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Ovarian toxic effects of micro- and nanoplastics (Review)

SHUORAN ZHAO[1*], WEITING YUAN[2*], PING LI[1] and JIEYONG YANG[3]

[1]Department of Critical Care Medicine, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong 264100, P.R. China;
[2]Emergency Department, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong 264100, P.R. China;
[3]Department of Obstetrics and Gynecology, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong 264100, P.R. China

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Abstract. Microplastics and nanoplastics (MNPs) have become widespread contaminants with notable impacts on reproductive health. MNPs have been found in human specimens, including follicle fluid, causing concerns regarding their negative impact on female fertility. The present review aimed to comprehensively examine the ovarian deleterious impacts of MNPs, and to analyze their toxicological mechanisms, impact on folliculogenesis and oocyte quality, transgenerational effects and influencing factors. Previous evidence suggests that MNPs can trigger oxidative stress, inflammatory responses, disruption of endocrine function, programmed cell death, endoplasmic reticulum stress, membrane structural damage, epigenetic modifications and DNA lesions in the ovary, resulting in impaired folliculogenesis, disrupted steroidogenesis and reduced reproductive capacity. The present review emphasized the impact of the MNP polymer type, size and surface characteristics on ovarian reproductive toxicity, and highlights some knowledge gaps that require attention, providing a reference for deeper understanding and mitigation of MNPs-induced ovarian toxicity.

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1. Introduction

Plastics, due to their several advantages, including low cost, versatility and outstanding endurance, have been widely employed in industries such as packaging applications and medical apparatuses (1). However, due to their extensive use and imperfect waste plastic recovery, plastics continue to accumulate in the ecological environment. Common plastic pollution includes microplastics (MPs; spanning 100 nm-5 mm) and nanoplastics (NPs; spanning 1 to 100 nm), collectively termed as MPs and NPs (MNPs) (2). Currently, the output of medical and household plastic waste continues to increase, with a marked portion remaining in the environment. Coupled with the fact that MNPs themselves can adsorb other toxic pollutants, this has led to notable health issues (3). Some commonly used disposable plastic products can release hundreds of millions MPs/l water during normal use (4). There are two key sources that account for the occurrence of MNPs: i) Direct manufacture and ii) formation through degradation by light, mechanical abrasion or biological processes (5). Common polymeric types of MPs include polystyrene (PS), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET) and polyvinyl chloride (PVC). MNPs exhibit persistent environmental existence and gradual aquatic accumulation, as well as in soil, atmosphere and inside organisms, thus posing substantial challenges to ecosystems and human health (6). MNPs can enter the human body via several exposure pathways, mainly covering oral intake, inhalational exposure and dermal contact (7). Oral intake appears to be the dominant exposure route (6). Notably, female mosquitoes may also inject NPs into humans and animals, as NPs can accumulate in their organs, particularly in the salivary glands (8). MNPs are detectable in tissues of lung, placenta and liver, as well as in body fluids of blood and follicular fluid of humans (9-11).

A key aspect of MNPs toxicity is associated with its function as a medium carrying chemical contaminants. With inherent features of small dimension, high specific surface area and hydrophobicity, MNPs are capable of efficiently adsorbing and carrying various pollutants such as

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Correspondence to: Dr Jieyong Yang, Department of Obstetrics and Gynecology, Yantai Affiliated Hospital of Binzhou Medical University, 717 Jinbu Street, Yantai, Shandong 264100, P.R. China
E-mail: 18753512078@163.com

Dr Ping Li, Department of Critical Care Medicine, Yantai Affiliated Hospital of Binzhou Medical University, 717 Jinbu Street, Yantai, Shandong 264100, P.R. China
E-mail: 2414434024@qq.com

[*]Contributed equally

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endocrine-disrupting chemicals (EDCs) and heavy metals, producing a 'Trojan horse' effect and thereby exacerbating their reproductive toxicity (12). It has been documented that MNPs are able to cross the biological barriers, including the intestinal, blood-brain, blood-testis and blood-follicle barriers, with accumulation in organs and tissues such as the ovary, further inducing a series of adverse biological effects, including reproductive toxicity (12).

Multiple studies have confirmed multi-pathway systemic exposure to MNPs, as demonstrated by Zuri *et al* (13), who systematically reviewed 91 studies and verified the detectable presence of MPs in human tissues and other specimens. MNPs pose potential health hazards by inducing oxidative stress (OS), inflammatory response and DNA damage (14), which are closely linked to the development of cardiovascular (15) and respiratory diseases (16) as well as cancer (17). Notable concentrations of MNPs exist in multiple physiological systems, including the digestive, reproductive, circulatory and respiratory systems, where PE, PP and PS predominate. The detection of NPs (<1 μm) remains inadequate due to technical limitations. Currently, no single technique can fully characterize NPs. Spectroscopic methods such as Fourier transform infrared spectroscopy and conventional Raman are limited by the optical diffraction limit, rendering identification below 1 μm unreliable (18). Electron microscopy (scanning/transmission electron microscopy) provides nanoscale morphology but lacks routine chemical identification, while destructive methods like pyrolysis-gas chromatography/mass spectrometry (Py-GC/MS) sacrifice particle size and shape information (19). Population-based techniques (e.g., dynamic light scattering and nanoparticle tracking analysis) cannot chemically distinguish NPs from natural organic matter and struggle with polydisperse samples (20). Emerging tools like surface-enhanced Raman spectroscopy and atomic force microscopy-infrared spectroscopy show promise but are not yet standardized (18,21). Consequently, reliable detection remains particularly problematic for particles below 100-200 nm in real environmental matrices. This analytical gap critically hinders exposure assessment and risk evaluation since the smaller size of NPs is expected to confer higher bioavailability and potential to cross biological barriers, yet the true extent of contamination and toxicity remains largely unknown. Balali *et al* (11) further summarized the multi-level effects of MNPs focusing on female reproductive health, covering molecular mechanisms spanning animals to humans.

Montano *et al* (22) were the first to confirm the presence of MPs at an average of 2,191 particles/ml within the follicular fluid sampled from 14 of 18 women subjected to assisted reproductive treatment. Follicular fluid MPs concentrations were positively associated with serum follicle-stimulating hormone (FSH) levels, a well-acknowledged biological indicator reflecting the impairment of ovarian reserve (23). Ni *et al* (24) further identified 1,739 MP particles belonging to 30 polymer types in human follicular fluid, such as PE (with a content as high as 22.284 mg/kg), PP, PS and PVC. In *in vitro* experiments using the same concentration and size range, it was verified that all particle types markedly inhibited the *in vitro* maturation of mouse oocytes; among them, 50 nm PE particles could directly impair the maturation of meiosis and oocyte developmental competence (24). The concentration of MNPs detected in human follicular fluid has reached the level that can induce oocyte maturation dysfunction and granulosa cell injury in experimental systems, and their polymer composition highly overlaps with materials demonstrated to exert ovarian toxicity in animal models (such as PE, PS and PVC). Although prospective cohort studies directly demonstrating that MNPs exposure leads to reduced human fertility are still lacking, considering the non-renewable nature of the ovarian follicle pool, MNPs exposure is sufficiently regarded as a potential risk factor for unexplained infertility, poor ovarian response and even premature ovarian failure.

There is currently no consensus on the human safe concentration or lethal dose of MNPs. Current toxicological evidence mainly originates from animal and *in vitro* studies (25-27), in which the MNPs concentrations adopted are generally notably higher than actual environmental exposure levels, leading to substantial uncertainties in the low-dose extrapolation of dose-response associations. Despite the meta-analysis conducted by Volsa *et al* (28) which confirmed concentration-dependent toxicity, the dose ranges used in individual studies vary markedly, ranging from μg/l (29,30) to mg/l levels (31), and unified standards are lacking. Notably, due to variations in MNPs regarding polymer composition and size profile, surface chemistry and environmental aging degree, it is challenging to establish a single safety threshold similar to that of chemical toxins.

As the central organ governing reproduction and endocrine function in female mammals, the ovary undertakes key functions, including follicular development, oocyte maturation and sex hormone secretion. As the basic unit of ovarian reserve and reproductive lifespan, normal follicular development is precisely regulated by endocrine and paracrine signals, and any disruption to this process can severely compromise female fertility (32). The ovary is vulnerable to environmental toxins mainly for the following reasons: First, the non-renewable nature of ovarian reserve means that any damage is likely irreversible (33); second, the high metabolic activity of growing follicles predisposes them to generate ROS, with these deleterious impacts further worsened by other toxicants; and third, the steroidogenic pathway is notably susceptible to EDCs (34,35). It has been documented that MNPs lead to a reduction in follicle quantity and ovarian dimensions, accompanied by impaired pregnancy rate, fertility and embryo formation, which causes severe damage to the female reproductive system (36). Notably, toxic effects on female reproduction induced by MNP exposure appears to be more notable than those in males (27). Given that MNPs have been found to accumulate in ovarian follicular fluid and reproductive tissues, understanding their adverse impacts on ovarian function has become a research hotspot (22). Various previous studies on ovarian-related toxicity following MNP exposure are summarized in Table I.

GCs are the major component of follicles, and their apoptotic process is tightly linked to follicular structural atrophy and subsequent atresia. The majority of follicular atresia is mediated by apoptosis (37). The growth and maturation of oocytes rely heavily on GCs. Oocyte developmental competence and follicle development can be impaired by GC dysfunction and defective communication between GCs and oocytes (38). As an important cell type in the ovary, E2 and

Table I. Ovarian reproductive toxic effects induced by MNPs.

Author, year	Species	MNPs types	Exposure method	Dosage	Exposure duration	Major reproductive toxic effects	(Refs.)
Hou *et al*, 2021	Wistar rats	PS- MPs	Potable water	0.015, 0.15 and 1.5 mg/kg/day	90 days	OS may trigger pyroptosis and apoptosis of ovarian GCs via the NLRP3/caspase-1 signaling cascade	(45)
Saeed *et al*, 2023	Wistar rats	PS-NPs	Co-culture with oocytes	2.5, 5 and 10 mg/kg/day	45 days	FSH, estradiol and testosterone concentrations increased, which was accompanied by a reduction in ovarian CAT and SOD levels	(247)
An *et al*, 2021	Wistar rats	PS-MPs	Potable water	0, 0.015, 0.15 and 1.5 mg/day	90 days	Wnt/β-catenin pathway activation mediates ovarian fibrosis and GC apoptosis via OS, which was accompanied by diminished ovarian reserve	(25)
Liu *et al*, 2022	ICR mice	PS-MPs	Oral administration	30 mg/kg body weight	35 days	Provoked ovarian inflammatory responses and deteriorated oocyte competence	(50)
Haddadi *et al*, 2022	Wistar rats	PS-MPs	Oral administration	0.1 mg/day	4 estrous cycles	Disrupted the estrous cycle and impaired follicular development	(26)
Wei *et al*, 2022	C57BL/6 mice	PS-MPs	Oral administration	0.1 mg/day	44 days	Diminished ovarian volume and follicle quantity, and reduced the secretion of FSH, LH and testosterone	(27)
Feng *et al*, 2022	C57BL/6 mice	PS-MPs	Oral administration	PS-MPs, 0.1 mg/day/mouse and Pb (1 g/l)	28 days	OS and PERK/eIF2α pathway activation triggered apoptosis, leading to eventual ovarian damage	(63)
Zhang *et al*, 2023	Kunming mice	PS-NPs	Potable water	0.4, 4 and 40 mg/kg/day	30 days	Oocyte maturation, fertilization, embryonic development and fertility are impaired via induction of ROS overproduction, apoptosis activation, mitochondrial dysfunction, meiotic spindle abnormalities and actin cytoskeleton disruption	(100)
Wu *et al*, 2023	Mice	PS-MPs	DEHP and PS-MP + DEHP group via diet, PS-MP and PS-MP + DEHP group via potable water	DEHP and PS-MP + DEHP group was fed with 200 mg/kg DEHP diet, while the PS-MP and PS-MP + DEHP group was administered 100 mg/l PS-MPs	35 days	Elevated ROS levels contribute to DNA damage, cell cycle arrest and necroptosis in mouse ovarian GCs	(31)

Table I. Continued.

Author, year	Species	MNPs types	Exposure method	Dosage	Exposure duration	Major reproductive toxic effects	(Refs.)
Zeng *et al*, 2023	Balb/c mice	PS-NPs	Oral administration	1 mg/day	5 weeks	GC apoptosis and ovarian dysfunction were induced, resulting in declined fertility of female mice, which was mediated by OS and abnormal Hippo pathway activation	(51)
Gholiof *et al*, 2025	C57BL/6 mice	PS-NPs	Potable water	100 or 1,000 μg/l daily	29 days	Declined antral follicle size, lowered corpora lutea density, elevated atretic follicle density, extended estrous cycle duration and reduced serum progesterone concentrations	(29)
Zhang *et al*, 2024	Zebrafish (*Danio rerio*)	Polylactic acid powder	Culture water	10 mg UPLA or DPLA with 2 l circulating water, 5 mg/l exposure fluid changed once a day	5 weeks	Disrupted OS homeostasis in zebrafish ovary	(248)
Adhikari *et al*, 2024	Zebrafish (*Danio rerio*)	PS-MPs	Culture water	40.1 μg/l/day	21 days	Potentially triggered PMOS and subsequent progression to ovarian fibrosis	(32)
Wang *et al*, 2025	SD rats	MP	Oral administration	0.6, 6 and 60 mg/kg/day MP	Once a day for 3 days for non-pregnant female rats; intraperitoneally injected on days 1, 2 and 3 of gestation for pregnant rats	Decrease in primordial follicles coupled with notably enhanced primary and secondary oocytes implied oocyte pool aberrant overactivation	(249)

MNPs, microplastics and nanoplastics; PS- MPs, polystyrene microplastics; NPs, nanoplastics; OS, oxidative stress; GCs, granulosa cells; NLRP3, NLR family pyrin domain containing 3; Caspase-1, cysteinyl aspartate specific protease 1; CAT, Catalase; SOD, superoxide dismutase; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ROS, reactive oxygen species; UPLA, unphotodegraded polylactic acid; DPLA, photodegraded polylactic acid; PMOS, polyendocrine metabolic ovarian syndrome; DEHP, di(2-ethylhexyl) phthalate.

estrogen are mainly produced by GCs upon FSH stimulation and exert critical functions in oocyte maturation and normal follicular development (39). GC dysfunction commonly leads to pathological folliculogenesis. E2 produced by GCs, together with other gonadotropins in serum, serves as an indispensable regulator for antral folliculogenesis (26). With regard to the intrafollicular microenvironment, on the one hand, cytokines derived from GCs regulate oocyte activation and maturation in quiescent primordial follicles, as well as antral follicle growth (40). On the other hand, cumulus cells differentiated from GCs are required for nourishing oocytes throughout the late phase of oocyte maturation (41). GCs cooperate with theca cells to participate in estrogen production, folliculogenesis, oocyte ripening and ovulatory process that are tightly modulated by estrogen (42). Aggravated GC apoptosis may cause impaired estrogen production (43) and progression of follicles to the antral stage (44). In mammalian *in vivo* models, including rat, mouse and porcine models, GC apoptosis acts as the primary mechanism of follicular atrophy (27,45,46).

Regarding direct evidence for human health concerns, it must be acknowledged that there is currently a lack of prospective epidemiological evidence directly linking MNPs to human ovarian dysfunction. The existing studies closest to providing direct evidence cover the following two aspects: i) Montano *et al* (22) reported for the first time the presence of MPs in human follicular fluid and observed a positive association between their concentration and FSH (22); and ii) Ni *et al* (24) confirmed that fluorescence-labeled MP beads at comparable concentration and particle size ranges to MNPs within the follicular fluid of humans could inhibit *in vitro* oocyte maturation in mice. Although these observational evidence are suggestive of toxic effects, current experimental models rely on high concentrations of virgin polymers. Thus, caution is still required when extrapolating findings to real human exposure scenarios, and additional mechanistic and epidemiological studies at environmentally relevant exposure levels are needed.

The present review aimed to systematically summarize the latest scientific evidence concerning the ovarian-associated toxic impacts of MNPs on the reproductive system; elaborate on the molecular mechanisms underlying MNPs-induced OS, inflammation, endocrine disruption, programmed cell death, endoplasmic reticulum stress (ERS), membrane structural damage, epigenetic modification and DNA damage; and explore the potential pathways through which MNPs affect reproductive outcomes via interfering with endocrine and epigenetic regulation. By sorting out the complete cascade from environmental exposure to intracellular injury, the present review aimed to increase the current understanding of MNPs-mediated ovarian-related reproductive toxicity and provide support for risk assessment and mitigation strategies.

2. Ovarian toxicity induced by MNPs

Detrimental impacts of MNPs on ovarian reserve and follicular development. Folliculogenesis is the developmental process of primordial follicles into mature ones, named ovulatory follicles, and is notably sensitive to environmental perturbations. Exposure to MNPs can perturb follicular development throughout multiple developmental stages, spanning the maturation from primordial follicles to antral ones, and exert adverse effects on ovarian reserve, reproductive lifespan and fertility (34,38,47,48).

Adverse impacts of MNPs on ovarian functional reserve. The primordial follicle pool can, to some extent, represent ovarian reserve, and its depletion or premature activation accelerates reproductive aging and potentially lead to ovarian dysfunction. In the context of female fertility, ovarian reserve generally refers to abundance and developmental quality of ovarian follicles (49). MNP exposure at 0.1/1 mg/d, 30 mg/kg body weight or 100 mg/l in mice induces a marked decline in follicle abundance and an accumulation of atretic follicles, thereby disrupting ovarian reserve capacity and fertility (27,31,50,51). PS-MPs can activate the NLRP3 inflammasome/caspase-1 signaling cascade through OS, triggering pyroptotic and apoptotic processes in granulosa cells (GCs) (45) (rat model, exposure at 0.015, 0.15 or 1.5 mg/kg/d). As supporting cells for follicular development, GCs primarily provide nutrients and growth factors to oocytes. Excessive apoptosis of GCs induces aberrant folliculogenesis, aggravated follicular atresia and reduced ovarian reserve capacity (25). Furthermore, exposure to EDCs carried by MNPs can deplete the primordial follicle pool, disrupting folliculogenesis and steroidogenesis (52). Exposure to bisphenol A (BPA), the most common type of EDC, markedly decreases the follicle and corpus luteum counts across all developmental stages (53), and increases the atretic degeneration of follicles and the proportion of multi-oocyte follicles, eventually causing a decline in ovarian functional reserve (54).

MNPs can harm the initial follicle reserve by increasing the atretic degeneration of follicles or premature activation (38,48). PS-NPs exposure in murine models leads to declined ovarian reserve in the female offspring, characterized by a marked decrease in the abundance of primordial and primary follicles in adult ovaries (38,48) (mice model, exposure at 30 mg/kg/day or 0.5 to 144 mg/kg). Precocious primordial follicle activation consumes the pool of quiescent primordial follicles (48), driven by dysregulation of the PI3K/Akt/forkhead box protein (FOX)O3a/mTOR signaling pathway to maintain the quiescent state of primordial follicles (48). Meanwhile, mTOR signaling is upregulated, promoting follicle activation and growth (48). Although primordial follicle activation is essential for reproductive function, premature or excessive activation leads to prematurely depleted ovarian reproductive reserve.

MNPs reduce ovarian reserve through multiple mechanisms. In addition to the aforementioned aberrant induction of GC apoptosis, MNP exposure can also trigger OS and inflammation, which further disrupt ovarian endocrine homeostasis and the follicular microenvironment, and interferes with the function of essential enzymes for hormone biosynthesis, thereby downregulating anti-mullerian hormone (AMH) and estradiol (E2). As a notable marker reflecting the status of ovarian reserve, AMH levels can influence the rate at which the ovarian reserve is depleted by inhibiting primordial follicle activation and modulate the development of growing follicles via reducing their sensitivity to FSH (55). MNP exposure can induce a reduction in AMH levels and accelerate depletion of the follicle pool, suggesting that MNPs exposure impairs ovarian reserve function (56). In addition, ovarian fibrosis induced by MNPs can also lead to the depletion of ovarian reserve capacity (25) (rat model, exposure at 0, 0.015, 0.15 or 1.5 mg/d).

Interference of MNPs with follicular growth and maturation. In addition to effects on the primordial follicle pool, MNP exposure exerts detrimental effects on follicle development. It elevates the abundance of atretic and cystic follicles, interferes with maturation, differentiation and functional specification of follicles, perturbs the hormonal balance in females, and consequently undermines intact reproductive function in females (25,26,57). Furthermore, MNP exposure leads to a notably decreased abundance of preovulatory follicles and growing follicles in marine medaka (30) (*Oryzias melastigma*, exposure at 0, 2, 20, or 200 mg/l). Gastrointestinal exposure to MNPs reduces the number and volume of growing follicles in the ovary, and results in a thinner granulosa layer in secondary follicles, as well as decreased numbers of GCs and corpora lutea (25,27) (rat at 0, 0.015, 0.15 or 1.5 mg/d; mice at 0 or 0.1 mg/d), indicating that MNPs can notably damage follicular development and maturation.

Ovarian infiltration by MNPs induces inflammation and OS, ultimately reducing the abundance of antral follicles in mice (25,50). OS, a major cause of cellular damage induced by exogenous chemicals, is markedly involved in the progression of follicular developmental dysfunction and may be one of the initiating factors of selective follicular atresia (58). Furthermore, it is widely regarded as a prevalent mechanistic pathway contributing to EDC-related reproductive malfunction (59). Under OS, prolonged JNK and ERK activation could counteract the AKT-dependent survival pathway by upregulating PTEN or activating FOXO transcription factors (60). In GCs, MNPs may induce follicular atresia by inhibiting the AKT pathway (38). OS, hormonal imbalance or impaired GC function will accelerate follicular atresia (61). Antioxidants and reactive oxygen species (ROS) are implicated in the modulation of ovarian follicular development. Age-related decline in follicular quality is directly attributed to excessive ROS generation (62,63), leading to GC apoptosis and follicular atresia (25). GCs mediate folliculogenesis through facilitating the conversion of testosterone into E2. GC apoptosis triggered by ROS accounts for the reduction in E2 levels (64). Treating mice with oxidants results in increased apoptotic GCs and atretic follicles in the ovary, as well as elevated FoxO1 levels in GCs (65). FoxO1 regulates the expression of pro-apoptotic target genes such as *BIM, FASL,* p53 upregulated modulator of apoptosis and *TRAIL*. This process facilitates GC apoptosis and ultimately contributes to follicular degeneration (66).

As one of the most common EDCs, BPA can induce OS, interfere with ovarian steroid hormone synthesis, impair oocyte ripening and induce follicular developmental disorders (67). BPA interferes with the follicular levels of cell cycle-related proteins to induce cell cycle dysregulation. It arrests the G_2/M phase transition in GCs of mouse antral follicles, markedly elevates the levels of Bax and Bcl-2, triggers GC apoptosis and ultimately facilitates antral follicle atresia (68). BPA exposure also downregulates genes related to follicular development such as FIGLA and H1FOO (69) and impairs follicular development by reducing the expression of StAR and P450 aromatase (70). Furthermore, BPA blocks oocyte CpG DNA demethylation in Lhx8, thereby inhibiting follicular growth to certain extent (71).

Exposure to another type of EDC, di(2-ethylhexyl) phthalate (DEHP), may also reduce E2 levels by downregulating aromatase expression (72), probably involving a PPAR-mediated signaling pathway in GCs. By regulating cell cycle- and apoptosis-related factors, phthalate mixtures are capable of inhibiting the proliferation of antral follicles in mice (73). As a derivative of DEHP, phthalates can impair follicular development via modulating genes involved in folliculogenesis including c-KIT, KITl, GDF9 and ATM (74). By inducing miRNAs, DEHP inhibited GC proliferation and KITL/GDF9-mediated anti-apoptosis, while elevating Bax/Bcl-2 to drive apoptosis. Monomethyl ether of phthalate, another derivative of DEHP, can damage follicular health by inducing OS and reducing the expression of antioxidant enzymes (75). The growth of antral follicles can be inhibited by cell cycle arrest induced by dibutyl phthalate (76).

MNPs also induce metabolic disorders and exert an indirect detrimental effect on reproductive outcomes. Folliculogenesis and energy metabolism are disrupted in female mice upon MNPs exposure, which is accompanied by diminished mitochondrial membrane potential and dyshomeostasis of calcium. Imbalance in ovarian energy homeostasis will exert negative impacts on follicular development and function (50,77).

Reproductive cyclicity responses to MNP exposure. Estrous cycle disturbance can be induced upon exposure to MNPs, with PS-NPs-exposed rats exhibiting prolonged or irregular estrus cycles (78) (rat, exposure at 0 or 0.015 mg/d). This cyclical disruption is associated with reduced serum progesterone levels and decreased luteal cell numbers (78). Exposure of adult rats to PS-MPs results in a markedly shortened estrus cycle, accompanied by abnormal follicular maturation and differentiation (26). The decrease in E2 concentration caused by PS-MPs exposure may be due to disruption of the hypothalamic-pituitary-gonad (HPG) axis, leading to increased FSH and luteinizing hormone (LH) concentrations (79) (rat, exposure at 0, 1, 3, 6 or 10 mg/kg bw-day). Apoptosis of GCs may contribute to E2 depletion. GC apoptosis leads to E_2 depletion through mechanisms involving multiple levels, with the core being that apoptotic signals can directly or indirectly inhibit the expression and activity of the rate-limiting enzyme for estradiol synthesis-aromatase (CYP19A1) (80). LRH-1 is a key transcription factor regulating CYP19A1 expression (80,81), while endoplasmic reticulum stress can trigger GC autophagy (82) and impair estradiol synthesis (83). The two pathways are involved in coupling apoptosis with impaired hormone synthesis (80,83). Ovarian GCs are the primary site of estradiol synthesis under physiological conditions in the body, and their reduction in number and functional decline may ultimately lead to E_2 depletion (84). Within the ovary, the synthesis of E2 is primarily mediated by GCs through the well-established 'two-cell, two-gonadotropin' model. In this model, theca cells produce androgens under the stimulation of luteinizing hormone, and subsequently, GCs convert these androgens into estrogens via the action of aromatase (CYP19A1) under the regulation of follicle-stimulating hormone (85). Thus, in the follicular microenvironment, aromatase expression in GCs represents the main local source of E2 (86,87). Although extra-gonadal tissues such as adipose tissue, skin, and brain also express aromatase and can synthesize estrogens from circulating androgen precursors (88,89), these peripheral sources primarily influence systemic E2 levels, particularly in postmenopausal women, rather than local intrafollicular E2 (88). Therefore, in the context of this article, E2 depletion is mainly attributed to the loss of ovarian GCs. Additionally, the adverse outcomes induced by PS-MPs on theca and luteal cells may also lead to E2 imbalance (79). Furthermore, altered lipid metabolism induced by PS-MPs may also account for the reduced serum E2 concentration observed in PS-MPs-exposed animals (90,91) (Zebrafish, exposure at 20 mg/l, or 100 and 1,000 mg/l). In histopathology, it induces the accumulation of lipid droplets in the liver (90). At the molecular level, it upregulates lipogenesis-related genes (such as ACC1, FAS and SREBP1A) while downregulating fatty acid β-oxidation genes (such as ACO and CPT1) (91).

Given that cholesterol is an essential precursor for steroid hormone synthesis, this PS MP-induced disruption of lipid metabolism may directly impair the availability of precursors or signaling pathways required for E2 production, thereby leading to reduced serum E2 levels. Decreased E2 levels result in disrupted estrous cycles or menstrual cycle disorders via the HPG axis. The shortened estrous cycle is attributed by to follicular loss, elevated apoptotic activity and hormonal disturbance (92). In addition, irregular estrous cycles were also observed in rats after exposure to BPA. Level changes in the clock circadian regulator of Per1 and reproductive peptide phoenixin within the hypothalamus indicates that BPA interferes with hypothalamic regulation of the preovulatory LH surge (93), which may be mediated by changes in estrogen (94). However, Wei *et al* (27) found that exposure to larger PS-MPs (5-5.9 μm) did not markedly alter the estrous cyclicity of mice, which may underscore the size-dependent nature of MNP toxicity (mice, exposure at 0 or 0.1 mg/d). Furthermore, inflammatory cytokines and ROS can disrupt estrous cycles and steroidogenesis, and meiosis and the maturation of oocytes' cytoplasm (95).

Therefore, MNPs can disrupt the estrous cycle through multi-target and multi-pathway mechanisms. MNPs may disturb hormonal homeostasis via targeting the hypothalamic-pituitary-ovarian (HPO) axis. MNPs themselves or derived EDCs can affect the release of gonadotrophin-releasing hormone (GnRH), FSH as well as LH (96), while downregulating crucial enzymes (Cyp11a and Cyp19a) participating in ovarian steroidogenesis, resulting in imbalanced E2 levels (38,97) and interfering with follicular development, ovulation and corpus luteum function (29). This represents one of the core mechanisms by which MNPs disrupt the estrous cycle. In addition, NPs are capable of traversing the follicular blood barrier and trigger direct impairment of oocytes, GCs and theca cells, inhibiting follicular development and ovulation (29,98,99). Finally, following cellular internalization, MNPs stimulate excessive production of ROS, inducing oxidative DNA lesions, cell cycle detention and necroptotic cell death in GCs, aggravating follicular atresia and thereby impairing the estrous cycle. The mechanistic evidence described in this section is derived from *in vitro* cell lines (human KGN GCs), rodent animal models (rats/mice), aquatic model organisms (zebrafish/medaka) and livestock models (pigs/cattle). There are differences in ovarian physiological structure and MNP metabolic kinetics among different species. Among the available evidence, only previous rat and mouse studies have provided a complete *in vivo* evidence chain of ovarian toxicity, while human research is currently limited to the identification of follicular fluid-derived MPs and *in vitro* culture experiments of GCs (22,24). Direct evidence of MNP toxicity obtained from human ovarian tissues is still lacking. The systematic review conducted by Volsa *et al* (28) indicated that the majority of published studies on MNPs' reproductive detrimental effects in mammals are based on experimental animals (*Mus musculus*/*Rattus norvegicus*), while only a few studies have adopted human cell models (such as the KGN GC cell line). The effect endpoints are inconsistent between *in vitro* and *in vivo* experiments, and direct extrapolation of such findings from high-concentration *in vitro* exposure to chronic low-dose *in vivo* conditions merits considerable caution.

Effects of MNPs on the quality and developmental potential of oocytes. Advances in understanding the influence of MNPs on oocyte quality rely entirely on non-human models, including mouse superovulated oocytes (100), porcine oocytes (101,102), bovine oocytes (103) and zebrafish oocytes (104). Direct research on human oocytes is only derived from indirect associations in assisted reproduction clinical practice. Montano *et al* (22) reported that follicular fluid MPs concentration was positively associated with FSH, whereas no notable association was observed with fertilization efficiency, abortion rate or live delivery rate. Ni *et al* (24) confirmed that various MPs detected in follicular fluid at physiological concentrations markedly inhibited mouse oocyte maturation *in vitro*. However, there is still no experimental evidence regarding direct MNPs exposure to donated human oocytes. Oocyte quality is determined by the complex regulatory mechanisms governing follicular and oocyte developmental maturation. MNP exposure impairs oocyte quality through multiple mechanisms (34,105). Exposure to MNPs has been demonstrated to reduce the rates of first polar body emission and viable oocytes after superovulation, exerting adverse effects on their quality (50) (mice, exposure at 30 mg/kg body weight). In a mouse model, consecutive 30-day PE-MP exposure could elicit oocyte DNA damage, apoptotic cell death, OS and mitochondrial dysfunction and lead to a decreased germ cell maturation rate (100) (mice, exposure at 40 mg/kg per day). In zebrafish, NPs exposure can trigger OS in oocytes, and induce DNA damage and apoptosis, thereby disrupting normal oocyte development and maturation (104) (postvitellogenic follicles, exposure at 100 or 400 ng/ml). Furthermore, women with elevated serum BPA levels exhibited reduced proportion of mature oocytes (106).

Impaired meiotic maturation. The process of oocyte maturation consists of meiotic reinitiation from meiotic arrest in prophase I, advancement to the first meiotic metaphase, release of the first polar body and maintenance of the second meiotic metaphase arrest until fertilization occurs. This process requires precise coordination of the cytoskeleton and metabolic control. Exposure to MNPs can impair the meiosis process of oocytes (105) (mice, exposure at 16.67 mg/kg/d).

Low-dose exposure to PS-MPs can induce meiotic maturation defects in oocytes (107) (mice, exposure at 100 μg/l PS-NPs in drinking water), which are associated with meiotic apparatus assembly (108) and chromosomal segregation abnormalities (109). Elevated OS levels resulting from PS-MPs exposure disrupt the cytoskeleton, spindle assembly and chromosomal alignment (110). BPA inhibits meiotic maturation of oocytes by suppressing MAPK phosphorylation, reducing actin expression and interfering with cumulus-oocyte gap junction communication, leading to cell cycle delay, centromere protein degradation, spindle structural abnormalities and chromosomal alignment disorder (111-113). It also disrupts steroidogenesis and affects fetal meiotic initiation (114,115). Exposure to cadmium (Cd) adsorbed by MNPs can block the meiotic process by inducing mitochondrial damage (116). Therefore, MNPs may cause impaired meiotic maturation of oocytes by disrupting the cytoskeleton, interfering with energy metabolism and inducing OS.

Mitochondrial dysfunction. Mitochondria can produce ATP and regulate calcium signaling as well as apoptosis, serving as a key role in determining oocyte maturation and quality (117). Exposure to MNPs leads to mitochondrial dysfunction in oocytes, commonly manifested as reduced membrane potential, decreased ATP content and altered mitochondria distribution (118). A marked decrease in ATP levels is associated with impaired oocyte maturation and developmental capacity (38). Mitochondria act as both source and target of ROS. Excessive ROS can lead to a cyclic aggravation of oxidative injury and energy exhaustion (119). Due to the maternal inheritance characteristics of mitochondria, their dysfunction in oocytes may also pose transgenerational effects (120).

ROS can oxidize oocyte mitochondrial proteins, trigger mitophagy and disturbed mitochondrial distribution, resulting in impaired oxidative phosphorylation and reduced ATP production (121), which in turn disturbs cell cycle regulation, and assembly of the mitotic spindle and chromosome segregation, leading to blockade of physiological meiotic progression from prophase I to metaphase II (118). PS-MPs and PLA-MPs suppress lipid supply in GCs by downregulating lipoprotein lipase (LPL, a key enzyme in lipid metabolism), disrupt the oocyte energy microenvironment and induce OS and apoptosis (122) (mice, exposure at 25 mg/kg/d). PS exposure also interferes with PPAR function, impairs vitellogenin structure and yolk energy reserves and affects oocyte development (123) (zebrafish, exposure at 0.5 mg/l PS in fish water). MPs further inhibit choline and creatine metabolism, deplete glutathione (GSH), disrupt redox homeostasis and aggravate DNA damage and apoptosis (102) (oocytes, exposure at 1, 10 and 50 μg/ml). DEHP exposure elevates mitochondrial ROS levels, reduces ATP production and exacerbates spindle abnormalities and the risk of chromosomal aneuploidy (124). Pollutants such as PE in follicular fluid can also indirectly impair oocyte quality via metabolic disorders, immune responses and dysregulated steroidogenesis (125). MNPs and chemical contaminants systematically disrupt oocyte maturation and developmental potential through mitochondrial dysfunction, metabolic imbalance and OS.

Oocyte death. He *et al* (101) reported that exposure to PS-NPs could trigger iron-dependent cell death in swine oocytes and cause marked toxic damage to the cytoskeletal network and mitochondrial organelles (oocytes, exposure at 0, 25, 50 and 100 μg/ml). The underlying mechanism may involve elevated ROS and malondialdehyde (MDA), which further upregulate the levels of both transferrin receptor (TfRC) and acyl-CoA synthetase long-chain family member 4 (ACSL4). Several studies have observed negative effects of MP exposure on oocytes in different models. In mice, MP exposure disrupts oocyte maturation and quality through excessive ROS production and subsequent increased apoptosis (100) (mice, exposure at 40 mg/kg per day). In *Drosophila*, multigenerational continuous exposure to PS-NPs causes oocyte apoptosis, necrosis and reduced oocyte production (126) (*Drosophila melanogaster*, exposure at 1,10, 50, and 100 mg/l). In bovine oocytes, MP exposure leads to maturation arrest, proteomic alterations and elevated expression of apoptotic genes (127). Exposure of PS-MPs to fish oocytes may impair vitellogenin expression levels via modulation of the SIRT-1/p53 cascade and steroid synthesis, thereby affecting oocyte development and maturation (128) (zebrafish, exposure at 50 and 500 μg/l).

Cumulus cell dysfunction. The bidirectional crosstalk between oocytes and cumulus cells plays a key role in regulating oocyte quality. Cumulus cells represent a specialized subtype of GCs that provide nutrients and facilitate information exchange for oocytes through gap junctions and paracrine signaling (129). Transzonal projections (TZPs) serve as a bridge for molecular exchange between cumulus cells and oocytes. Exposure to MNPs disrupts this communication through various mechanisms, such as MNPs-induced apoptosis or dysfunction of granulosa/cumulus cells, which can lead to decreased external support for oocytes (45,50). Exposure to MPs can markedly reduce TZPs, altering the microenvironment for oocyte maturation and ultimately leading to abnormal oocyte development (122).

BPA and its analogue bisphenol S (BPS) can lead to decreased oocyte maturity, potentially by disrupting the secretion of key oocyte proteins and communication with cumulus cells (130). Exposure to BPA/BPS may cause an imbalance in cAMP/cGMP within oocytes, thereby inducing premature activation of meiosis (130). Dysfunction of GCs and disruption of communication with oocytes severely impair oocyte quality and follicular development (38).

Collectively, the aforementioned findings indicate that the impairment of oocyte quality by MNPs is not mediated by isolated pathways but rather by an interlinked network of cellular disturbances, in which OS and mitochondrial dysfunction are the central hubs. MNP exposure initially triggers excessive generation of ROS, which simultaneously damages mitochondrial membranes (reducing ATP output), oxidizes cytoskeletal proteins (disrupting spindle assembly and chromosome alignment) and activates apoptotic and ferroptotic cell death cascades, which is accompanied by upregulated TfRC together with ACSL4 under elevated MDA levels. The resulting ATP deficit further compromises energy-intensive processes such as meiotic progression and cortical actin maintenance, while mitochondrial collapse and ROS leakage constitute a self-amplifying loop that aggravates DNA damage and organelle injury. Concurrently, MNPs impair the metabolic and communicative functions of cumulus cells by downregulating LPL and depleting GSH, leading to shortened TZPs, imbalanced cAMP/cGMP signaling and premature meiotic resumption. Co-contaminants (such as BPA and Cd) further intersect with this network by perturbing MAPK phosphorylation and steroidogenesis, exacerbating gap-junction disruption and energy depletion. Thus, the decline in oocyte developmental competence results from a cascade in which OS, mitochondrial failure, cumulus cell dysfunction and cell death pathways are mechanistically coupled and mutually reinforcing, rather than operating in parallel.

Transgenerational effects of MNPs-induced ovarian toxicity. One of the most concerning adverse impacts of MNPs-mediated reproductive toxicity is its transgenerational effects, namely the impacts on offspring and subsequent generations not directly exposed to MNPs. Gestational and lactational exposure to MNPs can cause adverse impacts on the reproductive function in progeny (100).

PS-NPs can facilitate their transgenerational transfer by interfering with plasma proteins associated with oocytes, thereby triggering marked reproductive toxicity (131) (zebrafish, exposure at 1 mg of PS NPs per gram of fish). Maternal exposure exerts detrimental effects on oogenesis, gamete fusion and embryogenesis, as well as provoking ROS overproduction and mitochondrial structural and functional abnormalities, while reducing fertility in the offspring (100). Budhwar *et al* (132) systematically summarized the transgenerational transport and bioaccumulation of MNPs via the placenta and mammary gland, which reveals that MNPs induce developmental toxicity, OS, DNA damage, inflammation and metabolic and endocrine disorders in offspring, with a positive feedback amplification mechanism of ROS-induced ROS release. The cross-generational impacts of PS-NPs may originate from up taking pollutants from maternal bodies into oocytes. Previous research using zebrafish models has validated the transgenerational transfer of PS-NPs from parental generation to their progeny, accompanied by abnormal growth and development (133) (zebrafish, exposure at 10, 25, 50 and 100 μg/l). This progression is notably associated with the quality of parental germ cells and fluctuations in sex hormone levels (134). For instance, altered estrogen levels can disturb gametogenesis and transmit adverse effects to offspring (135). Zhang *et al* (136) found that maternal exposure to PS-NPs (zebrafish, exposure at 0, 200 and 2,000 μg/l) led to a notable decline in E2 and testosterone levels of F1 generation, upregulated Sox9a expression and downregulated Fox12a in F1 larvae, indicating that it mediates reproductive toxicity and affects progeny by perturbing the HPG axis. Fluorescent tracing showed the presence of PS-NPs in placenta and the gastrointestinal tract, indicating their capability to cross the placental barrier and be transmitted through breast milk (48). Regarding MNP transplacental transmission, two major pathways of placental transport during gestation and lactational transfer via breast milk are currently recognized. Although limited MNPs could be transferred from placenta to the embryo during pregnancy (137) and transmission via breast milk is the main route after parturition, a systematic review by Budhwar *et al* (132) indicated that MNPs can pass through the placenta into fetal bloodstream and deposit in the fetus, with endocytosis and transcytosis in placental villous trophoblasts serving as the primary transmembrane mechanisms. The quantity of MNPs transported to the embryo/fetus is mainly affected by particle size (NPs <100 nm are more permeable), surface charge (positively charged particles cross more easily) and protein corona formation. Notably, MPs have been identified in human placenta (138), and the abundance of MPs in human breast milk can reach several μg/l (138). Therefore, for human fetuses and neonates, MNP exposure may persist from the intrauterine stage to the end of lactation, resulting in a dual-hit effect. Cheng *et al* (48) found that gestational and lactational exposure transfers PS-NPs to progeny ovaries through placental transfer and lactational exposure, activates the AKT-FOXO3a pathway to trigger primitive follicle precocious activation, and ultimately reduces follicular reserve and fertility in adult female offspring.

In addition, MNPs can also be transferred from maternal oocytes to the embryonic yolk sac via vitellogenin (131). Intergenerational reproductive toxicological impacts induced by PS-NPs is also manifested as suppressed reproductive capacity and impaired gonadal development. The underlying mechanisms involve dysregulation of genes associated with germ cell apoptosis. DNA damage enhances apoptosis by activating the ATL-1 and the p53 counterpart CEP-1, alongside suppressing the levels of RAD-51-mediating DNA recombination and repair, leading to the accumulation and inheritance of DNA damage (139). The presence of MPs in human placental tissue further substantiates the potential transgenerational risks (138). Transgenerational toxicity relies not only on the deposition of DNA lesions in germ cells but also on epigenetic reprogramming. Yu *et al* (140) revealed that PS-NPs and butyl paraben synergistically trigger transgenerational reproductive toxicity at the highest dose that did not cause any detectable harm. At the mechanistic level, SET-2 drives the elevation of H3K4me3, and this modification can be inherited to the non-directly exposed F4 generation, indicating the epigenetic basis of transgenerational effects. Similarly, Chen *et al* (141) reported that photochemically aged PS-NPs exert intergenerational reproductive impairment by altering H3K4 and H3K9 methylation levels, which involves the regulation of key histone-modifying enzymes (Spr-5, Met-2 and Set-17) (larvae, exposure at 0.1-100 μg/l). Therefore, the transgenerational reproductive toxicity of MNPs is not caused by a single mechanism, but is achieved through the synergistic effects of physical transport via the placenta/breast milk, accumulation of germ cell DNA damage (RAD-51 inhibition and activation of the ATL-1/CEP-1 apoptotic pathway), disruption of the HPG axis endocrine programming and reprogramming of histone modifications (H3K4me3 and H3K9me). Hormonal disruption, OS, DNA damage and epigenetic alterations collectively contribute to intergenerational reproductive impairment.

Impacts of MNPs on GC function. Following gastrointestinal absorption, MNPs can penetrate the blood-ovarian barrier, and GCs represent major targets of MNPs, eliciting multiple cytotoxic effects (27,50,51). Accumulating evidence indicates that PS-NPs intensify OS via blocking the PI3K-AKT signaling cascade, activating p53 while suppressing superoxide dismutase (SOD)2 expression (142). The inactivation of this pathway leads to reduced mTOR activity and induces excessive autophagy, thereby reducing E2 synthesis by suppressing CYP19A1 and FSH receptor expression (143). AKT inhibition promotes Bax/caspase-7 upregulation and Bcl-2 downregulation, driving cell apoptosis, ultimately resulting in GC dysfunction, decreased AMH levels and ovarian fibrosis (25,144). BPA can reduce E2 and progesterone levels by increasing the ratio of Bax to Bcl-2, inducing G_2-to-M stage blockade and triggering autophagy mediated by AMPK/mTOR/ULK1 (46). MNPs-induced OS can directly damage the ER structure by generating excessive ROS, indicating that OS may be upstream of ERS (63). GC dysfunction gives rise to elevated gonadotropins (LH/FSH) through the negative feedback mechanism of the HPO axis, thereby leading to endocrine disorders (27). In summary, PS-NPs and BPA collectively disrupt the ovarian microenvironment through multiple pathways, including PI3K-AKT inactivation, OS, dysregulated autophagy and activated apoptosis, posing a threat to female reproductive health.

MNPs-induced ovarian fibrosis. MNPs can accumulate in animal ovaries and GCs, induce ovarian fibrosis through multiple pathways and impair ovarian function (25,145,146) (rat, exposure at 0, 0.015,0.15 and 1.5 mg/d). OS serves as a core inducer. MNPs exposure promotes ROS accumulation, upregulates MDA levels and suppresses the antioxidant enzymatic activities of SOD, catalase and glutathione peroxidase 1 (147). Furthermore, low-dose MNPs can temporarily activate the Nrf2/antioxidant response element antioxidant pathway, whereas high-dose or long-term exposure inhibits this pathway, further exacerbating OS and leading to ovarian fibrosis (148). OS can activate multiple signaling pathways involved in regulating fibrotic alteration in the ovary, with the Wnt/β-catenin pathway being particularly critical. ROS can promote enhanced levels of key proteins within this cascade and nuclear translocation of β-catenin, upregulate fibrotic markers such as TGF-β, fibronectin, α-SMA and type I/III collagen, and drive the proliferation and transition of fibroblasts to myofibroblasts alongside extracellular matrix accumulation (25,144,149). This process can be reversed by N-acetyl-L-cysteine (NAC) intervention (25). PS-MPs can trigger impaired ovarian reserve by triggering the NLRP3-mediated caspase-1 cascade and induce ovarian fibrosis through the toll-like receptor (TLR)4/NOX2 signaling pathway (45,144) (rat, exposure at 0.015, 0.15 and 1.5 mg/kg/d; mice, exposure at 100 mg/l). Furthermore, MNPs induced GC apoptosis, PINK1/Parkin-mediated excessive autophagy of ovarian mitochondria and inflammatory responses, all of which contribute to the process of ovarian fibrosis (32) (zebrafish, exposure at 0 and 40.1 μg/l/d or letrozole 1 mg/kg/d).

MNPs also disrupt the intercellular junctional structures crucial for maintaining intercellular communication and tissue homeostasis, and affect ovarian size (150). Zeng *et al* (51) verified that PS-NPs exposure disrupts the KGN GC integrity of intercellular junctional structures and notably downregulates the expression of connexin 43, a core connexin protein of gap junctions. This destructive effect of MNPs on GCs is linked to OS activation together with Hippo signaling pathways (151). There are notable discrepancies in literature reports on ovarian size following MNP exposure. Haddadi *et al* (26) (rat, exposure at 0 or 0.1 mg/day) reported that the relative ovarian weights of rats were markedly declined following PS-MPs exposure, accompanied by a reduction in ovarian size (26,27,99). However, Zeng *et al* (51) detected no changes in ovarian weight upon PS-NPs exposure (51) (mice, exposure at 1 mg/d). The study by Liu *et al* (99) provides an explanation for this discrepancy. In pubertal female mice subjected to 35-day PS-MNPs exposure, 100-nm-sized PS-NPs induced notably declined ovarian volumes, whereas 5-μm MPs exerted markedly weaker effects on ovarian volume than nanoscale particles, revealing that particle size- and dose-dependent trend serves as the key contributor to such heterogeneous variations in ovarian size.

In view of the inconsistencies in reported ovarian size changes across the literature, the available evidence can be comprehensively explained from the following aspects: Firstly, nanoscale particles (<100 nm) possess the ability to cross the follicular blood barrier and access the ovarian parenchyma, directly disrupting follicular structure and inducing GC apoptosis, thereby resulting in ovarian atrophy. By contrast, microscale particles are mainly retained in the ovarian stroma, causing relatively limited direct damage to follicles. Secondly, low-dose and short-term exposure may only trigger oxidative damage and apoptosis at the cellular and molecular levels, without accumulating into organ-level weight changes, whereas prolonged high-level exposure causes evident follicle depletion besides fibrosis, which are macroscopically manifested as reduced ovarian weight. In addition, the ovaries of prepubertal animals possess strong compensatory and repair capacity with relatively low sensitivity to MNPs, while adult animals have limited ovarian reserve and diminished repair capability, making them more susceptible to organic damage. Finally, absolute ovarian weight and body weight-normalized relative ovarian weight may yield entirely different conclusions, which warrants caution in the comparison of different studies.

3. Influencing factors of MNPs-induced ovarian toxicity

The ovarian toxicity induced by MNPs may be affected by types of plastics, particle dimension, surface functionality, ambient parameters, laboratory modeling type, exposure length, administration means and concentration/dosage (152-155).

MNPs polymer type. Ovarian toxic effects vary markedly among different polymer types. Both PET and PS NPs inhibit follicle growth exhibiting dose-dependent effects, but PET-NPs specifically induce pregnenolone accumulation and suppress Cyp17a1 expression, whereas such effects are not observed with PS-NPs (156). Biodegradable polylactic acid (PLA)-MPs exhibit stronger direct cytotoxicity to GC *in vitro*. However, *in vivo*, PS-MPs exacerbate gut barrier impairment and perturb the composition of gut microbiota, thereby inhibiting ovary LPL, impairing TZP structures and oocyte maturation. This reveals that the two types of MP induce ovarian damage through distinct gut-ovary axis pathways (122).

The majority of experiments exploring MNP-induced reproductive detrimental effects have been conducted using PS particles, particularly fluorescently labeled nanospheres that are easy to track. However, PS only accounts for a small portion of environmental plastic pollution, and other types of polymers may demonstrate differential toxicological characteristics. For example, both PS-NPs and PET-NPs impair follicular growth in a concentration-related manner, with differences in both effect magnitude and concentration-effect profiles (156). In terms of steroidogenesis, PS-NP exposure exerted apparent modulatory impact on steroid hormone, while 10 μg/ml PET induced notably elevated pregnenolone levels. Transcriptomic analyses showed that PS-NPs and PET-NPs activated partially overlapping but distinct sets of stress-response genes and modulated different signaling pathways in follicular cells. This indicates that cellular responses to MNPs are influenced by polymer-specific physicochemical properties (156).

PE dominates environmental plastics in terms of abundance and exhibits the maximum detection prevalence in human follicular fluid. Wang *et al* (157) performed Raman microspectroscopic analysis on follicular fluid samples from

44 infertile women receiving fertility-associated therapy. The results showed that PE ranked first among all detected polymers with a detection rate as high as 86.4%, and PE concentration was notably negatively associated with fertilization rate. Follicular fluid metabolomics revealed that this association was accompanied by marked alterations in the metabolite profile, mainly involving metabolic cascades, iron-dependent cell death and ovarian steroid biosynthesis. In mouse validation experiments, PE treatment induced substantial reduction in the quantity of retrieved oocytes, decreased fertilization rate, increased the proportion of poor-quality oocytes and notably elevated ROS levels. RNA-sequencing analysis revealed elevated expression of inflammatory genes. The study initially identified a direct association between PE and oocyte quality at both human population and animal experimental levels.

PVC exhibits a unique ovarian toxicity pattern due to its chemical duality of high chlorine content and phthalate plasticizers. Yang *et al* (158) systematically evaluated the reproductive toxicity of PVC-MPs among female rodents. Exposure treatment led to a notable reduction in ovarian follicle quantity, concomitant with pronounced declines in the volume of the uterus and oviduct, as well as myometrial thickness. Its toxic mechanisms involve not only local ovarian damage but also notable alterations in structural characteristics of the gut microbial flora and reduced species diversity, revealing an indirect reproductive toxicity pathway mediated by the gut-ovary axis.

In human studies, Kong *et al* (159) conducted quantitative detection of NPs within follicular fluid and seminal plasma derived from 51 IVF paired individuals using Py-GC/MS. The results demonstrated that PE- and PVC-NPs exhibited the highest detection frequency. Follicular fluid analysis revealed mean PE and PVC concentrations of 1.21 and 1.85 μg/g, respectively, and their increased abundance was linked to a notable reduction in fertilization rate. In addition, Afreen *et al* (160) cited multiple studies in their review, confirming that PE-MPs can decrease ovarian follicle count in *Mus musculus* (157), while exposure to PP-MPs elevates the abundance of caspase-3 and -9 in the ovary and decreases follicle numbers (161), further supporting the reproductive deleterious impacts of PE, PP and PVC in women.

Polymer-specific effects may involve differences in cellular uptake kinetics, intracellular trafficking, interactions with cellular components and release of polymer-specific degradation products or additives. PS is currently the dominant material used in animal toxicity assessments. However widespread human exposure to different MNPs exists during daily activities, including PS, PE and PVC (162). For MNPs, smaller particle sizes correspond to stronger adsorption capacity. The loading capability of MNPs is proportionally associated with their surface specific area. This property is tightly governed by size distribution, polymer composition and structural organization (163).

Therefore, risk assessments based solely on previous studies focused on PS may not accurately predict the ovarian-related reproductive toxicity of other ubiquitous MNPs. This requires comprehensive toxicological characterization of major polymer types to identify more hazardous microplastic categories and guide material substitution strategies.

Particle size of MNPs. Particle size notably governs the toxic effects of MNPs, affecting biodistribution, cellular uptake and subcellular localization. With smaller sizes, NPs can cross biological barriers more easily than MPs, including cell membranes, as well as the blood-testis and blood-brain barriers (25,27,51). Variations in particle size markedly influence the ovarian toxicity of MNPs, with toxic effects showing marked size dependence. Numerous studies (99,164-166) have confirmed the direct internalization of NPs by ovarian GCs and accumulation in ovarian tissues, causing damage via mechanisms such as OS induction (51). By contrast, microscale particles hardly penetrate ovarian tissues and exert markedly weaker impacts on ovarian volume and follicle development than nanoparticles, further confirming that particle size is one of the core determinants of the biodistribution and toxic effects of MNPs (99). However, the size-toxicity association is not monotonically linear. Environmental MNPs are mostly irregular in shape; their sharp edges and high-curvature structures can physically puncture cell membranes, triggering patterns of inflammation and cell death distinct from those induced by spherical particles, which complicates the actual toxicity assessment (167).

Particle size of MNPs exerts a fundamental influence on the adsorptive capability of pollutants within identical polymer type, and finer particles exhibit an increased specific surface area to facilitate relevant reactions (168).

Surface properties and adsorbed contaminants of MNPs. Surface charge also profoundly influences the types of toxic effect induced by MNPs. Xu *et al* (169) systematically investigated the effects of surface-bound functional moieties and charge on ovarian toxicity from PS-MPs. Ovarian accumulation of functionalized PS-MPs was in the descending order of PS-NH_2, PS and PS-COOH. PS-NH_2 treatment resulted in the most notable sex hormone imbalance, OS and mitochondrial damage, while negatively charged PS-COOH particles polarized macrophages to proinflammatory M1 phenotypic state, exacerbating ovarian inflammatory injury.

As carriers of contaminants, MNPs markedly enrich organic pollutants and heavy metals by means of interfacial sorption coupled with void infiltration (170,171), with their adsorption capacity 2-6-fold compared with sedimentary substrates and marine water (172). This mainly relies on the synergy of multiple mechanisms, including intermolecular forces, H-bond interactions, aromatic ring stacking and coulombic interactions (173). The adsorption capacity is positively associated with specific surface area, and is regulated by polymer type, particle size, surface functional groups and environmental conditions (163). In organisms, MNPs rarely induce toxicity individually (174), and their toxicity mostly derives from the combined effects with coexisting contaminants, showing distinct synergistic or additive toxicity (31,175,176). For heavy metals, MNPs exert dual effects: They can enhance the accumulative enrichment of heavy metal contaminants such as Pb in female mice via adsorption, exacerbating oxidative and ERS-mediated ovarian toxicity (63), while also assimilating Cd to reduce its bioavailability in embryos, thereby exerting a detoxification effect (177). Such toxic effects are co-regulated by particle size, surface charge, exposure duration, concentration and cell type. Furthermore, contaminants may desorb under low pH or in the presence of surfactants, further altering the toxicity profile (178). Adsorption capacity is a key parameter determining the intensity of combined toxicity, whereas competitive adsorption in environmental media, biotransformation and additive leaching lead to high complexity and difficult attribution in predicting MNPs toxicity in real environments. A close association has been verified between the surface roughness of MPs and their cellular damage potential. MPs featuring sharp boundaries and high curvature are capable of triggering pronounced inflammatory responses and cytotoxicity, the core mechanism of which is that sharp boundaries are prone to inducing cell membrane injury upon physical contact with cells (179). The aging of MPs may make them more prone to adsorbing other toxic substances by altering their surface physicochemical properties, thereby amplifying their reproductive toxicity (180-182).

Critical determinants of persistent organic contaminant adsorption on MPs include MP properties (polymer type, polarity, functional groups), environmental properties (pH, ionic strength) and pollutant properties, with mechanisms involving interactions driven by hydrophobicity, pore occupancy, van der Waals intermolecular forces, H-bond interactions, aromatic ring stacking, coulombic interactions, fragmentation and cation bridging (183,184). NPs provide greater contact surfaces owing to their large surface area, enabling more interactions with biological structures. By contrast, the toxic effects induced by MPs are regulated by a range of determinants, including particle dimensions, morphology, interfacial electrical charge and associated chemicals (185,186). Notably, spherical particles commonly used in experiments differ from irregular particles in the environment in terms of uptake and toxicity (167). Smaller plastic particles exhibit stronger cytotoxicity and higher cell-penetrating ability, can promote ROS accumulation and trigger oxidative impairment of proteins, lipid biomolecules as well as DNA, with its toxic effects enhanced in a concentration- and time-dependent manner (187). NPs cause greater damage than microscale MPs (188). Positively charged NPs exhibit greater toxicity than their negatively charged counterparts. Anionic or carboxyl functionalization enhances the adverse effects of MNPs, while cationic MNPs show specific toxicity due to higher cellular uptake and stronger impacts on cellular and lysosomal membranes. In addition, larger specific surface area exhibits more available adsorption sites for polymers (189). Hydrophobic interactions are the principal adsorption mechanism of lipophilic organics on MPs. Hydrophobic organic pollutants with higher hydrophobicity are more readily adsorbed onto MPs and exhibit low desorption over prolonged periods under altered environmental conditions (190).

The adsorption of environmental pollutants by MNPs is not a simple physical attachment process; instead, it is transformed into amplified reproductive toxicity stepwise in ovarian tissues via specific molecular pathways. Li *et al* (191) found that NPs with nearly zero intrinsic cytotoxicity act as transmembrane transport carriers for Cd by adsorbing this heavy metal, markedly enhancing intracellular Cd accumulation and disrupting calcium homeostasis, thereby upgrading low-toxicity exposure into marked cytotoxicity. After adsorbing the plasticizer DEHP through hydrophobic interactions and van der Waals forces, PS-MPs enter ovarian GCs synergistically. They activate the molecular axis composed of CNR1, CRBN, YY1 and CYP2E1 to drive aberrantly high ROS generation, resulting in oxidative DNA lesions, cell cycle arrest and necroptosis (31). Further research verified that this combined treatment also worsens ovarian fibrotic remodeling, increases the counts of cystic and atretic follicles, and induces polyendocrine metabolic ovarian syndrome (PMOS)-like phenotypes by persistently activating the TGF-β1/Smad3 signaling cascade (192). In combined exposure with heavy metals, PS-MPs adsorb lead (Pb) through surface functional groups and electrostatic interactions, notably increasing Pb accumulation in ovarian tissues. Excessive ROS generated by their synergistic effect continuously activates the PERK/eIF2α ERS pathway, upregulates the Bax/Bcl-2 ratio via CHOP and consequently triggers GC apoptosis. The pathological damage to ovarian tissues and sex hormone disturbance caused by combined exposure are far more severe than those induced by single exposure (63). In the synergistic effects with persistent organic pollutants, MPs adsorb phenanthrene (Phe), a polycyclic aromatic hydrocarbon, via π-π stacking and hydrophobic interactions, causing substantially increased ovarian deposit of Phe in *Oryzias melastigma*. The follicular atresia rate and ovarian maturation inhibition induced by combined exposure are notably higher than those induced by Phe exposure alone. MPs also serve as carriers for the transgenerational transport of Phe from the maternal ovary to offspring embryos, extending toxic effects to unexposed progeny (193). In addition, combined exposure to PS-NPs and perfluorobutyric acid triggers NLRP3/caspase-1-mediated GC pyroptosis through the gut-ovary axis, causing more severe primordial follicle loss and sex hormone disorder than single exposure (194). The absorbed contaminants do not remain confined to the MNPs surface but are sequentially converted into specific reproductive toxicity through multiple pathways in ovarian tissues.

In reality, MNPs rarely exist as pure particles. Their 'Trojan horse' effect as carriers of hazardous substances serves as a core link that markedly amplifies ovarian toxicity. Even with markedly low intrinsic cytotoxicity, NPs can immobilize metallic toxicants such as Cd to employ as transmembrane transport delivery vehicles, substantially enhancing intracellular accumulation and oxidative damage of heavy metals (191). In ovarian tissues, co-exposure of PS-MPs and DEHP drives excessive ROS production via the molecular axis composed of CNR1, CRBN, YY1 and CYP2E1, synergistically triggering DNA oxidative impairment, cell cycle blockade and necroptosis within GCs. Furthermore, this combined exposure contributes to the onset of PMOS-like phenotypic characteristics (31,192). Joint exposure to PS-MPs and Pb notably aggravates histological lesions in the ovary and sex hormone disorder through persistent induction of the PERK/eIF2α-mediated ERS signaling cascade (63). Co-exposure to microplastics and phenanthrene (a typical polycyclic aromatic hydrocarbon) not only increases phenanthrene accumulation and follicle atresia rate in the ovary but also enables transgenerational toxic transfer from the maternal ovary to offspring embryos (193).

Biomonitoring of human MNPs exposure has advanced from peripheral samples to *in situ* detection in reproductive

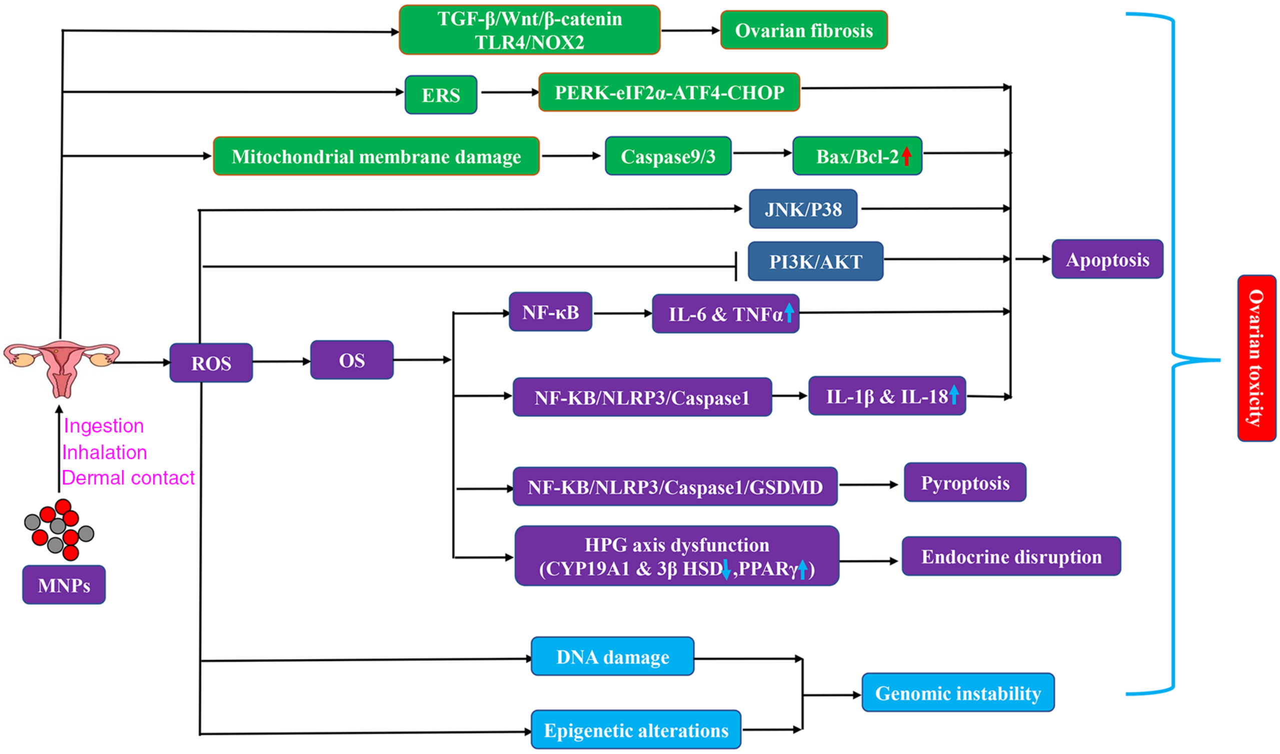

Figure 1. Molecular mechanisms of MNPs-induced ovarian toxicity. Inhalation, ingestion and skin contact serve as the primary pathways for MNPs to accumulate in the ovary. MNPs promote ovarian fibrosis via the TGF-β/Wnt/β-catenin and TLR4/NOX2 signaling cascades. Meanwhile, MNPs mediate apoptosis through multiple pathways. MNPs-induced OS triggers pyroptosis via the NF-κB/NLRP3/caspase-1/GSDMD axis. OS also leads to endocrine disruption by inducing dysfunction of the HPG axis. Moreover, MNPs-induced ROS cause DNA damage and epigenetic alterations. Collectively, these multiple effects exerted by MNPs ultimately result in ovarian toxicity. MNPs, microplastics and nanoplastics; TGF-β, transforming growth factor-beta; TLR4, toll-like receptor 4; NOX2, NADPH oxidase 2; OS, oxidative stress; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; Caspase-1, cysteinyl aspartate specific protease 1; GSDMD, Gasdermin D.

tissues. Montano *et al* (22) reported a notable positive association between MPs concentrations and serum FSH, whereas no notable association was observed for AMH, suggesting that MNPs may indirectly cause gonadotropin feedback dysregulation by impairing GC function rather than directly accelerating primordial follicle depletion (22). Ni *et al* (24) reported that PE and PVC levels in human follicular fluid were both negatively linked to fertilization rates, but not to implantation rates or pregnancy rates. That study established for the first time a dose-response association between follicular fluid NPs concentrations and key outcomes of assisted reproduction at the human population level, indicating that the early impairment of fertility induced by MNPs is concentrated at the gamete fertilization stage (24). Wang *et al* (157) further validated the inverse association for PE concentration and fecundation rate in 44 infertile women and revealed how PE impairs oocyte competence through mouse models and follicular fluid metabolomics. Clinically, MNP concentrations in follicular fluid have reached the effective levels that induce reproductive toxicity in animal models. Two independent cohorts using different detection techniques have cross-validated the association between MNPs and reduced fertilization rates. The interindividual variation in follicular fluid PE concentrations spans up to three orders of magnitude, with a maximum level of 4,783 μg/g, highlighting a need to identify populations at high exposure risk and develop targeted exposure reduction strategies.

4. Mechanisms of ovarian toxicity induced by MNPs

MNPs enter cells via active uptake and passive transfer. For active uptake, phagocytosis and clathrin/caveolin-mediated endocytosis mediate the internalization of larger particles, with smaller ones via pinocytosis (195). Ultra-small NPs can directly penetrate cell membranes through membrane pores via passive transfer (196). The ovarian toxicity of MNPs arises from a network of interconnected mechanisms, among which OS acts as the central hub linking inflammation, programmed cell death, endocrine disruption, ERS, membrane damage, epigenetic alterations and DNA damage (Fig. 1).

OS as the central mechanism. OS, referring to an imbalance of ROS production overwhelming cellular antioxidant defenses, is considered as the central mechanism underlying MNPs induced reproductive toxicity (197,198). MNPs raise ROS levels through both generating oxidants and inhibiting antioxidant enzymes, and smaller particles at higher concentrations are more effective in this regard (25,199). After entering the lipid rich ovary, MNPs can accumulate in GCs and increase MDA, deplete GSH and suppress antioxidant enzyme activities (27,45,144). Mitochondrial impairment, manifested as disrupted electron transport and ATP synthesis, can further amplify ROS production, thus creating a cycle (200).

Various pathways can be activated by OS, including TLR4/NOX2, NLRP3/caspase-1 and PERK/eIF2α/ATF4/CHOP. They can promote GC apoptosis and pyroptosis, alter cytoskeletal proteins and impair follicular development (25,45,144,201). ROS also stimulates JNK and p38 MAPK, inhibits the PI3K/Akt survival pathway, and perturbs Nrf2/Keap1/HO-1, Hippo and AMPK PGC 1α signaling, resulting in primordial follicle activation, glycolysis and ovarian aging (60,202-205). Furthermore, undegraded MNPs cause lysosomal rupture, and the released hydrolases can attack mitochondria and worsen oxidative damage (206). Calcium overload and oxidative damage to mitochondrial DNA then aggravate the cytotoxicity (205,207). The fact that the ROS scavenger NAC can alleviate OS-mediated DNA damage and apoptosis confirms the central role of OS in this process (25).

Inflammation. Inflammatory responses are triggered mainly by OS, lysosomal dysfunction and the physicochemical properties of MNPs. Small particles with sharp edges and high specific surface area can directly damage cell membranes and release surface adsorbed oxidants, thereby initiating inflammation (179,208). Upon OS stimulation, NF-κB translocates into the nucleus and subsequently initiates the transcription of proinflammatory mediators, including IL-1β, IL-6 and TNF-α (45). At the same time, the NLRP3 inflammasome detects OS, and processes pro IL-1β and pro-IL-18 into their mature forms through caspase-1, driving sterile inflammation (45,209). The involved inflammatory network involves the TRAF6/NF-κB, MAPK, TLR, complement and PPAR pathways (45,161,210-213).

Within the ovary, chronic inflammation increases immune cell infiltration, disrupts folliculogenesis, steroidogenesis and meiotic progression and accelerates ovarian aging (214,215). Inflammatory cytokines and ROS play a notable role in a positive feedback loop that amplifies reproductive injury (154,216). Insufficient Nrf2 activation and subsequent excessive NF-κB activity contribute to the maintenance of chronic inflammation (217).

Programmed cell death. MNPs can trigger several types of programmed cell death, most of which as the downstream of OS and inflammation; apoptosis is the dominant death mode. Mitochondrial dysfunction leads to the release of cytochrome *c* and triggering of caspase-9/3, together with Bax upregulation and Bcl-2 downregulation (45,92). Apoptosis can also be induced via ERS (PERK/eIF2α/ATF4/CHOP), the Hippo (MST1 LATS1) cascade, JNK/ERK signaling, p53-mediated gene regulation and the death receptor pathway (caspase-8) (51,63,218,219). Pyroptosis relies on the NLRP3/caspase-1/gasdermin D axis, often co-occurs with apoptosis and contributes to follicular atrophy (45,209). Ferroptosis is an iron overload- and ROS-driven mode of cell death featured by upregulation of TfRC, SLC7a11 and ACSL4, and can be blocked by ferrostatin 1 (101). Necroptosis can be driven by OS-mediated activation of Hippo signaling, which suppresses YAP1 nuclear translocation, and by a TNF-α/ROS positive feedback loop (220). These cell death pathways induced by MNPs are dose- and particle size-dependent and can be enhanced by co-exposure to Pb, DEHP and other toxicants (63,220).

Endocrine disruption and steroidogenic dysfunction. MNPs can disturb ovarian endocrine homeostasis by interfering with the HPG axis and steroid hormone synthesis. MNPs and their adsorbed EDCs represented by BPA together with phthalates can downregulate the regulatory genes of GnRH, FSHβ and LHβ, alter KiSS1/GPR54 and impair follicular development and oocyte maturation (176,221-223). Within GCs, MNPs inhibit aromatase and 3β HSD, resulting in diminished E2 synthesis and an altered E2/testosterone ratio (51,222,224). Adsorbed EDCs on MNPs amplify the toxicity. PS MPs with phthalic acid activate the molecular axis composed of CNR1, CRBN, YY1 and CYP2E1 to increase ROS levels along with follicular atresia (31), while DEHP activates PPARγ to suppress aromatase (225). Steroidogenesis is further compromised by the SIRT1/p53 pathway and by receptor-mediated effects of EDCs (70,128,226,227). At the same time, OS lowers ovarian antioxidant defenses and this worsens the endocrine toxicity.

ERS and membrane damage. Concurrent treatment with PS-MPs and Pb promotes the accumulation of unfolded proteins, upregulates BIP and activates the IRE1 and PERK/ATF4/CHOP branches of the unfolded protein response, culminating in GC apoptosis (63,228,229). PS NPs also accumulate adjacent to ER, impair oocyte translation efficacy and induce meiosis-related defects associated with OS (98). The ERS inhibitor Salubrinal can restore eIF2α phosphorylation and improves ovarian function (63).

In parallel, MNPs injure both the plasma membrane and organelle membranes. Direct physical disruption and ROS driven lipid peroxidation increase membrane permeability and undermine the membrane integrity (230,231). Mitochondrial membranes show swelling, cristae loss, dissipation of membrane potential and Drp1-mediated fission (119,232). Destabilization of lysosomal membranes releases hydrolytic enzymes that further intensify OS and inflammation (216). NPs and certain surface functional groups lead to greater membrane damage, which in turn further disturbs reproductive hormone regulation (206,233,234).

Epigenetic alterations and DNA damage. MNPs and their chemical additives can modify the oocyte epigenome. PS MPs reduce HDAC3 levels, leading to increased H4K16 acetylation. This upregulates metabolic genes, drives excessive ROS production and causes DNA damage and apoptosis (107). HDAC3 and HDAC2-mediated deacetylation is essential for meiotic maturation and spindle assembly (108,109,235). Plastic additives can further destabilize the epigenome. DEHP interferes with DNA and histone methylation and acetylation (124,236), while Cd lowers H3K9me3 and H3K9ac levels, leading to aneuploidy (116). BPA causes global methylation abnormalities and histone modification changes that impair meiosis (237,238).

Epigenetic alterations often overlap with DNA damage. MNPs induce DNA damage to mediate ovarian toxicity dominated by OS-mediated indirect damage, and direct particle-DNA interaction also contributes (239). Excessive ROS induced by MNPs targets both mitochondrial and nuclear DNA, causing oxidative damage, strand breaks and base damage, while also inhibiting DNA repair capacity such as downregulated repair protein RAD-51 (139,240,241). This forms a vicious cycle where DNA damage impairs respiratory chain function to further promote ROS accumulation. PE-NPs can also activate nuclear receptor NHR-14 to jointly induce ovarian toxicity with DNA damage (242).

DNA damage triggers multiple downstream toxic effects. It induces apoptotic cell death of germ cells via the signaling cascade of HUS-1/CEP-1/EGL-1/CED-9/CED-4/CED-3, leading to defective oocyte maturation, impaired gonadal development and reduced fertility (243). In addition, PS-NPs can induce transgenerational reproductive toxicity via this mechanism, as demonstrated by enhanced DNA impairment markers, spindle abnormalities and misaligned chromosomes in oocytes (104). Notably, co-exposure with DEHP or exposure to UV-degraded PS-MPs can exacerbate DNA damage and enhance ovarian toxicity (31,243).

5. Challenges and prospects

Current research on the ovarian toxicity of MNPs faces several key bottlenecks that constrain population-based risk assessment and the development of clinical intervention strategies. At the exposure assessment level, Fitch *et al* (244) conducted a rigorous quality assessment of 24 mammalian MP reproductive toxicity studies using the NTPOHAT framework and rated all studies as having high risk of bias. Among them, 67% of the studies relied solely on PS microspheres, none independently verified the administered concentration or recorded water intake and female studies all lacked estrous cycle monitoring, a standard method for assessing ovarian function. This evaluation implies that the current body of evidence on MNP ovarian toxicity is insufficient to directly support the establishment of regulatory thresholds, highlighting the urgency of reconstructing standardized exposure characterization protocols by referencing OECD 421/443 reproductive toxicity test guidelines. In terms of epidemiological evidence chain, the Women's Hospital of Zhejiang University School of Medicine (Hangzhou, China) has conducted a prospective cohort study (registration No. ChiCTR2400091308, target enrollment, 240 cases) aiming to systematically investigate the association between MPs concentrations in follicle fluid and IVF/ICSI clinical outcomes and offspring development. The dose-effect association between NP concentration and fertilization rate established by Kong *et al* (159) provides critical pilot data for this cohort. The authors found that PE and PVC NPs are widely present in human follicular fluid and seminal plasma. High concentrations can reduce sperm quality and significantly decrease the normal fertilization rate, suggesting that NPs impair male and female fertility. Regarding the environmental relevance of mechanistic studies, current models over-rely on pristine spherical PS particles, which present a triple disconnect from real human exposure, because environmental MNPs exist in irregular shapes, aged/degraded states and complexed forms with coexisting pollutants. Jeong *et al* (187) and Choi *et al* (167) verified the pronounced impacts of particle size along with shape on MP toxicity, respectively, while Cui *et al* (181) observed that senesced PS-MPs induce a differential tissue-specific Nrf2 defense response compared with pristine particles. Therefore, research regarding MNPs-induced ovarian toxicity should prioritize solving the following issues: Adopt standardized exposure characterization protocols and OECD reproductive toxicity guidelines to rebuild a low-risk-of-bias *in vivo* evidence base; complete the registered prospective cohort study and simultaneously conduct reproductive health surveillance in high-exposure occupational populations; establish a comparative system for ovarian toxicity of multiple environmentally relevant polymers under uniform conditions, incorporating aged particles and irregularly shaped particles and using actual measured concentration ranges in human follicular fluid as dose benchmarks; and establish pre-market safety assessment norms for alternative plastic materials, mandating ovarian toxicity as a compulsory testing endpoint.

There is still no direct evidence demonstrating that MNPs induce identical ovarian toxic effects in humans as observed in animal models. However, the following indirect evidence supports cross-species conservation: i) Concentrations of MNPs within human follicle fluid have reached the levels at which ovarian toxicity is observable in animal experiments; ii) treating human GC of KGN with PS-NPs under *in vitro* conditions induces OS, apoptosis and steroidogenesis dysfunction consistent with those observed in animal GCs (51); and iii) MNPs isolated from human follicular fluid can directly inhibit mouse oocyte maturation *in vitro* (24). Given the uniqueness of human ovarian physiology and the complexity of exposure patterns, caution is still required when extrapolating findings from animal models to humans. MNPs of different polymer types exert toxicity through partially distinct pathways. Alahmadi *et al* (156) reported that PS- and PET-NPs activate partially overlapping distinct sets of stress-related genes and signaling pathways in mouse follicles, indicating the existence of polymer-specific toxicological pathways. Xu *et al* (169) further revealed that surface functional groups markedly affect ovarian accumulation, mitochondrial damage patterns and macrophage polarization induced by PS-MPs. Accordingly, the activation of toxic pathways depends on the complex interactions among the polymer type, particle size, surface chemistry, protein corona composition and environmental exposure scenarios of MNPs. OS is widely recognized as the most upstream and core initiating mechanism underlying MNPs-induced ovarian toxicity. First, OS directly triggers a vicious cycle of oxidative damage consisting of DNA oxidative injury, mitochondrial dysfunction and lipid peroxidation. In addition, OS acts as an upstream activator of the NLRP3 inflammasome/caspase-1 axis, TLR4/NOX2 and PERK/eIF2α signaling cascades. Finally, antioxidants can effectively alleviate MNP-induced apoptosis and pyroptosis of ovarian GCs as well as oocyte maturation arrest, providing causal evidence for the central role of OS (25,103,105).

Measures can also be taken to prevent or eliminate MNPs. At the level of exposure source control, filtration technologies for MNPs can be improved from potable water and food (activated carbon adsorption and reverse osmosis membrane filtration), reduced consumption of disposable plastic commodities and promoted application of degradable alternative materials. However, it should be noted that MNPs produced during the degradation of certain biodegradable plastics (such as PLA) have been demonstrated to be toxic to murine ovarian reserve and developmental maturation of oocytes (122). Therefore, the safety assessment of alternative materials cannot be ignored. In addition, the application of antioxidants, Nrf2 activators, PERK pathway inhibitors and other agents can counteract ovarian reproductive toxicity caused by MNPs. Furthermore, mesenchymal stem cell-derived exosomes exhibit prominent ovarian reparative capacity in models mimicking early ovarian dysfunction. Chen *et al* (245) found that human umbilical cord mesenchymal stem cells exosomes mitigate OS-triggered early ovarian dysfunction by activating the AMPK pathway and regulating autophagy homeostasis (245). Another study indicated that MSC-derived exosomes ameliorate ovarian performance in cyclophosphamide-induced early ovarian dysfunction mice via inhibiting NLRP3-mediated granulocyte pyroptosis (246). Given that the mechanisms underlying MNPs-induced ovarian toxicity notably overlap with those of premature ovarian insufficiency (OS, NLRP3/caspase-1 pathway and GC apoptosis/pyroptosis), future studies may explore MSC-exosomes as a potential therapeutic strategy for ovarian protection after MNPs exposure.

From the perspective of clinical translation, the following research studies need to be promoted: Establishing a large prospective cohort study on the association between MNPs concentrations in follicle fluid of women of childbearing age and the core outcome indicators of assisted reproduction, including the counts of recovered oocytes, oocyte maturation rate, proportion of fertilized oocytes, percentage of top-grade embryos, clinical gestation ratio and live delivery ratio, is a decisive step to establish causality at the population level. In addition, it is imperative to develop a standard quantitative assay method for MNPs in follicular fluid based on Raman spectroscopic analysis and pyrolysis GC-MS and establish the reference value range for women of childbearing age to support clinical risk assessment. Given that Montano *et al* (22) observed that a marked positive association between MNP levels and FSH, no such association was found for AMH; however, it is still necessary to carefully evaluate the sensitivity and specificity of MNPs before their clinical application as biomarkers of ovarian function, and it is particularly essential to clarify the biological basis behind the FSH-MNPs association. In addition, waste human oocytes and GC obtained from the oocyte donation research system should be fully utilized to carry out *in vitro* MNP exposure experiments in order to clarify whether there are substantial differences in the dose-response effects of human germ cells to MNPs compared with animal models.

6. Conclusions

MNPs exert notable adverse impacts on ovarian function and women's reproductive health. Current research evidence indicates that MNPs impair folliculogenesis, oocyte quality, steroidogenesis and fertility through core mechanisms, including OS, inflammatory response, hormonal disruption, regulated cell death, ERS, membrane structural impairment, epigenetic alterations and DNA damage. The toxicity of MNPs represents a novel environmental health crisis that may exert transgenerational impacts on population fertility. As plastic pollution intensifies, the exposure burden is expected to increase, necessitating urgent multi-level actions, including individual exposure reduction and policy interventions (production restrictions, and improved waste recycling and reuse). Future research should prioritize human exposure assessment, studies on the association between mechanisms and reproductive outcomes, comprehensive research on polymer types, and the development of intervention strategies. The combination of sustained scientific research and preventive strategies in public health is necessary for understanding and mitigating the reproductive toxicity risks induced by MNPs.

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SZ, WY, PL and JY conceived and designed the study. SZ and WY collected the literature. SZ, WY, PL and JY analyzed the literature and drafted and reviewed the manuscript. All authors read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing of interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this manuscript, an artificial intelligence-assisted tool was used in order to improve the readability and language of the manuscript.

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