Balali *et al.*
Reproductive Biology and Endocrinology (2024) 22:141
https://doi.org/10.1186/s12958-024-01314-7

Reproductive Biology and Endocrinology

REVIEW

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Concerning influences of micro/nano plastics on female reproductive health: focusing on cellular and molecular pathways from animal models to human studies

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Abstract

The female reproductive system can face serious disorders and show reproductive abnormalities under the influence of environmental pollutants. Microplastics (MPs) and nanoplastics (NPs) as emerging pollutants, by affecting different components of this system, may make female fertility a serious challenge. Animal studies have demonstrated that exposure to these substances weakens the function of ovaries and causes a decrease in ovarian reserve capacity. Also, continuous exposure to micro/nano plastics (MNPs) leads to increased levels of reactive oxygen species, induction of oxidative stress, inflammatory responses, apoptosis of granulosa cells, and reduction of the number of ovarian follicles. Furthermore, by interfering with the hypothalamic-pituitary-ovarian axis, these particles disturb the normal levels of ovarian androgens and endocrine balance and delay the growth of gonads. Exposure to MNPs can accelerate carcinogenesis in the female reproductive system in humans and animal models. Animal studies have determined that these particles can accumulate in the placenta, causing metabolic changes, disrupting the development of the fetus, and endangering the health of future generations. In humans, the presence of micro/nanoplastics in placenta tissue, infant feces, and breast milk has been reported. These particles can directly affect the health of the mother and fetus, increasing the risk of premature birth and other pregnancy complications. This review aims to outline the hazardous effects of micro/nano plastics on female reproductive health and fetal growth and discuss the results of animal experiments and human research focusing on cellular and molecular pathways.

Keywords Reproductive system, Female fertility, Environmental pollutants, Microplastics, Nanoplastics

Introduction

Reproductive health, as one of the most important indicators of quality of life, is strongly related to the condition of the human reproductive system and can be changed under the influence of many factors [1, 2]. Infertility, which refers to the failure to develop a pregnancy after 12 months of regular unprotected sex, currently affects the lives of 50 to 80 million women [3]. According to WHO reports, female factors contribute to about 37% of infertility problems, while male factors account for about 29%, and combined female and male factors account for about 18% of the causes. The remaining 16% are genetic factors or unexplained or idiopathic infertility [4, 5]. The female reproductive system, in addition to controlling the development of secondary sexual characteristics, is also the location of gametogenesis and secretion of sex hormones and embryo development [6]. Any impairment in the function and even the structure of this

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system can lead to reproductive disorders such as premature puberty, abnormal cycle, premature ovarian insufficiency/menopause, endometriosis, fibroids, and adverse pregnancy outcomes and eventually cause this system to fail in females [7, 8]. Some of the damages inflicted on the female reproductive system may result from biological pollutants, which can stem from various sources such as medications, agricultural chemicals, chemicals found in cosmetic and hygiene products, and food items [9].

Currently, due to their versatility, durability, and cost-effectiveness, plastic materials are considered the most widely used substance globally. However, these substances are permanent pollutants in every ecological part of the world [10]. Bottles, bags, disposable materials, and untreated wastewater are among the most common and main sources of plastics [11, 12]. The term microplastics (MPs) was used in 2004 to describe microscopic plastic particles in the marine environment [13] and finally, microplastics were defined as particles 100 nm to 5 mm, and nanoplastics (NPs) were defined as particles less than 100 nm. These small particles are classified into two categories, MPs and NPs, which are collectively known as micro (nano) plastics (MNPs) [10, 14]. These particles with different sizes, colors, and shapes are found in freshwater, soil, air, and some food products [15–17]. Plastics and small particles resulting from them damage the ecosystem and all life on earth, especially human health, and continuous exposure to these substances, including MNPs, can be the main source of diseases and disruption of human fertility [18].

In recent years, the negative effects of MNPs on fertility have been widely investigated in animal models. Evidence shows that MNPs cause reproductive toxicity by disrupting the structure and function of the uterus, ovaries, and endocrine glands as well as the hypothalamus-pituitary axis [19, 20]. Exposure to these polluting particles causes fibrosis in these organs through the accumulation of reactive oxygen species (ROS) and the activation of the relevant signaling pathways [21, 22]. Induction of oxidative stress, inflammation, apoptosis, and malignancy in the reproductive organs of females can affect the process of ovulation and generally put their fertility and health at risk [23]. By inducing apoptosis in granulosa cells and also reducing the number of ovarian follicles, these substances change the levels of androgens in this organ and then disrupt the reproductive endocrine system [24].

In human studies, the negative effects of MNPs on women's fertility have received much attention in recent years. The available evidence points to a significant relationship between continuous exposure to MNPs and the reduction of women's fertility [25, 26]. These substances, by accumulating in human reproductive organs and exerting toxic effects, can compromise their function [27]. It has been shown that these pollutant particles can damage cell components through intracellular pathways and disrupt the cell cycle [28]. MNPs, in addition to maternal damage, during pregnancy and lactation by passing through the placenta and penetrating various organs of the fetus, including the heart, liver, lungs, and spleen [29], and affecting their reproductive and nervous systems, cause transgenerational toxicity and disturb the embryonic development [30, 31]. The invasion of these particles into the human trophoblast and the change of gene expression in its cells can lead to common disorders in the immune system of the mother and the fetus [32]. Following the suppression of the mother's immune system due to exposure to these substances, the risk of miscarriage increases, and the mother's health is also endangered [33]. The toxic effects of MNPs, as well as the vulnerability of the female reproductive system to these exogenous substances, have raised concerns about female fertility and focused much attention on the identification of these environmental hazards [34]. This review aims to describe the harmful impacts of micro/nano plastics on various aspects of female reproductive system and discuss the animal and human research focusing on cellular and molecular mechanisms.

Effects of microplastics and nanoplastics on reproductive health: evidences from animal studies

Microplastics and nanoplastics, as toxic substances, can accumulate in reproductive organs and disrupt the reproductive capacity of various animal species [35]. So far, numerous studies have been conducted on various animals and animal models regarding the effects of microplastics on the female reproductive system, summarized in Table 1. In male rats, MNPs could enter the lumen of the seminiferous tubule by disrupting the integrity of the blood-testis barrier (BTB) and reducing the number of seminiferous epithelial cells and Sertoli cells [19, 36, 37]. Acute exposure to polystyrene nanoplastics (PS-NPs) in mouse Sertoli cells causes the destruction of BTB through the destruction of tight junction proteins and the reduction of antioxidant capacity [38, 39]. BTB damage may lead to further disruption of the internal structure of the spermatogenic tube including lumen atrophy and hyperplasia [19, 40], which can lead to testicular histological changes, abnormal spermatogenesis, and serum hormone secretion interference in mice [20]. The effect of MNPs on testosterone secretion is dose-dependent [41] and various studies show that exposure to NPs can significantly reduce luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels [19,

Table 1 Effects of microplastics on the animal reproductive system

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
A) Rat and mice experimental models										
Wistar rat	32	PS-MPs	0.5 µm	0, 0.015, 0.15 and 1.5 mg/kg/d	90 days	Drinking deionized water with microplastics	- TEM observation - Hematoxylin-eosin (HE) staining - Protein extraction - Immunohistochemistry - ELISA - Fluorescence microscopy - TUNEL staining - Flow cytometry - Western blot assays	NLRP3/Caspase-1 signaling pathway, Oxidative stress	Involvement in apoptosis and pyroptosis of granulosa cells in the ovary through the NLRP3/Caspase-1 signaling pathway; decrease in the levels of SOD, CAT, and GSH-Px, AMH, and increase in the levels of MDA, IL-1β, and IL-18	[46]
Wistar rat	32	PS-MPs	0.5 µm	0, 0.015, 0.15 and 1.5 mg/kg/d	90 days	Direct drinking deionized water with microplastics	- Hematoxylin-eosin (HE) staining - TEM observation - ELISA - Flow cytometry - Immunohistochemistry - Masson's trichrome and Sirius red staining - Enzyme assay - Western blot assays	Wnt/β-Catenin signaling pathway, Oxidative stress	Ovarian fibrosis and pyroptosis through the Wnt/β-Catenin signaling pathway, apoptosis in granulosa cells, decrease in ovarian reserve capacity and AMH levels, reduction growing follicles number, and upregulation of TGF-β, fibronectin, Wnt, β-catenin, p-β catenin, and α-SMA	[21]
Wistar rat	30	PS-MPs	876 nm	2.5, 5, and 10 mg/kg/d	45 days	Gavage	- ELISA - Folin phenol method - Enzyme assay - Compound microscopy	Inflammation, oxidative stress, metabolic and endocrine disruption	Increase the serum level of NF-κB and IL-6, decrease the catalase and SOD activity in the ovary, increase oxidative stress in the ovary, alteration of lipid profile, and increase the levels of FSH, T, and E2	[50]
Wistar rats *Rattus norvegicus*	21	PS-MPs	5 µm	0, 0.1 mg/d	within 24–26 days (four estrus cycles)	Oral gavage	- RNA extraction - Hematoxylin-eosin (HE) staining - Optical microscopy - Immunofluorescence - Enzyme assay - Estradiol assay - RT-PCR	Oxidative stress and disturbance of cytoskeleton	Change in the folliculogenesis and estrous cycle duration, decrease in ovarian weight, decrease in the levels of serum E2, increase in the levels of MDA and CAT and Sod, decrease in the levels of PSH in the ovary, and a significant decrease in DAAM-1 and α-tubulin expression in ovary	[51]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
Time-pregnant Sprague Dawley rats	21	PS-NPs	21.86 nm ± 0.026	2.64 × 1014 particles in 300 µl	Only once before the experimental operation	Intratracheal instillation	- Fluorescent Optical Imaging - Fluorescence spectroscopy - Hematoxylin-eosin (HE) staining	Reproductive and developmental health	A significant decrease in placental and fetal weight, particle accumulation in the placenta, maternal heart, lung, and spleen, and maternal lung-to-fetal tissue nanoparticle translocation	[29]
C57BL/6 mice	40	PS-MPs	5.0–5.9 µm	Saline and 0.1 mg/d	30 or 44 days	Gavage	- ELISA - SEM microscopy - Fluorescence microscopy - Fluorescence spectroscopy - Hematoxylin-eosin (HE) staining	Oxidative stress, Reproductive and developmental health	PS-MP accumulation and oxidative stress in the ovary, reduction in the size of ovary and number of follicles, decreased the rate of pregnancy and produced fewer embryos, increase in the levels of LH, T, and FSH, decrease in the levels of E2	[24]
C57BL/6 mice	32	PS-MPs and Pb	100 nm	0.1 to 2 g/day	28 to 35 days	Gavage	- Hematoxylin-eosin (HE) staining - Optical microscopy - RT-qPCR - Fluorescent microscopy - Immunofluorescence (IF) assay - Immunohistochemistry (IHC) assay - Sex hormone analysis and oxidative stress analysis	Oxidative stress, PERK/eIF2α signaling pathway	Histopathological damage in the uterus and ovaries, increase in serum MDA levels, and decrease in sex hormone levels and serum SOD, increase ER stress in the ovary by activating the PERK/eIF2α signaling pathway, which leads to apoptosis, induced oxidative stress, and decreased the quality of the oocyte	[52]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
SPF C57BL mice	30	PS-NPs and PS-MPs	100 nm and 1000 nm	10 mg/mL solution	1 to 17 gestational days	Intragastric gavage	- Fluorescence imaging - Fluorescence microscope - Immunofluorescent staining - TUNEL assay - RNA-sequencing - Optical microscopy - Hematoxylin-eosin (HE) staining - RNA extraction - qPCR - TEM microscopy - ELISA - Enzyme assay - Cell culture - Western blotting - Flow cytometry - Bioinformatic analysis	Reproductive and developmental health	Accumulation of particles in the uterus, brain, alimentary tract, and placenta in maternal mice	[53]
C57BL/6-mated BALB/c mice	18	PS-MPs	10 µm	250 µg/ 200 µL saline	11 days	intraperitoneally injection	- RNA extraction - Flow cytometry - Hematoxylin-eosin (HE) staining - qRT-PCR	Immune disturbance	Spontaneous abortion	[33]
Balb/C nude mice with human EOC cell line HEY	16	PS-NPs	100 nm	10 mg/L/d	27 days	Drinking water with PS-NPs	- Hematoxylin-eosin (HE) staining - Cell culture - Confocal microscopy - Cell wound healing analysis - Transcriptional assay - RNA extraction - RNA sequencing - RT-qPCR - Bioinformatics analysis	Alteration in tumor growth microenvironment	Increased EOC tumor growth, reduction in the relative viability of EOC cells via changing the microenvironment of tumor growth, increase in mitotic counts in EOC tumor tissues, immune-related responses, and the tumor microenvironment pathway	[54]
ICR mice	60	PS-NPs	50 nm	0, 5, 25 mg/kg/d	8 weeks	Intragastric administration (Gavage)	- Hematoxylin-eosin (HE) staining - Fluorescence microscopy - Enzyme assay - Cell viability assay - ELISA - Flow cytometry - Immunofluorescence staining - Western blotting - TUNEL assay	Nrf2 signaling pathway, Oxidative stress	Increase in oxidative stress and apoptosis levels, decrease in the quantity of offspring, cell viability, and the occurrence of cell cycle arrest, decrease in the ovarian reserve capacity, increase in a higher ratio of metestrus and diestrus phases, and decrease in proportion of the estrous phase	[55]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
ICR Mice	20	PE-MPs (modified to contain acid and hydroxy groups)	40–48 µm	0, 3.75, 15, or 60 mg/kg body weight-day	123 days	Gavage	- Hematoxylin-eosin (HE) staining - TEM observation - Flow cytometry	Reproductive and developmental health	Increase in the number of abnormal neonates, dilation of the abdominal aorta and fallopian tubes in parent mice, decrease in the number of live births, alteration in body weight and sex ratio of the pups, and increase in the proportion of neutrophils in the blood	[56]
ICR Mice	Conducted in triplicates using 20 fertilized embryos for each one replica and for control	PS-MPs	0.7918 ± 0.00273 and 0.7939 ± 0.00282 µm	30 mg/kg body weight-d	35 days	Oral gavage	- Fluorescence spectroscopy - ELISA - Fluorescence microscopy - Light microscopy - Laser scanning confocal microscope - Parthenogenic activation -MMP and ATP assay - qRT-PCR	Inflammation and oxidative stress	Increase in the IL-6 level, decrease in MDA levels in the ovary, GSH and MMP and $[Ca^{2+}]$ ER reduction, increase in ROS levels, and reduced the first polar body extrusion rate and the survival rate of superovulated oocytes	[57]
Kunming mice	60	PE-MPs	10–150 µm	0.4, 4, and 40 mg/kg/d	30 days	Daily oral doses	- Immunofluorescence (IF) staining - Breeding assay - Fluorescence microscope - Enzyme assay - Apoptosis assay	Oxidative stress, DNA damage, Reproductive and developmental health	A decrease in the oocyte maturation and the rate of fertilization, development of embryo, and fertility, increased the level of ROS in oocytes and embryos, resulting in oxidative stress, dysfunction of mitochondrial, and apoptosis, causing the damage of DNA in oocytes	[58]
Mice	12	PS-MPs	5–10 µm	0.01 mg to 1 g	42 days	Drinking	- Optical microscopy - Immunohistochemistry - Fluorescence microscopy - Western blotting - Intracellular ROS assay - Real-time quantitative PCR analysis	TLR4/NOX2 signaling pathway, Oxidative stress, Notch and TGF-β signaling pathway	Endometrial thinning and severe collagen fiber deposition, increased the expression of HMGB1 and acetyl-HMGB1, activating the TLR4/NOX2 signaling pathway and increase cause oxidative stress, activation of Notch and TGF-β signaling pathway, and increase in the levels of fibrotic proteins and collagen,	[22]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
B) Other species										
Drosophila melanogaster	Continued exposure of 5 generations	PS-NPs	100 nm	1, 10, 50, and 100 mg L^{-1}	5 days	PS-NPs solution mixed with the standard cornmeal fly feed	- Fluorescence microscopy - RNA extraction and transcriptome sequencing - qRT-PCR - Transcriptome analysis	Reproductive and developmental health	PS-NPs accumulation in the crop, gut, and ovaries, decrease in the number of egg production and eclosion rate, and delay in development	[59]
Caenorhabditis elegans	-	PS-MPs	0.01 to 2 µm	0.1 to 100 µg/L	28 days	Environmental exposure	- SEM microscopy - XPS - FTIR - Fluorescence microscopy - RT-qPCR	DNA damage, Apoptosis, Reproductive and developmental health	Increased the number of HUS-1::GFP foci and the gene expression essential for DNA damage, including egl-1, and cep-1, clk-2, proposing DNA damage induction, the number of cell corpses and apoptosis-related gene expression (e.g., ced-9, ced-4, and ced-3) were changed, suggesting the apoptosis induction	[60]
Folsomia candida	20	PE-MPs	< 500 µm	≥ 0.1% w/w in dry soil	28 days	Artificial soil contaminated with MPs	- Counting - DNA extraction - PCR - Sequencing	Reproductive health	Reduction in reproduction by 70.2%	[61]
Oysters	240	PS microsphere (Micro-PS)	2 and 6 µm	0.023 mg/L	2 months	Particles were supplied continuously to the tanks by peristaltic pumps from a concentrated micro-PS solution, maintained in a glass flask on a magnetic stirrer	- Electronic particle counting - Flow Cytometry - Gamete Quality Analyses - Inverted microscopy - Protein Extraction and Proteomic Analysis - RNA Extraction, Amplification, Labeling, and Microarray Hybridization - Preprocessing and Microarray Data Analysis	Reproductive health, feeding modifications	Substantial reductions in oocyte number (-38%) and diameter (-5%), Alterations in feeding behavior, and reproduction impairment in oysters with outstanding influences on offspring, revealed molecular signatures of endocrine disruption	[62]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
Zebrafish	12	PS-MPs + MT	5 µm	0 or 50 ng L-1 MT, 0.5 mg·L-1 PS-MPs, or 50 ng·L-1 MT + 0.5 mg·L-1 PS-MPs	7, 14, and 21 days	adding an equal concentration of MT and PS-MPs to the aquatic environment in which they are placed	- Hematoxylin-eosin (HE) staining - Light microscopy - RNA extraction and cDNA synthesis - qRT-PCR - ELISA - Stereomicroscopy	Disruption of gene expression and hormone levels, reproductive health	Increase in the ratio of mature oocytes, a decrease in the levels of E2, LH, and FSH in the (after 14 d of exposure), reduction in cyp11a mRNA expression in all groups after 7 days but an increase in StAR and cyp19a1a mRNA expression in MT + PS-MPs group after 14 days	[63]
Zebrafish (*Danio rerio*)	3	PS-MPs	1 µm	10, 100, and 1000 µg/L	21 days	The exposure was performed in a flow through system	- µ-FT-IR - Infrared Microscopy - Fluorescence microscopy - TUNEL assay - ROS levels analysis - Hematoxylin-eosin (HE) staining - qPCR	histological alterations, Reproductive and developmental health	ROS levels significantly enhanced in gonads and liver (At concentrations above 100 µg/L), Alteration in histological and molecular response in gonads of fish	[64]
Carp	30	PE-MPs	8 µm	1000 ng/L	21 days	-	- Hematoxylin-eosin (HE) staining - TUNEL assay - Fluorescence microscopy - Enzyme assay - RT-PCR - UV spectrophotometry - Western blotting - ELISA	TRAF6/NF-kB signaling pathway, Oxidative stress, inflammation	Inflamed ovarian tissues and impaired oocyte development, elevated apoptosis in ovarian cells, reduced miR-132 expression alongside increased CAPN expression, heightened calcium ion concentration in tissues leading to increased CAPN enzyme activity, raised expression of genes associated with mitochondrial damage, and lowered expression of genes that inhibit apoptosis. Changes in the levels of bcl-2, caspase-3, Bax, AIF, and bcl-xl, activation of the p65 factor via the TRAF6/NF-kB pathway leading to increased production of pro-inflammatory factors IL-1β, IL-6, and TNF-α, which contribute to the development of ovarian inflammation	[65]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
Marine medaka (*Oryzias melastigma*)	20	PS-MPs	10 µm	0, 2, 20, and 200 µg/L	60 days	A semistatic system with daily seawater replenishment	- Light microscopy - Oxidative stress analysis - Hematoxylin-eosin (HE) staining - qPCR	Oxidative stress, HPG axis alteration	Histological changes, oxidative stress, disruption of HPG axis, imbalance in sex hormone, delayed development of reproductive glands and decreased fecundity (2, 20, and 200 µg/L), down-regulation of the genes involved in the steroidogenesis pathway, decrease in E2 and T	[66]
Daphnia magna	200 individuals/pe treatment	PE-MPs	34.43 ± 13.09 µm and 17.23 ± 3.43 µm	5 mg/L	7 days	particles with a latex bead-like shape in the aquatic environment in which they are placed	- Fluorescence microscopy	Reproductive and developmental health	Reduced reproductive output was noted in particles of smaller sizes, resulting in a decrease in the number of offspring	[67]
Daphnia magna	-	nano-PS beads	70 nm	0.22 and 103 mg nanoPS/L	21 days	Through the aquatic environment in which they are placed	- Microscopy - Spectrophotometry	Reproductive and developmental health	Reduced population growth, malformation changes, reduced body size and reproduction	[68]
Daphnia magna	20	Pristine polymer microspheres	1–5 µm	0.1 mg/L	21 days	Exposure to powder	- Fluorescence microscopy	Growth, reproductive and developmental health	Parental mortality, reduced growth, decreased reproduction, and decline in population growth rate ultimately led to the extinction of the model population exposed to microplastics in the F1-F3 generations. It takes a minimum of three generations to mitigate the reproductive and developmental abnormalities caused by this exposure	[69]
Poecilia reticulata	60	PS-NPs	23.03 ± 0.266 nm	50 µg/L	30 days	Semi-static exposure system	- ELISA	Reproductive health	A decrease in the pregnancy rate, fewer offspring being produced, the transfer of these nanomaterials from mother to offspring, and physiological impacts on the offspring	[70]
Oryzias melastigma	5 replicates in F and NF groups each including 30 larvaes	PS microspheres	10–11 µm	1×10^5 particles/L	120 days	Stock PS suspension in artificial seawater in which animals are placed	- Microscopy - MPs content analysis - Fluorescence microscopy	Reproductive and developmental health	Decreased rate of egg production, reduced reproduction, and slowed growth, accompanied by elevated mortality	[71]

Table 1 (continued)

Organism	Sample size	Type of MPs	Particle size	Dose	Exposure duration	Exposure method	Employed experimental methods	Influenced pathway	Outcomes	Reference
Japanese medaka *(Oryzias latipes)*	Three replicate tanks ($n=60$) were randomly assigned to each treatment group	PS-MPs	10 µm	500, 1000, or 2000 µg/g	10 weeks	mixed with ultrapure water and then put in a glass tube	- SEM microscopy - ATR-FTIR spectroscopy - Gel permeation chromatography - X-ray photoelectron spectroscopy (XPS) - EPR spectroscopy	Oxidative stress	Reduced egg number in a dose- dependent way	[72]
Tigriopus japonicus	200	PE-MPs and polyamide-nylon 6 (PA 6)	10–30 µm and 5–20 µm	12.5 mg/L	24 h	In artificial seawater in which animals are placed	- SEM microscopy - Fluorescence microscopy	Reproductive and developmental health	Detrimental effects on feeding, egestion, reproduction, survival in a dose-dependent manner, and damage to reproductive organs	[73]
Tigriopus japonicus	10	PS-MPs	0.05, 0.5, and 6 µm	1.25–25 µg/mL	24 h	In artificial seawater in which animals are placed	- Fluorescence microscopy - Oxidative stress analysis - Acute and chronic toxicity tests	Oxidative stress, Reproductive and developmental health	Decrease in fecundity at all concentrations, and caused the mortality in the F0 generation at a concentration greater than 12.5 µg/mL	[74]
Calanus helgolandicus	60	PS-MPs beads	20 µm	75 beads/mL	9 days	glass bottles were filled with either control or microplastic enriched stock solution	- Dissecting microscopy - Analysis of carbon - Ingestion rate, respiration rate, survival rate, egg production rate and egg size determination	Reproductive and developmental health	Decrease in reproductive output, reduced reproductive fertility, eggs with smaller size, and reduced percentage of eggs that successfully hatch	[75]

20, 41]. In addition, MNPs can enter testicular cells, including Leydig cells, Sertoli cells, and spermatogonia, and cause the production of large amounts of ROS. Studies have shown that NPs increase the production of ROS by disrupting the function of the mitochondrial membrane, which causes more damage to the mitochondria [36, 42–44]. Exposure to MNPs through the gastrointestinal (GI) tract causes apoptosis in mouse sperm cells at all stages, and on the other hand, it can also lead to an inflammatory response in that area by stimulating the migration of T helper 17 cells in the testis [41, 45–47]. Long-term exposure to NPs, by inhibiting the autophagy system, can cause serious damage to the cell and also lead to the formation of abnormal acrosome [40, 48]. Finally, it can be mentioned that for male, the damage caused by microplastics includes the creation of the abnormal structure of the testicles and sperm, reduction of sperm life, and endocrine disorders caused by oxidative stress, inflammation, apoptosis of testicular cells, autophagy, abnormal cytoskeleton, and abnormal axis of hypothalamus-pituitary-testis [49].

In females, exposure of the GI tract to MNPs can reduce the ovarian mass-to-body mass ratio, the number and volume of growing follicles, and antral follicles. It can also lead to a reduction in the thickness of the granular layer of secondary follicles or a decrease in granulosa cell count. Also, exposure to MNPs can increase ovarian fibrosis, primary cysts, and atretic follicles and affect female ovarian reserve and fertility [21, 24]. By damaging the structure of the uterus and endometrium, as well as narrowing the uterine glands, these substances can cause embryo implantation to fail [22, 55, 57]. Also, exposure to MPs can be an indirect reason for abortion by disrupting the balance in maternal immunity during pregnancy [33]. MNPs GI tract exposure, also by decreasing the level of estradiol and progesterone and increasing the level of LH and FSH in the serum, causes disorders in female endocrine glands [24, 52]. The effects of exposure to MNPs are dose-dependent and can increase oxidative stress by reducing the level of antioxidant enzymes and increasing the level of lipid peroxide [21, 51, 52]. Also, MNPs increase inflammation by increasing the level of inflammatory cytokines and decreasing the level of anti-inflammatory cytokines, thereby disrupting the structure of the ovary and uterus and endocrine function [46, 47, 76]. So, exposure to MNPs is associated with a decrease in the number and diameter of small uterine arteries and a reduction in endometrial thickness, leading to implantation failure. These small particles can also induce oxidative stress, inflammation, increased apoptosis, and even malignancy in the female reproductive system (Fig. 1). The transfer of NPs from the mother's body to the fetus can accumulate in their various tissues, including the brain, liver, lungs, kidneys, and heart, causing disturbances in metabolism, reproductive function, immune function, neural development, and cognitive function [77, 78]. Also, maternal exposure to MNPs can cause transgenerational toxicity and premature death in children [49, 79].

Impacts of microplastics and nanoplastics on the female reproductive system: a focus on animal models

Studies conducted on animals have shown that MNPs, as hazardous particles, can affect the female reproductive system in various ways. The impacts of these substances have been thoroughly examined, particularly in animal models. By changing its structure, MNPs disrupt the normal function of reproductive system components, including the uterus and ovaries. The structural changes of the uterus can have extensive effects on female reproductive health by disrupting the implantation of the embryo [80]. This change in the structure and function of the ovaries may have unintended consequences, including a decrease in egg production or the creation of non-viable eggs, as well as disruption of the ovulation process [49]. MNPs can reduce the size and number of oocytes by activating or suppressing different signaling pathways, and also decrease the number of follicles in the ovaries, thereby affecting ovulation in the female reproductive cycle [25]. Since follicles and granulosa cells are crucial for hormone production and oocyte development, their loss leads to hormonal imbalance [81]. Exposure to MNPs increases LH, FSH, and testosterone levels while decreasing estradiol and progesterone, potentially leading to female infertility [24]. Additionally, exposure to MNPs by increasing the level of ROS and inducing oxidative stress increases the level of collagen and fibronectin in the uterine tissue, contributing to the progression of tissue fibrosis in this organ [49]. The accumulation of ROS in both ovaries and the uterus leads to increased expression of proteins associated with fibrosis and tissue damage [22]. Exposure to MNPs increases the level of inflammatory cytokines and decreases the level of anti-inflammatory cytokines, indicating the adverse effects of these substances on ovarian and uterine tissues [82]. Lower doses of MNPs temporarily enhance the expression of antioxidant enzymes by activating signaling pathways such as Nrf2/ARE. However, higher doses or prolonged exposure to MNPs inhibit these pathways, intensify oxidative stress, and promote ovarian fibrosis [83]. Also, exposure to high levels of MNPs may trigger inflammation and disrupt the immune system [84]. These substances also affect fertility by inducing gene mutation in gametes [85]. In mice, long-term exposure to MNPs causes a decrease in the

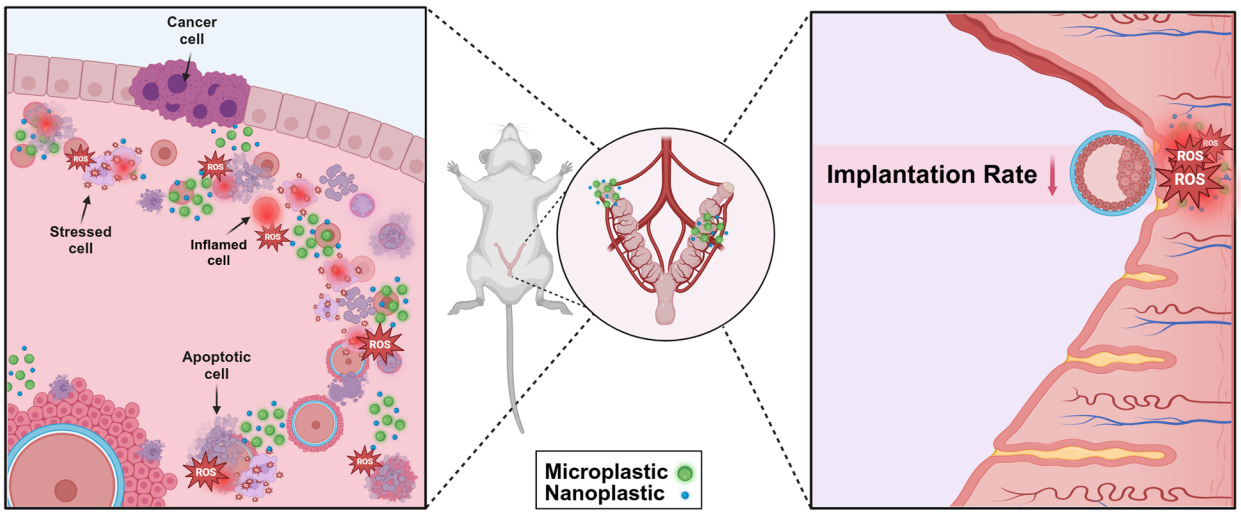

Fig. 1 The effects of micro/nano plastics against the female reproductive system. Accumulation of MNPs in the tissue of the uterus and ovaries leads to oxidative stress, inflammation, and apoptosis in the cells of these tissues, and by weakening the function of these organs, it disrupts their efficiency. In uterine tissue, the reduction of implantation rate can be one of the serious consequences of exposure to MNPs. These plastic particles may also cause ovarian tissue epithelial cells to become cancerous

quality of oocytes and an increase in cell apoptosis in the endometrium. In general, MNPs can accumulate in reproductive organs and, by inducing oxidative stress, apoptosis, reducing the number of follicles, and affecting the hormonal profile, have significant impacts on reproductive health [32, 49]. In the following, we will thoroughly assess and detail the harmful effects of MNPs on the female reproductive system in animal models.

Function and structure of ovaries and uterus

One of the main causes of infertility in females is dysfunction of the uterus and ovaries [46]. Exposure to polystyrene microplastics (PS-MPs) can disrupt female reproductive performance and fertility by causing damage to uterine and ovarian structures [24, 49]. Several studies have shown that MNPs GI tract exposure reduces the number and volume of growing follicles in the ovaries [21, 24, 52, 55] and causes a decrease in the thickness of the granular layer in secondary follicles and also reduces the number of granulosa cells and corpus luteum. On the other hand, these substances can increase ovarian fibrosis and primary cysts [21, 46, 51]. Also, exposure to MNPs reduces the number of antral follicles and increases the number of atretic follicles in the ovaries, which can ultimately affect female ovarian reserve and fertility [57, 86]. In a study, zebrafish that were treated with PS-MPs for 1 to 3 weeks showed the absence of oocyte-follicular cell layer linkage and oocyte vacuolation [63]. It has also been reported that gavage of rats with a certain dose of 5 µm PS-MPs leads to disturbance of the cytoskeleton by reducing the expression of dishevelled associated activator of morphogenesis 1 (DAAM-1) and α-tubulin in ovarian cells [51]. On the other hand, exposure of mice to different doses of PS-MPs with a size of 40–48 µm showed dilation of the abdominal aorta and fallopian tubes [56].

According to reports, MNPs GI tract exposure, by reducing the number and diameter of small uterine arteries and reducing the thickness of the endometrium, causes damage to the structure of the uterus and endometrium and in turn, disrupts the implantation of the fetus [52, 79]. Also, MNPs can lead to uterine fibrosis, narrowing of the uterine glands, and the density of its extracellular matrix [22, 49]. In one study, the histopathological examination of the uterus of mice exposed to a combination of PS-MPs and Pb showed a decrease in uterine glands and glandular lumen thickness and an increase in the number of atretic follicles and interstitium density. In addition, the thickness of the endometrium in these mice was significantly reduced with the loss of glands and lamina propria structures [52]. It has been shown that in Oryzias melastigma, a combination of PS-MPs and phenanthrene can inhibit ovarian maturation and increase the risk of follicular atresia [87].

The weight of the reproductive organs is an indication of the growth, health, and function of the reproductive system [88]. Exposure to PS-MPs significantly reduces the growth coefficient of the body and organs of the uterus and ovary, as well as the uterus and ovary coefficient in female mice [24, 52]. On the other hand, oxidative stress caused by exposure to MPs can cause histological abnormalities in ovaries such as vacuolation

in ooplasm, granulosa cells and interstitial cells, corona radiata disorder, and micronuclei formation in the egg nucleus [25]. Also, PS-MPs weaken the function of ovaries by reducing the level of FSH and can cause infertility in females [24]. Exposure of female mice to Bisphenol A, which is used in the manufacture of various plastics, also causes ovarian cysts and stromal polyps [89].

The ovulation process

The number of eggs produced is the main indicator to evaluate the functioning of the ovaries [90]. Environmental pollutants can have adverse effects on germ cells and the overall process of reproduction during maturation or egg formation [91]. Studies have shown that exposure to MPs affects the quality of eggs by increasing the production of ROS, disrupting oocyte maturation, and inducing apoptosis, and subsequently, reducing the blastocyst rate, fertilization, and fertility [57, 58]. MPs can reduce oocyte production through Wnt/β-Catenin and NLRP3/Caspase-1 signaling pathways, and in addition to reducing the number and size of oocytes, it also reduces their survival rate [62, 92]. Several findings have shown that PS-NPs can significantly increase apoptosis and necrosis in oocytes after several generations and by destroying the spindle structures or actin assembly, they can disrupt the meiotic maturation of oocytes [21, 46, 58, 59]. Also, exposure to PS-MPs decreases the first polar body extrusion rate, glutathione (GSH) level, mitochondrial membrane potential, and endoplasmic reticulum calcium ($[Ca^{2+}]ER$) in oocytes [57].

It has been found that exposure to PS-MPs leads to atrophy of the corpus luteum and eventually to a decrease in its number. Also, these substances play a role in reducing the growth and total number of ovarian follicles and can cause the production of empty follicles [24, 39, 66]. In confirmation of these findings, Haddadi et al. reported that PS-MPs can lead to altered folliculogenesis in rats [51]. In a study on zebrafish, it was found that exposure to a combination of PS-MPs and 17α-Methyltestosterone (MT) leads to vacuolization and a decrease in mature oocytes, as well as loss of communication between eggs and follicular cell layers, and this damage, becomes more severe over time. In addition, this decrease in the number of mature oocytes may occur due to the decrease in LH and FSH levels [63]. Estradiol, acting as a steroid hormone, inhibits apoptosis in granulosa cells and luteal cells, leading to follicular maturation and ovulation. However, its levels decrease under the influence of MPs [24, 93]. Furthermore, following external ovarian stimulation, female mice exhibited a reduced likelihood of ovulated oocytes, with a higher proportion of cumulus-free oocytes retrieved from the oviducts [94].

Female sex hormones and endocrine disorders

The development, maturity, and function of the female reproductive system are influenced by the endocrine system, which regulates the appropriate hormone levels for the proper functioning of reproductive processes [95]. As the main functional units of ovaries, follicles, and granulosa cells produce sex hormones and other growth factors required for oocyte development. Therefore, the loss of these cells causes a disturbance in the level of sexual and reproductive hormones [24, 96]. Estradiol (E2), as a steroid hormone, inhibits apoptosis in granulosa and luteal cells and regulates follicular maturation and ovulation [93, 97]. Granulosa cell apoptosis can lead to endocrine disorders. These cells play a crucial role as the primary producers of E2. When E2 levels decrease due to granulosa cell apoptosis, it triggers a chain reaction. This includes an increase in LH and FSH levels, mediated by negative feedback from the hypothalamic-pituitary-ovarian (HPO) axis. Consequently, this disruption in the endocrine system occurs [24, 51, 97, 98].

By accumulating in the reproductive organs and through the induction of oxidative stress and apoptosis, MPs disrupt the function of the endocrine glands as well as the reproductive system [11, 99, 100]. PS-MPs can enter hormone-producing cells in the ovaries and reduce the number of follicles [101]. These substances also affect the steroid synthesis pathway through the Hypothalamic-pituitary-gonadal (HPG) axis and then affect the reproductive endocrine system [102, 103]. During several studies, it was found that after MNPs GI tract exposure, serum LH, FSH, and testosterone levels increased in female rats, but serum E2 and progesterone levels decreased significantly, which could weaken ovarian function, and eventually lead to female infertility [24, 51, 52, 55]. Also, exposure to MNPs reduces the level of sex steroid hormones such as 17β-estradiol, hatching rate, and gamete formation in Oryzias melastigma, and by disrupting the HPG axis, it affects the development of ovaries and the female reproductive system [66].

MNPs may contain environmental endocrine-disrupting chemicals (EDCs), which are a group of compounds with hormone-like biological effects and can disrupt the endocrine balance by affecting the secretion and metabolism of sex hormones [104, 105]. Exposure of female zebrafish to PS-MPs and 17α-Methyltestosterone (MT) as an EDC for 7 days increased the expression of cyp19a1a mRNA in the ovaries, which in turn plays a role in the conversion of testosterone to estrogen. MT may disturb the hormonal balance in the body by increasing the level of testosterone and upregulating cyp19a1a mRNA and causing an increase in serum E2 level [63, 106]. On the other hand, Rong et al. reported that exposure to a certain dose of PS-MPs, MT, and PS-MPs + MT

for 14 days caused a significant decrease in the levels of LH, FSH, and E2 in female zebrafish ovaries [63]. A decrease in the level of LH and FSH, as key factors in regulating the level of expression of steroid hormones, reduces the number of mature ovules and delays the growth of gonads [63, 107, 108]. Also, a study on oysters has shown endocrine disruption in exposure to PS-MPs [62]. Long-term exposure to PS-MPs and MT often exacerbates hormonal imbalance by inhibiting the genes responsible for steroid hormone production and blocking their synthesis [63]. Also, exposure to PS-MPs along with Pb causes more severe damage to the follicles and causes a further decrease in the level of progesterone and E2 [52].

Triggering oxidative stress

The main toxicity caused by exposure to MNPs is increased ROS accumulation and induction of oxidative stress [109]. Oxidative stress can be described as an imbalance between the production of reactive oxygen species and the body's ability to deal with it [110], which can affect egg quality and fertility. Exposure to MPs causes oxidative stress in the female reproductive system by increasing the level of ROS [58]. Oxidative stress caused by contact with MPs appears in a dose-dependent manner [49]. Investigations revealed that exposure of the GI tract to MNPs resulted in increased levels of reactive oxygen species in the ovarian tissue of rats. Concurrently, there was a decrease in the levels of antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and total antioxidant capacity (TAC), while the levels of lipid peroxide and malondialdehyde (MDA) also increased [22]. While lower doses of MPs GI tract exposure (e.g. 0.1 mg/day) lead to an increase in the level of antioxidant enzymes such as SOD, and CAT, this increase is probably due to the activation of the Nrf2/ARE signaling pathway. In fact, as a result of oxidative stress, Nrf2 is separated from keap1 in the cytoplasm and after phosphorylation and transfer to the nucleus, it connects to the ARE part of the promoter of CAT and SOD genes and increases the expression of these enzymes [51, 111]. These findings are supported by reports indicating that the level of Nrf2 and its downstream proteins increases after exposure of ovarian granulosa cells to MPs for one day. However, with an increase in MPs dosage or exposure time, the Nrf2 signal is inhibited, and the levels of antioxidant enzymes decrease, intensifying oxidative stress [51, 55]. The accumulation of ROS in the ovary, by increasing the expression of the main proteins involved in the Wnt/β-catenin signaling pathway, causes more activity of this pathway and more β-catenin transfer to the nucleus of ovarian fibroblasts, and in the same way, the expression of transforming growth factor-β (TGF-β), α-smooth muscle actin (α-SMA), increase fibronectin and other protein factors related to fibrosis and eventually cause ovarian fibrosis [21].

Toll-like receptor (TLR4)/NOX2 signaling pathway can increase ROS production and then oxidative stress in different stress conditions. It has been reported that in the uterine tissue of female rodents exposed to MPs, the activation of Notch and TLR4 pathways and the production of ROS, followed by the increase of collagen and uterine proteins, cause uterine fibrosis [22]. PS-MPs by increasing the expression of high mobility group box 1 protein (HMGB1) and acetyl-HMGB1, which act as TLR4 ligands, cause the activation of this receptor, followed by the activation of NOX2, and finally by triggering the TLR4/NOX2 signaling pathway increases ROS and aggravates oxidative stress [22, 112]. The increase in ROS caused by exposure to MPs in the uterus increases the expression of a disintegrin and metalloproteinase kinase (ADAM kinase), γ-secretase, and Notch protein ligands (Delta and Jagged) and activates the Notch signaling pathway, which this pathway can directly increase the level of fibronectin and collagen and indirectly through cross-talk with TGF-β/Suppressor of Mothers against Decapentaplegic 3 (Smad3) signaling pathway may be involved in uterine fibrosis [22]. Indeed, following the activation of Notch signaling, the notch intracellular domain (NICD) increases the transcription of genes involved in fibrosis by transferring to the nucleus and interacting with DNA binding protein CSL. In addition, NICD can increase the activity of the TGF-β/Smad3 signaling pathway through direct interaction with phosphorylated Smad2/3, and thus increase the expression of proteins involved in fibrosis such as collagen, α-SMA, matrix metalloproteinases-2/9 (MMP2/9) and Hes family [22, 113] (Fig. 2). Inhibitors of TLR4/ NADPH oxidase 2 (NOX2) and γ-secretase signaling can effectively prevent increased ROS, Notch activation, collagen expression, and uterine fibrosis [22, 114, 115]. Experimental results have shown that PS-MPs can induce pyroptosis and apoptosis in ovarian granulosa cells through the NLRP3/Caspase-1 signaling pathway, which can be related to oxidative stress and the loss of its antioxidant capacity, and increase the risk of female infertility [46]. It has been found that co-exposed to PS-MPs and Pb, through the protein Kinase RNA-Like ER Kinase (PERK)/Eukaryotic initiation factor-2α (eIF2α) signaling pathway, causes oxidative stress and ovarian toxicity and reduces the number of follicles and oocyte quality in mouse ovaries [52].

Inflammation and reproductive aging

Exposure to high amounts of MPs may cause damage to the nervous system, followed by inflammation

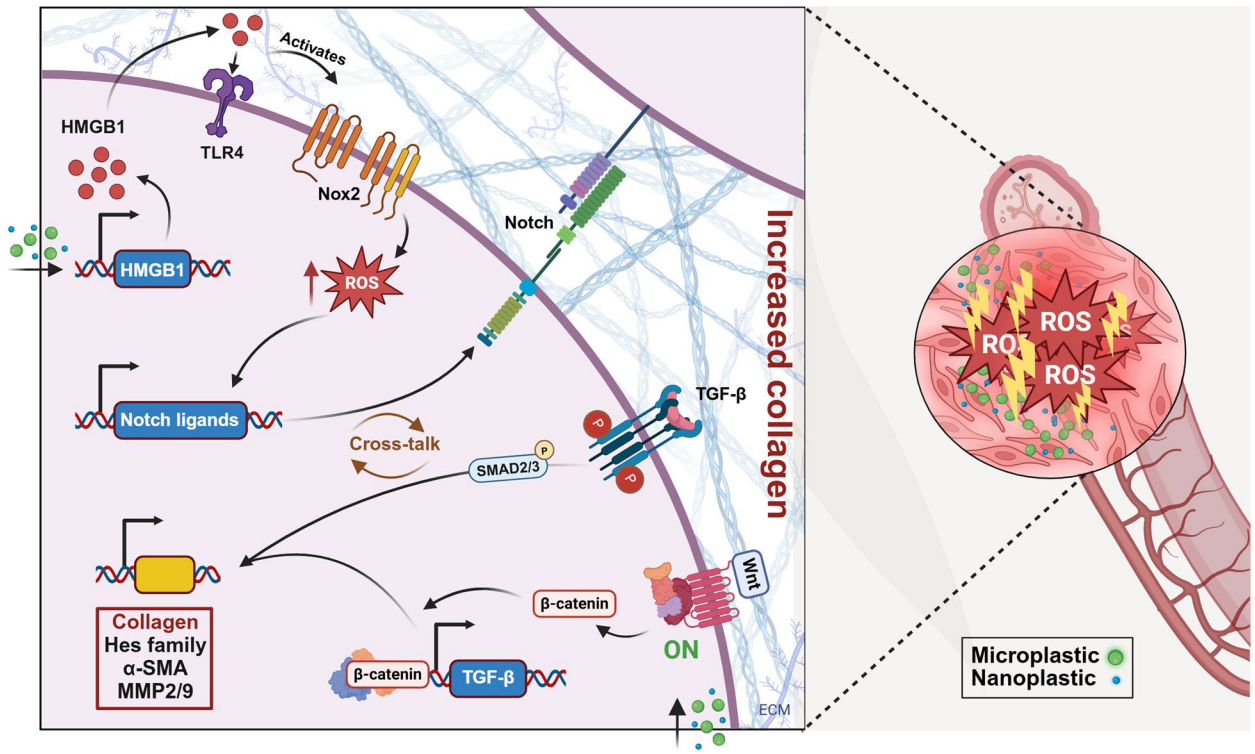

Fig. 2 Molecular pathways involved in the increase of fibrosis in the ovary and uterus by exposure to micro/nano plastics. The occurrence of fibrosis in the ovary and uterus can be caused by the accumulation of MNPs in these tissues. By increasing the expression of HMGB1, MNPs cause the activation of NOX2 after activating the TLR4 receptor, which ultimately increases the expression of Notch ligands by increasing the level of ROS and ultimately leads to the activation of the Notch signaling pathway. Through cross-talk with the TGF-β signaling pathway and the effective transfer of p-SMAD2/3 to the nucleus, this pathway activates the expression of collagen, α-SMA, MMP2/9, and Hes family, increasing the collagen fibers in the ECM. Also, the activation of the Wnt/β-catenin signaling pathway as a result of exposure to MNPs, with the effective transfer of β-catenin to the nucleus, increases the expression of TGF-β, followed by the increase of collagen in the ECM of the cell which eventually causes fibrosis in the uterus and ovaries

and disruption of the immune system [84]. Studies have shown that MPs can induce oxidative stress, inflammatory responses, and finally gene mutation in gametes and reduce fertility in animals [85, 116]. Oxidative stress with ion influx and cell lysis leads to the release of IL-18, IL-1B, and other inflammatory cytokines [82, 117]. Increased levels of inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-18, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) in serum, ovary, and uterine tissues [21, 57] and also the decrease in the level of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, are the main signs of inflammation caused by exposure to MPs [22]. TLR4, as a toll-like receptor, can stimulate the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) with the help of tumor necrosis factor receptor-associated factor 6 (TRAF6) and ultimately cause the release of inflammatory factors. MPs, such as polyethylene microplastics (PE-MPs), can increase the amount of ROS in ovaries and stimulate TLR4 receptors, causing the TLR4/TRAF6 signaling pathway and TRAF6 ubiquitination and then activate inhibitor of κB kinase (IKK) and finally cause the activity of NF-κB transcription factors [22, 118]. NF-κB, by regulating the transcription of precursor mRNAs, causes the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and also through the NLRP3 inflammasome pathway, by activating caspase-1, it leads to the transformation of pro-IL1β and pro-IL-18 into mature IL-1β and IL-18, respectively, and thus cause pro-inflammatory responses [46, 47, 76, 119]. Liu et al. showed that exposure of mice to PS-MPs for 35 days can lead to inflammation and reduced oocyte quality [57]. Also, MPs can cause severe apoptosis of epithelial cells and inflammatory responses in the endometrium [120]. In general, MPs can cause inflammation in the uterus and ovaries through the induction of oxidative stress and subsequently affect female fertility [49].

Although inflammation is considered a defense response, this process can also be harmful to body cells and tissues [49]. Inflammatory cytokines and reactive oxygen species can disrupt estrous cycles and steroidogenesis and, in addition, prevent meiotic and cytoplasmic

maturation of the oocyte [121]. Also, inflammation can lead to ovarian aging and ultimately reproductive aging in females [122]. Reproductive aging in women is defined by a gradual decline in the number of follicles and the quality of oocytes, which can lead to the loss of fertility and ovarian function. Inflammatory processes have been suggested as potential contributors to this decline [123, 124]. An animal study showed that the decrease in follicle numbers over the reproductive lifespan was associated with an increase in the percentage of CD^{4+} T cells, B cells, and macrophages within the ovary. Serum concentrations and intra-ovarian mRNA levels of several pro-inflammatory cytokines, including IL-1α/β, TNF-α, IL-6, and inflammasome genes ASC and NLRP3, also significantly increased with age [122]. Furthermore, oxidative stress, as one of the consequences of micro/nanoplastics, has been reported to act as an initiator of oocyte aging and reproductive pathology [125].

Cellular damage and apoptosis

MPs can cause apoptosis, DNA damage, and autophagic cell death by inducing oxidative stress and inhibiting metabolic pathways [126]. Long-term exposure to PS-MPs can induce apoptosis and pyroptosis in ovarian granulosa cells through the NLRP3/Caspase-1 signaling pathway, which is caused by oxidative damage. In fact, with the increase of oxidative stress, NLRP3 inflammasome is activated after the phosphorylation of NF-κB and causes the activation of caspase-1 through the factors involved in this pathway. Finally, caspase-1 leads to pyroptosis and apoptosis of ovarian granulosa cells by converting pro-IL-1β and pro-IL-18 to IL-1β and IL-18 [46]. It has been shown that exposure of Caenorhabditis elegans to PS-MPs can have deleterious effects on the reproductive system through induction of apoptosis and DNA damage. The researchers found that exposure of these nematodes to PS-MPs for 28 days could change the expression of genes related to apoptosis, such as ced-3, ced-4, and ced-9, and lead to the induction of apoptosis in them [60]. In a study, it was found that exposure of rats to PS-MP particles with a size of 0.5 micrometers and concentrations of up to 1.5 mg/kg per day led to various serious complications, including the induction of cell apoptosis, cell death in the ovary, and reduction of ovarian reserve capacity, excessive proliferation of ovarian fibroblasts, as well as the accumulation of extracellular matrix [46, 101]. It has also been found that the rate of early apoptosis in the oocytes of mice exposed to MP is significantly increased compared to normal oocytes [58]. Hou et al. reported that in rats exposed to 0.5 μm PS-MPs at a dose of 0-1.5 mg/kg/day, apoptosis and death of ovarian cells and hyperproliferation of ovarian fibroblasts were observed [46, 101]. Also, PS-MP particles can be deposited in the granulosa cells of the ovaries of female mice and induce pyrolysis and apoptosis in these cells [46]. Exposure to MPs can disrupt oocyte maturation and affect the quality of oocytes by excessive production of ROS followed by increased apoptosis [58]. Oxidative stress can lead to ER stress [127]. ER stress occurs as a result of increased protein synthesis, changes in calcium homeostasis, and ultimately the accumulation of unfolded or misfolded proteins in the ER lumen [128, 129]. Long-term ER stress can cause reproductive system disorders through apoptosis [130]. Exposure to PS-MPs along with Pb causes an increase in unfolded and misfolded proteins and finally increases the level of binding immunoglobulin protein (BIP) in the ovaries. To prevent ER stress and maintain ER homeostasis, ER transmembrane proteins including PERK, activating transcription factor 6 (ATF6), and inositol-requiring enzyme type 1 (IRE1) are separated from the Bip chaperone, and by activating the relevant signaling pathways, they increase protein folding and remove misfolded proteins [52, 131]. On the other hand, unfolded protein response (UPR) induces apoptosis through the PERK/CHOP signaling pathway. Active PERK causes the activation of ATF4 and increases the expression level of CHOP through the phosphorylation of eIF2α. Exposure to PS-MPs together with Pb increased the expression of PERK, ATF4, eIF2α, and CHOP and therefore induced ER stress through the PERK/eIF2α/CHOP pathway [132–135].

Tu et al. (2023) showed that in Drosophila, continuous exposure of developing oocytes to 10–100 mg L^{-1} PS-NPs in five generations caused apoptosis and necrosis as well as reduced oocyte production. Polystyrene nanoplastics have caused significant changes in the transcription of genes related to reproduction, metabolism, lifespan, and apoptosis in Drosophila and thus affect their reproductive capacity [59]. Buffy is a B cell lymphoma-2 (Bcl-2)/Ced-9-like and pro-survival protein in Drosophila [136]. Overexpression of Buffy increases apoptosis caused by γ radiation and exposure to PS-NPs causes apoptosis and necrosis of ovaries by regulating the expression level of buffy [59]. In a study on zebrafish, it was found that PS-NPs with 70 nm diameter cause behavioral changes, and the accumulation of these nanoparticles in gonads leads to apoptosis of germ cells and disruption of the reproductive system [137].

MNPs and cancers of the female reproductive system in animal models and human studies

Exposure to MNPs can accelerate the progression of carcinogenesis in certain types of cancer [138–140]. To support tumor growth and development, tumor cells produce significant cellular and molecular changes in their host tissue, and this change in the tumor microenvironment

plays an important role in cancer development [141, 142]. Studies have shown that PS-NPs can accelerate the growth of epithelial ovarian cancer (EOC) tumors in animal models. In vivo experiments on mice showed that exposure to PS-NPs through drinking water increased tumor weight and volume and accelerated tumor growth. These NPs can change the tumor's microenvironment by influencing the expression of genes and disrupting the cell's metabolic pathways, leading them to become cancerous. Also, it was shown that PS-NPs can strongly affect pathways related to immune responses and thrombomodulin regulators. These molecular changes can play an important role in accelerating the growth of ovarian cancer [54]. In addition, PS-MPs have been shown to increase apoptosis and oxidative stress, which are known to be key factors in cancer growth and spread, in ovarian tissues, hence, it can be considered as a background for ovarian cancer. The Keap1/Nrf2/HO-1 pathway, known as a key regulator of cellular antioxidant responses and playing a crucial role in protecting cells against oxidative stress, can be disrupted by MPs, especially PS-MPs. This disruption leads to an increase in ROS, causing extensive damage to DNA and other vital cellular molecules, ultimately triggering carcinogenic processes. However, long-term exposure to PS-MPs can promote the formation and progression of ovarian cancer through the induction of oxidative stress and apoptosis [143, 144].

Recent studies have shown that MNPs exist in human tissues including cervical tumors. Specifically, one study reported that MPs from polystyrene, polyvinyl chloride, and polyethylene were detected in 17% of cervical tumor samples [145]. The presence of MPs can change the tumor's immune microenvironment and affect therapeutic responses. Therefore, these findings can create new challenges in cancer treatment [146]. On the other hand, these nanoplastics can cause inflammation, oxidative stress, and cell dysfunction. These disorders may lead to genetic changes and faulty signaling that ultimately increase the risk of developing cancer, including cervical cancer. In addition, NPs can transport toxic substances into cells, which can seriously endanger human health [147]. Over time, as these NPs accumulate in the body, the risk of developing cancer also increases [148]. Although MNPs at low concentrations may have negligible negative effects on cells, at higher concentrations, they can cause cytotoxicity and induce them to become cancerous [149]. Also, long-term exposure to NPs may lead to chronic inflammation and changes in cells that are associated with an increased risk of cancer [150]. NPs may inadvertently penetrate cells and, by accumulating in tissues, exert toxic or stimulatory effects that can contribute to cancer growth [151, 152]. Polyethylene glycol is also a plastic compound that may exist as environmental MNPs. Its widespread use in nanotechnology and medical treatments raises concerns about the long-term stability of these materials in the body and their potential links to health issues, including cancers [153, 154].

The influence of microplastics and nanoplastics on the placenta and fetal development

Animal models

In this section, the effects of microplastics and nanoplastics on the female reproductive system and fetal growth in animal models are described. This content includes the effects of these particles on the placenta, fetus, and the health of future generations. MPs can be absorbed and accumulated in the placenta in a size-dependent manner, and by affecting embryonic development, it can lead to failure in reproduction [58]. The exposure of mothers to PS-NPs can cause the transfer of these substances to the tissues of the placenta and fetus and disrupt the growth and development of the fetus [29, 155]. Wan et al. (2024) used 50 nm PS-NPs to determine the effect of MNPs on trophoblast cells. They reported that PS-NPs induced abortion in pregnant mice and also suppressed rho-associated, coiled-coil-containing protein kinase 1 (ROCK1)-mediated migration and invasion in these cells. ROCK1 can reduce miscarriage by preventing the formation of migrasome, which is formed as an organelle after the migration of cells. It was found that exposure to PS-NPs caused suppression of SOX2-mediated ROCK1 transcription by activating autophagy and increasing autophagy degradation of SOX2 and eventually, affect the mother and fetus's health by increasing the risk of abortion [156].

Recently, researchers found that maternal exposure to PE-MPs, despite causing increased blood flow in the fetal umbilical artery and consequently disrupting the normal function of the placenta, does not alter fetal growth. This may be due to the lower toxicity of PE-MPs compared to other MNPs such as PS-NPs and their impact on placental and fetal growth in late pregnancy. The increased blood flow in the umbilical artery could be due to the higher extraction of oxygen from the mother's blood to sustain fetal growth, which is an adaptive response to compensate for the toxic effects of these pollutant particles [157]. Also, in another study, it was found that although MPs increase blood flow in the umbilical artery, NPs decrease blood flow in this artery. These results show that MNPs cause impaired placenta function, which is strongly dependent on the size of these particles [158].

In addition, significant changes in placental metabolism due to exposure to MPs have been reported, such that exposure to high concentrations of 5 μM PS-MPs caused a significant decrease in the relative concentration of placental lysine and glucose, and cause disturbances

in glycolysis, gluconeogenesis, biotin metabolism, and lysine degradation [159]. Also, PS-NPs disrupt cholesterol metabolism in the placenta and fetus and show significant metabolic disorders by affecting the concentration of sucrose and daidzein as well as complement and coagulation cascade pathways. On the other hand, these nanoparticles also affect the expression level of genes related to inflammation and iron homeostasis [160, 161].

NPs reach fetal tissues within 24 h after maternal exposure but are removed from fetal circulation before birth. The health of children after birth and adulthood is affected by the deposition of these particles in fetal tissues during its development [29]. Also, PS nanoparticles can cause abnormal cell morphology in both placenta and fetus [161]. It has been found that exposure to PS-MPs can reduce the fertility rate and the number of embryos and lead to abnormal conception and affect the formation of the embryo. PS-MPs also affect the fertility of male and female mice, reducing the survival and growth of embryos. It should be noted that the fertility of female mice is more affected by these substances than male mice [24, 62, 162].

Exposure of male and female mice to MPs, in addition to causing changes in sex ratio and body weight in the offspring, can also disrupt the metabolism of lipids and amino acids in the offspring and affect the health of the next generation [56, 163]. While MPs increase the level of ROS in oocyte, blastocyst, and embryo, by inducing oxidative stress, they increase apoptosis in embryonic cells and decrease the level of GSH in these cells [58]. To treat this condition, N-acetylcysteine (NAC) has been proposed as an antioxidant to reduce the oxidative damage caused by PS-MPs [83]. Oxidative stress caused by gestational and lactational MPs exposure in mice can also cause damage in their offspring [58].

The passage of NPs through the blood-placenta barrier (BPB) and their transfer via breast milk to offspring are the two main pathways through which offspring are exposed to nanoplastic particles [29, 78], and the transfer of these materials through the placenta depends on their size [164]. Exposure of mother mice to NPs during pregnancy and lactation can cause deposition of these nanoparticles in the intestine, liver, brain, lungs, kidney, and heart tissues of the next generation mice and disrupts their immune system, nervous system, metabolism, and reproduction [29, 77, 78].

After mother's exposure to MPs, glycolipid metabolism was reduced by the oxidative inhibition of fatty acids in the offspring, which is probably due to the reduction of carnitine levels in them. In addition, lipids were accumulated in the liver for a longer period of time and the absolute weight of the children's liver was greatly reduced due to inflammatory infiltration and oxidative stress [79, 163, 165]. It has been observed that when the mother is exposed to MPs during pregnancy, the weight of the testes in their male offspring is reduced and disorganized arrangement occurs in their spermatocyte layers [79]. By disrupting the homeostasis of the children's immune system, these substances cause a decrease in T cells and an increase in Th cells in their spleen and can also inhibit the maturation of dendritic cells [56].

MPs disrupt the balance and function of maternal and fetal immune systems and increase the number of T cells in the placenta; Also, they suppress the immune system by reducing the ratio of pro-/anti-inflammatory cytokines and ultimately indirectly increase the risk of miscarriage [33]. Recent studies show that exposure to MPs during pregnancy and early development in mice can lead to neurodevelopmental problems in the offspring. This includes defects in brain development, impaired brain function and metabolism, and cognitive impairment [79]. Although both MPs and NPs can accumulate in the placenta, only NPs can cross the BPB and enter the fetal brain, especially the thalamus, and disrupt the fetal brain development by inducing oxidative stress and inhibiting the production of γ-aminobutyric acid (GABA) [53].

Also, PS nanoparticles caused anxiety-like behaviors in eight-week-old offspring of mice, which can eventually lead to neurobiological disorders. It was found that the use of glutathione supplementation can reduce oxidative stress and apoptosis caused by PS-MPs in neuronal cell lines [53]. MPs also affect neural stem cells, prevent normal neural growth, and lead to reduced cell proliferation and abnormal production of glial cells in the hippocampus. These substances also change gene expression patterns in neural stem cells and lead to defective neurogenesis by reducing genes involved in cell division and proliferation [78].

In female offspring, MPs exacerbate cognitive dysfunction during brain development. In addition, prenatal and early postnatal exposure to MPs leads to decreased dopamine transporter protein, impaired glucose metabolism, altered gene expression, and autism-like behaviors in offspring and parental exposure to MPs exacerbates these neurodevelopmental disorders in offspring [79]. It has also been determined that the heart rate index of the middle cerebral artery in fetuses exposed to MNPs decreases significantly, which is caused by dilation of cerebral circulation vessels, a type of fetal adaptation preserve oxygen delivery. As a result, exposure to NPs during pregnancy can lead to adverse neurodevelopmental outcomes by causing hypoxia and impaired placental function and fetal brain development [158]. A summary of studies on placentas and fetuses of different animals

that were affected by exposure to microplastics and nanoplastics is summarized in Table 2.

Human studies

Here, we discuss the effects of microplastics and nanoplastics on the placenta, fetus, and other tissues related to female human reproductive system. MPs can enter the food chain and disperse as airborne particles, so involuntary ingestion and inhalation are not out of the question. Due to their small size, MNPs and especially NPs can pass through the digestive epithelium and be absorbed by the body. Although it is believed that only 0.3% of these particles can be absorbed, it has been determined that particles with a size of less than 10 micrometers enter the placenta by passing through the cell membrane and cause toxicity in the fetus [171–173]. Embryonic cells are very vulnerable to toxicity due to intense and regulated proliferation, differentiation, apoptosis and migration during organogenesis, and any disturbance in the growth, proliferation, and differentiation of cells before and after birth can lead to adult-onset disease [174, 175]. Exposure of pregnant mothers to nanoplastics can damage the developing fetal brain. These particles can cross the placental barrier, causing neuroinflammation, oxidative stress, and disruption of signaling pathways. These effects may lead to defects in brain development, cognitive impairments, and motor disorders [164, 176–179] (Fig. 3). However, these particles can cause developmental toxicity by accumulating in the placenta and damaging it, which may overshadow the health of the mother during pregnancy in addition to the health of the fetus [180]. Epidemiological data showed that preeclampsia, premature birth, stillbirth, and spontaneous abortion can be the results of exposure of pregnant mothers to (ultra)fine particles [180, 181].

Exposure to MPs results in placental growth disorders, oxidative stress and inflammation, activation of placental-like receptors (TLRs) and changes in hormone secretion [92]. Also, the absorption of MPs in the villous tissues, which are the main tissues of the placenta for the exchange of nutrients between the mother and the fetus, may significantly increase the risk of miscarriage [32]. So far, the presence of MNPs in placenta samples, meconium, infant feces, and breast milk samples has been reported [182]. Based on the studies, MPs with a size of approximately 5 to 10 μm were observed in placental tissue and chorioamniotic membranes [30, 163]. Also, the presence of 11 different types of MPs in placenta tissue has been identified, among which polyvinyl chloride (PVC)-MP has the largest share [183]. Grafmueller et al. showed that all PS-MPs accumulate in the placental syncytiotrophoblast, indicating transport of MPs in an energy-dependent manner in the placenta [184].

Examining the placenta tissue in several studies has shown the accumulation of MNPs particles in this tissue. Using Raman microspectroscopy, researchers revealed the presence of 12 MPs fragments in the placentas of 6 women [30]. Also, in confirmation of these findings, in another study, the existence of MPs in the tissue of 17 human placentas was evaluated and it was determined that polypropylene, polyvinyl chloride and polybutylene succinate particles with a size of 200–307.29 μm can accumulate in the placenta [183]. Amereh et al. showed the presence of MPs such as PE and PS in the placentas of 43 women who agreed to have their pregnancies checked for the presence of microplastics (2 to 38 particles per placenta). The results showed that these pollutant particles, which were mostly smaller than 10 μm in size, may cause disturbances in the mutual relations between the placenta and the fetus through disruption of gas and nutrient exchange [185].

Also, placental tissue analysis using pyrolysis-gas chromatography and mass spectrometry showed the presence of 12 types of MPs with different concentrations in this tissue that PE, PVC and nylon constituted the majority respectively [179]. In another study, the measurement of MPs in placenta, meconium, infant feces, breast milk, and infant formula samples of 18 cases, showed 16 types of MPs with an average size of 20–50 μm, with polyamide and polyurethane constituting the majority. Scrub cleaners, toothpaste, food bottles and plastic toys were also introduced as sources of exposure for these pregnant women and infants to MPs [182, 186]. In addition, MPs and plastic additives have also been observed in the amniotic fluid of women who experienced preterm prelabor rupture of membranes [187]. On the surface of villi containing MPs in placentas collected from some women, oxidative stress, cell death, and inflammatory reactions were observed [30].

Infants are at greater risk from these particles due to their insufficient production of metabolizing enzymes and reduced ability to eliminate MPs [188]. The heart, as a fetal organ targeted by MNPs, can face developmental disorders under the influence of these substances. By disrupting the differentiation of cardiomyocytes from human embryonic stem cells (hESCs), PS-NPs cause their immaturity and increase mitochondrial oxidative stress, and finally reduce the pluripotency of hESCs by activating the P38/Extracellular signal-regulated kinase (Erk) Mitogen-activated protein kinase (MAPK). It was also found that continuous exposure to PS-MPs reduces cardiac contractility and fetal blood flow [189].

The toxicity of MPs largely depends on their size and surface charge. A study has determined that NH2-labeled PS-NPs increase oxidative stress and toxicity in placental cells, inhibit protein kinase A activity, and cause cell cycle

Table 2 The influence of microplastics on various fetal structures and organs

Organism	Organ or tissue	Sample size	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
A) Rat and mice experimental models							
C57 BL/6 mice	Placenta, fetal growth, and metabolism	40	PS-NPs	100 nm	1 and 10 mg/L	At higher exposure concentrations, there was a notable decrease in fetal weights, along with the presence of abnormal cell morphologies in both the placenta and fetus. Additionally, alterations were observed in the distribution of pathways related to cholesterol metabolism, complement, and coagulation cascades.	[161]
C57BL/6J mice	Brain	10	PE-MPs	10–20 µm	100 ppm/100 µL	PE feeding resulted in ASD-like traits	[77]
Pregnant C57BL/6 J mice	Brain (central nervous system)	-	Carboxylated PS-NPs & PS-MPs	50 nm, 0.5 µm	0, 0.5, 10, 100, 500, 1,000 µg/cm3 PS-NPs contained in the agarose jelly cubes	Administration of polystyrene nanoplastics (PSNP) to mothers during gestation and lactation affected the functioning of neural stem cells (NSCs), the composition of neural cells, and brain histology in their offspring. Molecular and functional abnormalities induced by PSNP were also detected in cultured NSCs in vitro. Exposure to high concentrations of PSNP led to abnormal brain development, resulting in neurophysiological and cognitive impairments, which manifested in a gender-specific manner.	[78]
C57BL/6-mated BALB/c mice	Uterine	18	PS-MPs	10 µm	250 µg/200 µL saline	There was an increase in the resorption rate and a decrease in the quality and size of uterine arterioles, leading to reduced uterine blood supply in offspring. Additionally, there was an increase in helper T cells, a decrease in natural killer cells, and a shift in the M1/M2 ratio in macrophages toward a dominant M2 subtype in the placenta.	[33]
SPF C57BL mice	Brain	30	PS-NPs and PS-MPs	100 nm and 1000 nm	10 mg/mL solution	The offspring exhibited anxiety-like behavior, accompanied by a reduction in gamma-aminobutyric acid levels in the prefrontal cortex and amygdala at Week 8. Furthermore, the nanoparticles entered the fetal thalamus, leading to destruction via reactive oxygen species and apoptosis in neuronal cell lines.	[53]

Table 2 (continued)

Organism	Organ or tissue	Sample size	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Kunming mice	Reproductive system	60	PE-MPs	10–150 µm	0.4, 4, and 40 mg/kg/d	Maternal exposure to microplastics during pregnancy led to a decrease in birth weight and postnatal body weight in offspring mice. Additionally, there was a reduction in oocyte maturation, fertilization rate, and embryonic development in the female offspring.	[58]
Kunming mice	Liver and testis	32	PS-NPs	100 nm	0.1, 1 and 10 mg/L	Maternal exposure to polystyrene nanoparticles resulted in reduced birth weight and postnatal body weight in offspring mice. High doses of PS-NPs decreased liver weight, induced oxidative stress, triggered inflammatory cell infiltration, upregulated the expression of proinflammatory cytokines, and disrupted glycometabolism in the livers of male offspring mice. Both pre- and postnatal exposure to PS-NPs led to decreased testis weight, disruption of the seminiferous epithelium, reduced sperm count, and caused oxidative damage in the testes of offspring mice, as evidenced by increased malondialdehyde generation and alterations in the activities of superoxide dismutase and catalase.	[79]
Timed pregnant CD-1 mice	Ovary, uterus, uterine cervix, and oviduct	30	BPA (Plastic additives)	-	0.1, 1, 10, 100, and 1000 µg/kg/day	There was an increase in progressive proliferative lesions of the oviduct. Ovarian cysts were significantly increased in the 1-µg/kg BPA group, while ovarian cyst-adenomas were observed in the 0.1, 100, and 1000 µg/kg BPA groups. Maternal exposure to BPA also resulted in atypical hyperplasia and stromal polyps of the uterus, sarcoma of the uterine cervix, and mammary adenocarcinoma in the offspring.	[89]

Table 2 (continued)

Organism	Organ or tissue	Sample size	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Pregnant FVB/N mice	Placenta	-	Yellow-green carboxylate modified PS nanoparticles	20, 40, 100, 200, and 500 nm	< 500 µg/ml	Particles with a size of 500 nm were absorbed by the placenta and could traverse the placental barrier. The uptake of nanoparticles by placental tissue was notably higher for particles with a diameter of 40 nm. Nanoparticles with diameters of 20 nm (at a concentration of 200 µg/ml) and 40 nm (at a concentration of 500 µg/ml) were capable of inducing apoptosis in trophoblast cells, as evidenced by increased levels of cleaved caspase 3 and reduced cell proliferation.	[155]
A) Other species							
Drosophila melanogaster	Reproductive system	-	PS-NPs	100 nm	1, 10, 50, and 100 mg L^{-1}	Increased necrosis and apoptosis of oocytes in the F5 generation, and KEGG pathway with significant enrichment of differentially expressed genes	[59]
Oysters	Reproductive system	240	PS-MPs	2 and 6 µm	14 ± 2% of the 2-µm Particle and 69 ± 6% of the 6-µm particles	Offspring derived from exposed parents exhibited a 41% decrease in D-larval yield and an 18% decrease in larval development compared to control offspring.	[62]
Zebrafish (Danio rerio)	Reproductive system, skeletal system, digestive system	300	PE-MPs and benzo[α]pyrene (MP-BaP)	20–27 µm	355–700 µm	Microplastics induce changes in developmental traits, including reduced fecundity, yolk area, and altered egg shape from one month to three months post-fertilization. They also have a discernible impact on bone development, leading to intestinal inflammation, increased occurrences of skeletal deformities, decreased bone quality, and impairment of intergenerational bone formation.	[166]

Table 2 (continued)

Organism	Organ or tissue	Sample size	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Zebrafish (Danio rerio)	Eyes and reproductive system	-	PS-MPs	10 µm	200 particles/mL	A delay in hatching and changes in larval development were observed, with notable deformities primarily affecting the spinal column and tail. Additionally, there were compromised visual structures in the eyes. Furthermore, there was an increase in the transcription levels of genes related to oxidative stress (cat, sod1, and sod2) and cellular detoxification (cyp and gst).	[167]
Zebrafish (Danio rerio)	Chorion	-	PS-NPs	40 nm	0.1, 1, and 10 µg/ml	Microplastics are capable of penetrating the chorion of developing zebrafish, accumulating in their tissues, and exerting effects on physiology and behavior, potentially impacting organismal fitness.	[168]
Zebrafish	Reproductive system	180	PS-MPs	65 nm and 20 µm	20 mg/L	leading to lower hatching rates. Additionally, the effects of microplastics on thyroid hormone status might contribute to aggravated joint toxicity.	[169]
Zebrafish	-	12	PS-MPs + MT	5 µm	0 or 50 ng L-1 MT, 0.5 mg·L-1 PS-MPs, or 50 ng·L-1 MT + 0.5 mg·L-1 PS-MPs	Delayed incubation time and slow development in offspring, caused offspring mortality and malformations.	[63]
Prawn	Reproductive system, testis, heart	10	PS-MPs	5 µm	2 and 20 mg/L	Exposure to microplastics resulted in a decrease in the heart rate of prawn larvae. Oxidative stress in testis tissue indicated adverse effects on male prawn testicular function, including disrupted testicular germ cell quality and sex hormone imbalance, leading to reduced hatching success and survival of F1 larvae. Altered expression of steroidogenic genes and increased expression of apoptosis-related genes in the gonads were observed. Additionally, there was a decrease in immunity-related enzyme activities. Furthermore, there was a concentration-dependent increase in the bioaccumulation of polystyrene microplastics in different tissues of larval offspring.	[170]

Table 2 (continued)

Organism	Organ or tissue	Sample size	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Marine medaka (*Oryzias melastigma*)	-	20	PS-MPs	10 µm	0, 2, 20, and 200 µg/L	Postponed the incubation time and reduced the hatching rate and offspring's heart rate (20 µg/L), and decreased the body length.	[66]
Marine medaka (*Oryzias melastigma*)	Reproductive system	Each feeding and non-feeding groups included three replicates and each replicate contained 30 individuals	PS microspheres	10–11 µm	1×10^5 particles/L	The survival, growth, and reproduction of larvae were influenced.	[71]
Marine medaka (*Oryzias melastigma*)	Cardiovascular system	6	PS-MPs	13 µm	200 µg/L	Maternal uptake of phenanthrene (Phe) can be moved to the offspring and embryonic accumulation increases with the concentrations of MPs. Also, MPs aggravated Phe-induced bradycardia in embryos, proposing that MPs exacerbated the transgenerational toxicity of Phe.	[87]
Daphnia magna	Reproductive system	-	nano-PS beads	70 nm	0.22 and 103 mg nanoPS/L	The number and body size of neonates were lower, and the incidence of malformations among neonates increased to 68% of individuals.	[68]
Poecilia reticulata	-	60	PS-NPs	23.03 ± 0.266 nm	50 µg/L for 30 days	Transmission via the placenta and resulting in damaging impacts on offspring	[70]
Tigriopus japonicus	-	10	PS-MPs	0.05, 0.5, and 6 µm	1.25–25 µg/mL	The highest concentration of MP, 25 µg/mL, resulted in reduced survival in the F1 generation.	[74]

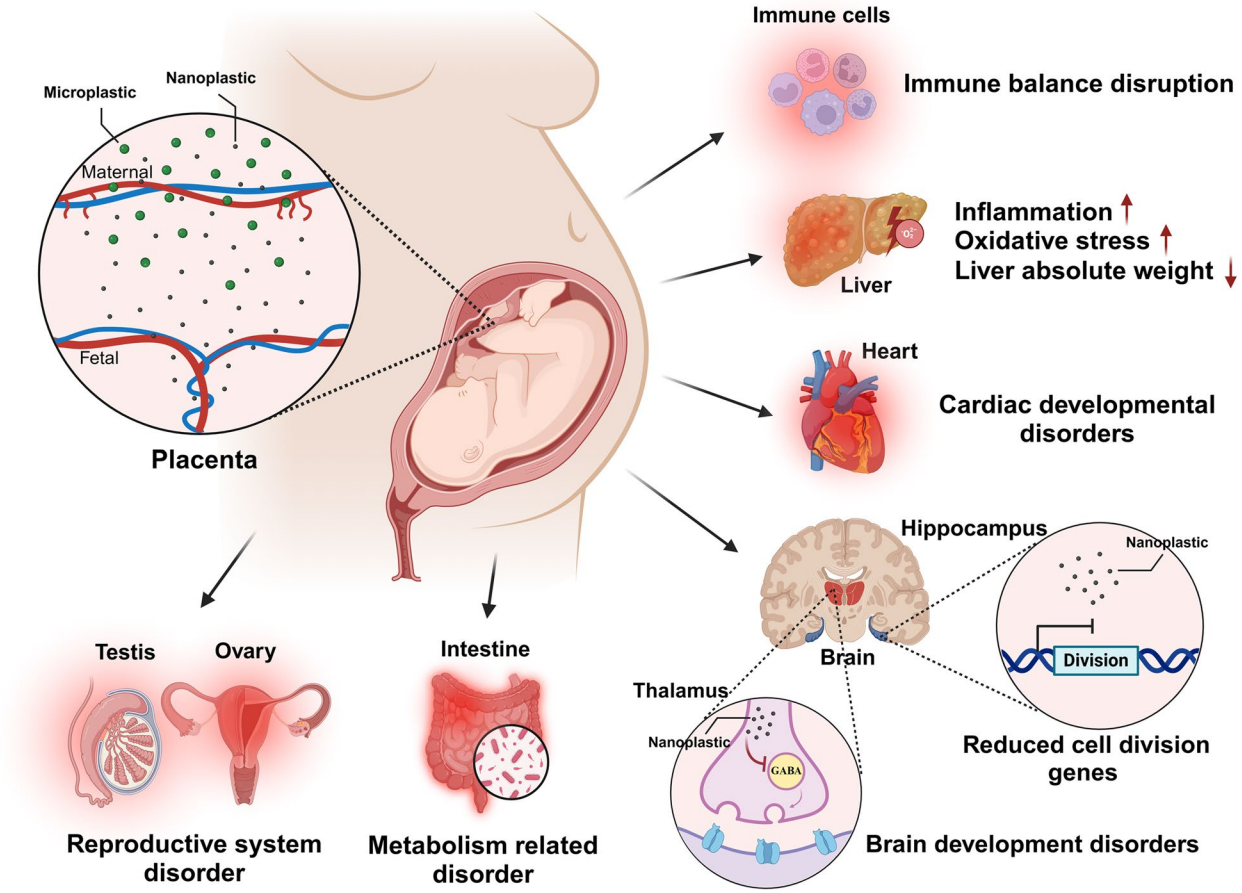

Fig. 3 Schematic representation of the impact of micro/nano plastics on the fetus, offspring, and its various organs. Maternal exposure to MNPs causes the accumulation of these particles in placenta tissue, but among them, only NPs can pass through the BPB and affect different fetal organs. These particles disrupt the fetal immune system and show their negative effects on this organ by increasing inflammation and oxidative stress as well as reducing liver absolute weight. MNPs particles have disturbed the growth and development of the heart and the brain, it leads to a decrease in the expression of genes related to cell division in the hippocampus, and on the other hand, inhibits thalamic GABA synthesis and causes problems in brain development. Also, disturbance in metabolism and reproductive system in both sexes is one of the results of exposure to these harmful particles

arrest in G1 or G2 phase [28]. Also, HTR-8/Svneo human trophoblast cells were used to measure the effect of 100 nm PS-NPs on placental trophoblasts at the mother-fetal interface. The results showed that these nanoparticles can reduce cell viability, stop the cell cycle, reduce the migration and invasion ability of cells, increase the intracellular ROS level, and produce TNF-α and IFN-γ pro-inflammatory cytokines in a dose-dependent manner, by entering the cytoplasm of trophoblast cells. In addition, RNA-sequencing results on HTR-8/Svneo cells showed the differential expression of 344 genes, which resulted in the activation of thyroid hormone, Hippo, TGF-β and FOXO signaling pathways [190]. NPs such as polycarbonate (PC), polyethylene terephthalate (PET), and PS, by inducing the highest toxicity, inhibit key placental enzymes and pose significant risks to the placenta [191]. In an in vitro study, the human ovarian granulosa COV434 cell line was exposed to different concentrations of NPs and it was found that COV434 cell line viability was significantly decreased at a concentration of 150 μg/ml. Also, the level of antioxidant markers SOD2 and GSH decreased, leading to oxidative stress [55]. Recently, extensive studies have been conducted on the role of MNPs with different sizes and doses on different human placenta cell lines (Table 3). These studies confirm the toxic effects of these polluting particles on the reproductive system and fertility of women. They confirm that MNPs particles can accumulate in the placenta and reduce the viability of its cells.

Conclusion

With the global increase in plastic consumption and human exposure to MNPs, attention has been drawn to the effect of these substances on the reproductive system

Table 3 Human cell cultures exposed to microplastics and assessment of their detrimental impacts

Tissue	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Placenta (Human umbilical vein endothelial cells (HUVECs)	PS-MPs	0.5, 1, and 5 µm	0, 20, 40, 60, 80, and 100 µg/mL	MP resulted in a significant decrease in cell viability with intracellular accumulation, prevention of angiogenic tube formation, blocking of angiogenic signaling pathways and inhibitory activity vs. cell migration and wound healing, repression of tube-forming capacity, necrosis-mediated cytotoxicity, and autophagy.	[192]
Placenta (In vitro, Human Umbilical Vein Epithelial cells (HUVECs)	PS-NPs	100–500 nm	0–100 µg/mL	PS-NPs with the size of 500 nm were only bound to the cell membrane surface, while PS-NPs with 100 nm were taken up by HUVECs and accumulated in the cytoplasm, elevating the release of lactate dehydrogenase from HUVECs, causing cell membrane impairment, and induced autophagy initiation.	[193]
Human umbilical vein ECs	PS-MPs and PS-MPs	20 – 10,000 nm	50–1000 µg/mL	MPs below 20 nm resulted in cytotoxicity. They elevated the LDH hormone level, and the levels of TNF-α, IL-6, and IL-1β. The smaller MPs lead to more critical EC damage, such as decreased cell movement, viability, and tubule formation, and elevated ROS and apoptosis.	[194]
Placenta	PS-NPs	50, 80, 240, and 500 nm	8.90 ± 1.80 µg/mL, 7.47 ± 1.77 µg/mL, 2.03 ± 0.29 µg/mL	It was demonstrated that polystyrene with a diameter of up to 240 nm was taken up by the placenta and could cross the placental barrier without influencing the placental explant viability.	[164]
Placenta, trophoblast (Epithelial cells BeWo b30)	PS-NPs	50, 100 nm	0.1–1000 µg/mL	10% of MPs were moved to the placenta and reduced cell viability.	[195]
Human placental perfusion model (BeWo cells)	Carboxylate Modified polystyrene particles	50 and 300 nm	1, 10, 100, and 1000 µM	The transport of MPs from the fetus to the mother was meaningfully higher vs. the opposite direction. The MPs could cross the placental barrier and accumulate in the syncytiotrophoblast of the placental tissue. The syncytiotrophoblast had a critical role in the regulation of nanoparticle transport across the human placenta.	[184]
Placenta, trophoblast (BeWo b30 cells)	PS-MPs and high-density polyethylene (HDPE)	< 50 µm	100 µg/mL	MPs with a diameter of 0.05 μm could damage cell membrane	[196]
Placenta (BeWo b30 transwell Model)	PS-NPs	50 nm	> 20 µg/mL	MPs could decrease the cell viability.	[197]

Table 3 (continued)

Tissue	Type of MPs	Particle size	Number of microplastic fragments/concentration	Results	Reference
Placenta (Human placental cells (JEG-3)	-NH2, -COOH and unlabeled PS-NPs	25, 50, 100, and 500 nm	0–5000 µg/mL	The gene regulation patterns correlated with toxicity pathways are affected by the surface charge and size of nanoparticles throughout induction. This results in increased levels of ROS within human placental cells, triggering DNA impairment and leading to cell cycle arrest in either the G1 or G2 phase, along with apoptosis and inflammation. Smaller nanoparticles exacerbate toxicity in human placental cells, and those labeled with NH2 show heightened influences on cytotoxicity, inhibition activity of protein kinase A, cell cycle arrest, and oxidative stress.	[28]
Placenta (Caco-2, a human adenocarcinoma cell line and HT29 MTXE12, a mucus-secreting subclone from colon adenocarcinoma HT29 cells)	COOH-modified PS-NPs	50–500 nm	0.01–100 µg/mL	Toxic impacts weren't observed; however, there was noteworthy cellular uptake and intracellular accumulation of both nano- and microparticles made of polystyrene.	[198]

and fertility in both sexes. Recent studies have confirmed the impact of these polluting particles on female infertility. MNPs can enter the body through various methods and affect its function by accumulating and changing the structure of the uterus, ovaries, and other components of the female reproductive system. These substances also affect the secretion and metabolism of sex hormones, disturb the balance of the reproductive endocrine system, and perturb the estrous cycle. Exposure to MNPs induces oxidative stress in the key components of the female reproductive system. It increases the risk of infertility in females by causing apoptosis in these cells and disrupting the ovulation process. Inflammation in the female reproductive system, which can lead to reproductive aging, is one of the main results of exposure to high amounts of MNPs. Also, they could trigger malignancies in the female reproductive system. In addition, MNPs have recently been found in human organs and tissues such as the placenta, which indicates their ability to cross the blood-placental barrier and transfer to fetal organs. MNP particles can show strong cytotoxic and genotoxic effects by passing through the placenta and accumulating in different tissues of the fetus and face serious problems in fetal growth and development. Also, maternal exposure to MNPs, in addition to intensifying disorders of the nervous system, immunity, and reproduction in offspring, may cause premature death and decrease the number of offspring. All these results show that MNPs as environmental pollutants have the potential to inflict irreversible harm on the reproductive system of females and the health of future generations and increase the rate of female infertility. Hence, managing microplastics to mitigate their risks and uphold reproductive health appears imperative. Addressing this concern entails implementing measures to diminish the prevalence of microplastics in the environment and to minimize human exposure to them.

Abbreviations

ADAM kinase	A disintegrin and metalloproteinase kinase
ATF6	Activating transcription factor 6
Bcl-2	B cell lymphoma-2
BIP	Binding immunoglobulin protein
BPB	Blood-placental barrier
BTB	Blood-testis barrier
CAT	Catalase
DAAM1	Dishevelled associated activator of morphogenesis 1
E2	Estradiol
EDCs	Environmental endocrine disrupting chemicals
eIF2α	Eukaryotic initiation factor-2α
EOC	Epithelial ovarian cancer
ER	Endoplasmic reticulum
Erk	Extracellular signal-regulated kinase
FSH	Follicle-stimulating hormone
GABA	γ-aminobutyric acid
GI	Gastrointestinal
GSH	Glutathione
GSH-Px	Glutathione peroxidase
hESCs	Human embryonic stem cells
HMGB1	High mobility group box 1 protein
HPG	Hypothalamic-pituitary-gonadal
HPO	Hypothalamic-pituitary-ovarian
IFN-γ	Interferon-gamma
IKK	Inhibitor of κB kinase
IL	Interleukin
IRE1	Inositol-requiring enzyme type 1
LH	Luteinizing hormone
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
MMP2/9	Matrix metalloproteinases-2/9
MNPs	Micro/nano plastics
MPs	Microplastics
MT	17α-Methyltestosterone
NAC	N-acetylcysteine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NICD	Notch intracellular domain
NOX2	NADPH oxidase 2
NPs	Nanoplastics
PBS	Polybutylene succinate
PC	Polycarbonate
PE-MPs	Polyethylene microplastics
PERK	Protein kinase RNA-Like ER kinase
PET	Polyethylene terephthalate
PP	Polypropylene
PS-MPs	Polystyrene microplastics
PS-NPs	Polystyrene nanoplastics
PVC	Polyvinyl chloride
ROCK1	Rho-associated, coiled-coil-containing protein kinase 1
ROS	Reactive oxygen species
Smad3	Suppressor of mothers against decapentaplegic 3
SOD	Superoxide dismutase
TAC	Total antioxidant capacity
TGF-β	Transforming growth factor-β
THBD	Thrombomodulin
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
TRAF6	Tumor necrosis factor receptor associated factor 6
UPR	Unfolded protein response
α-SMA	α-smooth muscle actin

Acknowledgements
We thank all the individuals who provided advice on this scientific work.

Authors' contributions
All authors equaly participated in writing, reviewing, and editing the manuscript.

Funding
The authors reported there is no funding associated with the work featured in this article.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 June 2024 Accepted: 4 November 2024
Published online: 11 November 2024

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