioxidant molecules *Nrf2*, *Cat*, *Sod1*, glutathione disulfide reductase (*Gsr*), and *Gpx* and decreased the levels of ROS compared to control in mouse antral follicles in vitro [65], suggesting that ZnONPs induce the antioxidant pathway, possibly in an attempt to protect cells from ZnONP-induced oxidative stress.

Interestingly, nanoparticle functionalization influences the ability of nanoparticles to induce oxidative stress. A comparative study assessed the effects of pristine TiO_2NPs compared to surface-modified TiO_2NPs (salicylic acid [SA-TiO_2NPs] and 5-aminosalicylic acid [5SA-TiO_2NPs]). Pristine TiO_2NPs and 5SA-TiO_2NPs reduced the glutathione to oxidized glutathione (GSH/GSSG) ratio, whereas SA-TiO_2NPs did not affect GSH/GSSG in the ovaries compared to control. Further, pristine and SA-TiO_2NPs decreased GSH/GSSG, whereas 5SA-TiO_2NPs did not affect GSH/GSSG in uteri [75]. In addition, pristine TiO_2NPs and SA-TiO_2NPs, but not 5SA-TiO_2NPs, decreased SOD1 activity in oviducts [75], suggesting tissue-specific response to differentially functionalized nanomaterials.

Similar to the ability of nanoparticle exposure to induce oxidative stress pathways in the female reproductive system, nanoplastic exposure can induce oxidative stress pathways in female reproductive tissues [64, 76] (Table 2). Polystyrene nanoplastic exposure orally for 42 days decreased serum GSH levels and CAT activity and total antioxidant capacity, and it increased serum MDA levels compared to control in mice [64]. Polystyrene nanoplastic exposure also decreased the antioxidant protein nuclear factor erythroid 2-related factor 2 (NRF2) and induced apoptosis in the ovary compared to control in mice [64]. Interestingly, polystyrene nanoplastic exposure initially increased NRF2 levels after 24 h of exposure, whereas it decreased NRF2 levels after 48 h of exposure compared to control in COV434 cells, suggesting that polystyrene nanoplastics cause an acute NRF2 activation response and subsequent depletion that is associated with induced apoptosis [64]. Polystyrene nanoplastics for 48 h increased ROS levels and induced apoptosis in KGN cells (human ovarian granulosa-like tumor cell line) through altered disruption of the Hippo pathway regulators such as macrophage stimulating 1 (MST1), large tumor suppressor kinase (LATS1), and yes-associated protein 1 (YAP1) compared to control [63]. Polystyrene nanoplastic exposure for 48 h increased superoxide anion and nitric oxide levels, whereas it decreased SOD activity in porcine luteal cells in vitro [76]. Polystyrene nanoplastic exposure for 35 days significantly increased CAT and GPx activity compared to control in mice [52]. Further, perinatal polystyrene nanoplastic exposure for 11 weeks decreased the ovarian expression of the antioxidant enzymes *Sod1* and *Gpx* compared to control in mice [61].

Collectively, abundant research has described a role for oxidative stress as an underlying mechanism in nanoparticle and nanoplastic toxicity in reproductive tissues. Several studies have described that nanoparticles and nanoplastics can lead to oxidative stress directly, not only by leading to the formation of ROS, but also by affecting the antioxidant response in reproductive tissues. However, it is unclear whether oxidative stress is the main driver of reproductive toxicity or if it is the consequence of reproductive toxicity. Thus, future studies should address this matter.

Endoplasmic reticulum stress

Nanomaterials have also been shown to cause female reproductive toxicity through mechanisms involving endoplasmic reticulum stress [54, 57] (Table 3). Silica nanoparticle exposure induced endoplasmic reticulum stress by activating inositol 1,4,5-trisphosphate receptor type 1 (IP3R1)–mediated calcium mobilization, leading to apoptosis through the protein kinase R (PKR)–like endoplasmic reticulum kinase (PERK)–activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP)–endoplasmic reticulum oxidoreductase 1 alpha (ERO1α) pathway in granulosa cells [57]. Zinc oxide nanoparticle exposure for 7 days induced endoplasmic reticulum stress in ovarian tissue as shown by increased expression of endoplasmic reticulum stress–related genes, eukaryotic translation initiation factor 2A (*Eif2a*), *CHOP*, c-jun N-terminal kinase, and activating transcription factor 4 (*Atf4*) compared to control in mice [54]. Although limited, research suggests that exposure to some nanomaterials can affect reproductive tissues through endoplasmic reticulum stress induction. More studies are needed to determine if other nanomaterials exert female reproductive

toxicity through pathways involving endoplasmic reticulum stress.

Autophagy

Nanomaterials have also been shown to induce autophagy in the female reproductive system [77]. Copper oxide nanoparticles blocked autophagic flux and impaired mitophagy, resulting in the accumulation of damaged mitochondria in mouse blastocysts [71]. Polystyrene nanoplastic exposure for 42 days increased the levels of the autophagy-associated proteins known as autophagy protein 5 (ATG5) and beclin-1 compared to control in mice [62], suggesting nanoparticle-induced autophagy. Overall, exposure to nanoparticles and nanoplastics can lead to autophagy dysregulation. More research, however, is needed to address whether other nanomaterials induce autophagy in the female reproductive system and to determine the impact of autophagy dysregulation on reproductive outcomes.

Signaling pathway interference

Nanoparticles and nanoplastics have also been shown to target several signaling pathways in the ovary [50, 68, 78]. Titanium dioxide nanoparticle exposure for 60 days increased ovarian protein levels of activin A, follistatin, bone morphogenetic protein 2, bone morphogenetic protein 4, transforming growth factor beta 1 (TGF-β), suppressor of mothers against decapentaplegic homolog 2 (SMAD2), SMAD3, and SMAD4, whereas it decreased the levels of inhibin α compared to control in mice [50]. Titanium dioxide nanoparticle exposure inhibited follicular development through the transforming growth factor beta (TGF-β) pathway [50]. Polystyrene nanoplastic exposure for 48 h caused a dose-dependent increase in the number of cytoplasmic vacuoles, increased total lysosomal area, and increased lipid droplet number compared to control in KGN cells, suggesting polystyrene nanoplastic–induced toxicity through metabolic pathways [78]. Polystyrene nanoplastic exposure from gestational day 0.5 to day 21 postpartum caused premature primordial follicle activation in the offspring through a mechanism that involves activation of the protein kinase B (AKT)-Forkhead box protein (FOXO3A) signaling pathway in mice [68]. Taken together, evidence suggests that nanoparticles and nanoplastics can affect several signaling pathways in reproductive tissues. However, the impact of the disrupted signaling pathways on reproductive function is not clear. More studies are needed to determine the consequences of nanomaterial-induced signaling disruption on reproductive function.

Protein corona

Nanoparticles and nanoplastics interact with biological fluids, resulting in the formation of a dynamic biological entity known as "protein corona" [79]. The nanoparticle/nanoplastic surface interacts with biomolecules including proteins, lipids, sugar moieties, nucleic acids, and metabolites present in biological fluid [80], resulting in the adsorption of some of those molecules onto the nanoparticle/nanoplastic surface. Protein corona formation results in a new physicochemical identity, leading to different nanoparticle and nanoplastic behaviors and toxicity profiles [79, 81]. For example, gold nanospheres, nanorods, and nanoflowers interact with saliva and urine [82]. Titanium dioxide nanoparticles interact with gastrointestinal fluids, with more diverse lipids interacting with nanoparticles after food digestion [83]. Further, polystyrene nanoplastics adsorb several proteins involved in blood coagulation including coagulation factor XII and plasminogen activator inhibitor-1 [84]. Polyethylene terephthalate nanoplastics interact with simulated biological fluids, including saliva, lysosomal fluid, and lung fluid [85].

Several studies have shown that nanoparticle protein corona interactions and protein corona influence nanotoxicity and nanomedicine [34, 79–81, 86], suggesting that protein corona may modulate the toxicity and underlying mechanisms of toxicity in the female reproductive system. Interestingly, studies on silicon dioxide nanoparticles demonstrated that the most abundant proteins found in the human protein corona included immunoglobulins, actin cytoplasmic 1, hemoglobin subunit beta, serotransferrin, ficolin-3, complement C3, and apolipoprotein A-1, whereas the mouse protein corona adsorbed serine protease inhibitor A3K, serotransferrin, alpha-1-antitrypsin 1–2, hemoglobin subunit beta, and fibrinogen gamma and beta chains [87], demonstrating interspecies differences in protein corona fingerprint and suggesting different biological responses. Although protein corona can regulate nanoparticle and nanoplastic interactions in reproductive tissues, most studies have not assessed whether nanomaterial toxicity is influenced by protein corona. Further, protein corona fingerprint may have interspecies differences, leading to different outcomes in animal models compared to what could be observed in humans. More research into the role of protein corona and interspecies fingerprint differences in protein corona composition is needed to better address the reproductive toxicity of nanoparticles and nanoplastics.

Mixture effects of nanoparticle and nanoplastic exposure

Nanomaterials are often found in mixtures with other pollutants in the environment [88]. Previous studies indicate that exposure to mixtures often results in different outcomes than exposures to single chemicals [88, 89], raising the possibility that the effects of nanomaterials in mixtures could differ from effects caused by single nanomaterial exposure. However, information on the effects of mixture exposure compared to single nanoparticles or nanoplastics on female reproductive health are limited. One study showed that co-exposure to TiO_2NPs and polystyrene nanoplastics significantly increased the ovarian coefficient and decreased serum estradiol and progesterone levels compared to control and to single exposures in mice [90]. Further, exposure to TiO_2NPs alone caused granulosa cell detachment, whereas TiO_2NP and polystyrene nanoplastic co-exposure resulted in granulosa cell detachment and structural disorganization in follicles [90]. Interestingly, co-exposure to TiO_2NPs and polystyrene nanoplastics resulted in higher TiO_2NP internalization compared to single TiO_2NP exposure in mouse ovaries [90], suggesting that co-exposure enhances TiO_2NP uptake and potentially exacerbates ovarian toxicity. Similarly, AuNP exposure plus radiofrequency exposure decreased cell viability in CHO cells at a higher rate compared to AuNP or radiofrequency exposure alone and to control [91], demonstrating synergistic effects of the co-exposure to AuNPs plus radiofrequency.

Co-exposure of polystyrene nanoplastics and cadmium during pregnancy and lactation led to increased LH and FSH levels and decreased AMH levels compared to control and to cadmium alone in rats [92]. In addition, the co-exposure reduced primary follicle numbers, increased atretic follicle

numbers, increased ROS, and increased MDA levels compared to control and to cadmium alone [92]. Polystyrene nanoplastic and lead co-exposure for 28 days increased the accumulation of lead in the ovaries, decreased endometrium thickness, and decreased estradiol levels compared to control and to single exposures in female mice [93]. In addition, co-exposure to polystyrene nanoplastics and lead induced endoplasmic reticulum stress in the ovary, leading to apoptosis [93]. In another study, co-exposure to polystyrene nanoplastics and triclosan increased ROS production, MDA levels, the levels of the autophagy protein LCB-II, and induced apoptosis, whereas it decreased SOD activity, antioxidant protein SESTRIN2 levels, and BCL2 levels compared to single exposures in KGN cells [94], demonstrating synergistic effects of the co-exposure in KGN cells.

A mixture of polystyrene nanoplastics and 3-tert-butyl-4-hydroxyanisole (3-BHA) for 35 days decreased the number of growing follicles, the number of uterine glands, and FSH levels and it increased the number of atretic follicles and the thickness of endometrium compared to control and to single exposures in mice [52]. Interestingly, co-exposure to polystyrene nanoplastics and 3-BHA had a higher pro-oxidant effect on the ovaries compared to single exposures [52]. Exposure to polystyrene nanoplastics and a phthalate mixture from gestational day 5 to gestational day 20 increased preimplantation loss and the number of small for gestational age fetuses compared to the single exposure and control groups [72]. Furthermore, co-exposure to polystyrene nanoplastics and a phthalate mixture increased the expression of targets in the placenta related to trophoblast cell differentiation (*Ppara*, *Pparg*) and angiogenesis-related growth factors (*Vegf*, *Hif-1*, and *Igf-1*) compared to controls in rats [72].

Interestingly, some studies have shown that co-exposure to nanoparticles and other contaminants has a protective effect compared to a single exposure [95, 96]. For example, arsenic exposure alone decreased the viability of CHO cells, but co-exposure of arsenic and AgNPs led to a protective effect on cell viability compared to control [95]. Mixtures of cerium dioxide nanoparticles (CeO_2NPs), used as additives in diesel fuels and as polishing agents, and benzo (a) pyrene led to different effects in human trophoblast cells compared to single exposures to CeO_2NPs or benzo (a) pyrene in human trophoblast cells [96]. Interestingly, a single exposure to benzo (a) pyrene caused DNA damage, increased γ-H2AX, stabilized tp53, and induced p21 compared to controls [96]. Co-exposure to benzo (a) pyrene plus CeO_2NPs caused similar effects, but the co-exposure did not induce γ-H2AX, suggesting a modulation of the genotoxic effect of benzo (a) pyrene by CeO_2NPs [96].

As many environmental chemicals, including nanoparticles and nanoplastics, can be found in the air, water, and food, it is highly likely that most humans and wildlife are exposed to nanoparticles and nanoplastics as mixtures rather than as single exposures. Research evaluating nanoparticle and nanoplastic exposure as mixtures with other environmental pollutants has been increasing, demonstrating different reproductive effects when compared to single exposures. More research in this regard is needed to better understand both nanoparticle and nanoplastic interactions with other pollutants.

Conclusions and future directions

Humans and other species are exposed to nanomaterials, leading to the absorption and distribution of nanomaterials in multiple reproductive organs and consequently, to reproductive toxicity (Tables 1 and 2). Specifically, nanomaterials disrupt the normal function of the HPG axis and impair ovarian function, altering folliculogenesis and steroidogenesis (Table 1). Furthermore, nanoparticles and nanoplastic exposure affect cyclicity, placental function, embryo development, and fertility, underscoring the broad impact of nanomaterial exposure on reproductive health (Table 2).

Assessment of human exposure levels to nanoparticles and nanoplastics is challenging. Using several models, recent research has estimated human exposure levels to nanoparticles and nanoplastics [97–99]. Despite the efforts, challenges in nanosized material quantification are still present as evidenced by several research studies [100, 101]. Some of the main key issues in measuring human exposure to nanomaterials include sample collection, preparation, and processing for quantitative and qualitative analysis [100, 101]. Detection of nanoplastics in complex biological samples remains challenging because of the low concentrations, diverse physicochemical properties, and interference from organic and inorganic matter [102, 103], leading to a lack of harmonized and reliable methodologies for pretreatment, separation, identification, and quantification of nanoparticles and nanoplastics [104, 105]. Thus, future studies should focus on the development of technologies that allow for better detection and quantification of nanoparticles and nanoplastics in the environment and biological matrices.

Notably, nanomaterial physicochemical characteristics and interactions with biological fluids and environmental factors can modulate nanomaterial interactions with reproductive tissues, potentially influencing their reproductive toxicity [1]. However, limited information is available on the mechanisms by which nanomaterials cause reproductive toxicity, including mechanisms that involve protein corona. Thus, future studies should investigate the interactions of nanomaterials with biological fluids, including reproductive fluids, to determine if nanomaterial-induced protein corona leads to toxicity in the reproductive organs. Future studies should also investigate the underlying mechanisms of nanomaterial-induced toxicity in reproductive organs because a better understanding of the mechanisms underlying nanomaterial-induced toxicity will set the foundation for the development of strategies to prevent or treat nanomaterial-induced adverse reproductive outcomes. Additionally, very few studies have examined the effects of nanoparticles and nanoplastics as part of mixtures, which is highly relevant given that humans are most likely exposed to nanoparticles and nanoplastics as parts of mixtures and not as single agents. Notably, the few studies that have examined the effects of mixtures on the reproductive system have described differential effects of the mixtures containing nanomaterials compared to single exposures. This raises concerns about the effects of nanomaterials alone as well as their potential to interact with other toxicants to affect reproductive functions. Thus, understanding physicochemical characteristics and interactions of nanoparticles and nanoplastics with environmental factors and biological fluids is essential for understanding the reproductive toxicity of nanoparticles and nanoplastics.

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Data availability

The raw data will be available upon reasonable request to the senior author.

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