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Article

Threats of nano/microplastics to reproduction and offspring: Potential mechanisms and perspectives

Mei Ha[1], Wanzhen Tang[1], Jichun Huang[1], Changjiang Liu[2,*]

[1] School of Nursing, Chongqing Medical and Pharmaceutical College, Chongqing 401331, China
[2] NHC Key Laboratory of Birth Defects and Reproductive Health, Chongqing Population and Family Planning Science and Technology Research Institute, Chongqing 401120, China
*** Corresponding author:** Changjiang Liu, cj_514@163.com

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Abstract: Due to their ubiquitous occurrence in the aquatic environment and terrestrial ecosystem and underlying eco-environmental risks, nano/microplastics (NPs/MPs) have sparked great public concerns. The purpose of this work is aimed to summarize the harmful influence of NPs/MPs on reproduction and offspring health and further explore the potential mechanisms of action, thereby facilitating the more comprehensive understanding of NPs/MPs features. Literature search databases included EMBASE, Web of Science, and PubMed. The study selection and data extraction were implemented according to the inclusion criteria. NPs/MPs could accumulate and trigger reproductive toxic responses and thereafter generate deleterious effects on the offspring's health. Accordingly, the reproductive toxicity of NPs/MPs was characterized as the sperm deformity, decline in sperm count and motility, follicular growth tardiness, ovarian fibrosis, granulosa cell death, disorder of reproductive hormone secretion, as well as the fetal growth restriction, glycolipid metabolism disorder, and inflammatory responses of the next generation. Additionally, mechanism research revealed that NPs/MPs exposure brought about inflammatory responses and oxidative stress and thereafter destroyed the blood-testis barrier (BTB) integrity, motivated spermatogenic cell apoptosis by activating the JNK and p38/MAPK-Nrf2/NF-κB pathways, and induced ovarian granulosa cell pyroptosis and apoptosis and subsequent ovarian fibrosis via the Wnt/β-Catenin and NLRP3/Caspase-1 pathways. Nevertheless, this work also highlighted the imperative requirements for scientific and systematic risk assessments of NPs/MPs, so as to identify feasible risk mitigation strategies.

Keywords: nano/microplastics; reproduction; offspring; adverse effects

1. Introduction

By 2015, more than 5 billion tons of plastic waste had been generated globally. According to the trend during this period, it is expected to produce a total of 40 billion tons by 2050, and approximately 12 billion of that will be disposed of in landfills and the environment [1]. Due to being hardly biodegradable, plastics in landfills are broken down into plastic fragments and then transferred into the soil and the ocean. Microplastics (MPs) are a type of plastic debris with a particle size less than 5 mm and divided into primary MPs and secondary MPs. The former could directly access the environment through various channels, such as personal care or cosmetic product use, accidental losses caused by leaks during production or transportation, wear and tear during washing, and so on [2]. The latter is generated from the deterioration or degradation of larger plastics, which usually occurs when larger plastics suffer from mechanical abrasive actions, biodegradation, UV

radiation, etc. [1]. The components of NPs/MPs are predominantly constituted of polyethylene (PE), polystyrene (PS), polypropylene, polyethylene terephthalate, as well as polyvinyl chloride [3].

From the soil, air, and water source exposure to product usage, NPs/MPs are closely associated with our daily lives. Moreover, NPs/MPs could be transported from the lower nutrient level to the higher nutrient level in the food chain, giving rise to biological accumulation [4]. Therefore, humans could be not only directly exposed to NPs/MPs-contaminated food and water but also indirectly exposed through the food chain. Thus, NPs/MPs are frequently detected in multiple biological samples, such as skin, hair, saliva, placenta, colon, stool, semen, fetal fluid, and so on [5–9]. In general, humans are exposed to NPs/MPs dominantly via ingestion, inhalation, and dermal contact (**Figure 1**). Senathirajah et al. [10] estimated that globally, humans might ingest an average of 0.1–5 g of MPs per week from diverse exposure pathways, while Mohamed Nor et al. [11] calculated that by 18 years of age, the intake of MPs could irreversibly accumulate to 8.32×10^3 particles per person and by 70 years of age to 5.01×10^4 particles per person. Besides, several studies have tested and compared the toxicity of NPs/MPs in different exposure routes. The inhalation of NPs/MPs could exacerbate the toxicity of the lung, while the oral exposure of NPs/MPs could localize in the gut and bioaccumulate in multifarious organs such as the brain, liver, kidney, and reproductive organ, thereby eliciting corresponding detrimental effects. In recent years, growing literature has revealed that NPs/MPs exposure could bring about a series of unfavorable health outcomes, such as the damage of the central nervous system and cerebral function [12], pulmonary injury [13], gut microbiota dysbiosis [14], hepatocellular apoptosis and necroptosis [15], kidney lesion [16], as well as reproductive impairment [17].

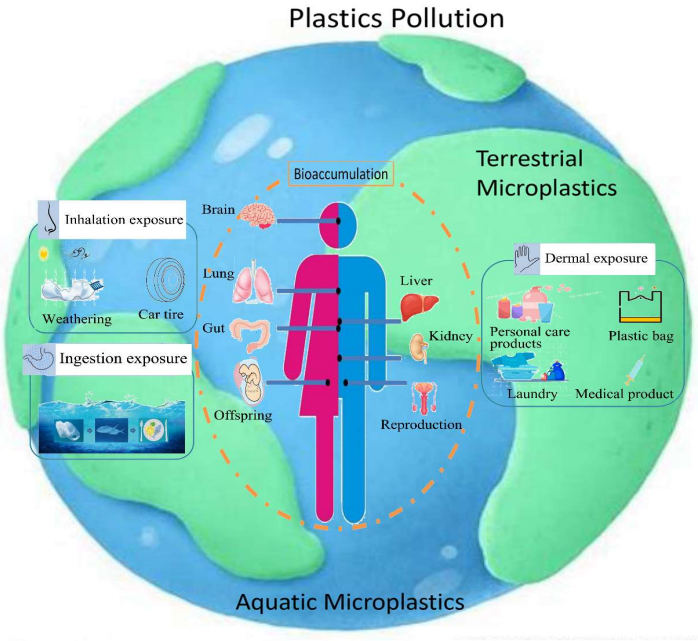

Figure 1. The multiple hazardous influence of plastics pollution on human health though various exposure routes.

Mounting epidemiological evidence has indicated that human fertility displays a

gradually declining trend in recent decades, and approximately 8%–12% of couples of childbearing ages worldwide are affected by infertility [18]. As a result, it is quite necessary and urgent to identify potential risk factors influencing human reproductive health. In recent years, a growing body of literature has suggested the interference effect of NPs/MPs on reproduction and fertility; however, the detailed mechanisms by which NPs/MPs mediate harmful reproductive health effects are still limited and ill-defined. Herein this review retrospected the relevant literature on NPs/MPs exposure to summarize the unfavorable reproductive effects and further explored the underlying molecular mechanisms. A more comprehensive and in-depth understanding of MPs will emerge from these insights.

2. Methodology

2.1. Literature search and relevant study screening

Search databases included EMBASE, Web of Science, Scopus, and PubMed up to September 2023. The two-round search process followed the workflow of PRISMA [19]. Search strategies were optimized using Boolean logical operators. Search terms were as follows: (a) microplastics (MPs), plastic particles, nanoplastics (NPs), or nanoparticles, and (b) reproduction, fertility, testis, ovary, generations, or offspring. Through these searches, studies evaluating the negative effect of NPs/MPs on reproductive health were screened out. Inclusion criteria were as follows: (a) plastic particles were orally administered; (b) the studies were conducted on terrestrial animals or marine animals; and (c) the studies displayed the harmful influence of NPs/MPs on reproductive health or the next generation. The studies were excluded if (a) they only performed the bio-assessment and/or determined the bio-accumulation of NPs/MPs in organisms without evaluating the toxic effects on reproduction, (b) the study tested the co-exposure effects of NPs/MPs and other hazards such as plastic additives, and (c) the unpublished literature or no peer-reviewed literature.

2.2. Literature analysis and data extraction

Two independent authors screened titles and abstracts. Endnote was used to import the full texts if the studies possibly met inclusion criteria. Afterward, a full-text analysis for the eligibility was conducted. Those full texts were examined by three independent authors who carried out the selection using the self-designed eligibility verification checklist, which mainly included research models (species, lineage, age, and sex), research designs (size and type of NPs/MPs, concentration, frequency, and duration), and toxic outcomes (testicular toxicity, ovarian toxicity, reproductive endocrine disturbance, and offspring threats).

2.3. Bias risk assessment

The SYRCLE's tool for bias risk, which was adapted from the Cochrane RoB tool, was employed to evaluate the underlying bias source in selected research, thereby facilitating critical appraisal of evidence [20]. The SYRCLE's tool consisted of ten entries related to the underlying bias source, such as the selection bias,

detection bias, friction bias, etc. Overall and individual data were obtained from SYRCLE's strategy.

3. Results

3.1. Bias risk

Bias analyses revealed that none of the studies selected could fulfill all the standards for methodological quality, suggesting an underlying risk of bias in various aspects of assessment. The aspects of the rational generation of the animal allocation sequence, animal grouping blinded, intervention design blinded for caregivers and/or investigators, as well as the outcome assessor blinded, were not identified in the methodological quality of all studies. Only five researchers selected experimental animals with random data collection (33.33%). Most studies conducted random housing of animals (80.00%). The baseline characteristics, incomplete research data, and selective outcome reporting were adequately addressed in all identified studies. Moreover, other possible sources of bias, such as the particle features and exposure manners, were also clearly described in all investigations. To sum up, the average score for bias risk of the included work was 52.66%, with six investigations (40%) exceeding the average value (**Table 1**).

Table 1. The unfavorable influence of NPs/MPs on male reproductive health.

Hazardous effects	Type of NPs/MPs	Particles size	Dosage	Duration	References
Decrease in sperm count, viable epididymis sperm count, and spermatogenic cell count in the testis	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		0.5 μm	0.015, 0.15, and 1.5 mg/d	For 90 days	[24]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		5.0–5.9 μm	0.1 mg/d	For 30 and 44 days	[26]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Increase in the sperm deformity rate	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	0.1 mg/d	For 30 and 44 days	[26]
		5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		0.5 μm	0.015, 0.15, and 1.5 mg/day	For 90 days	[24]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Triggering oxidative stress in the testicular tissue	PS-MPs	10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		5.0–5.9 μm	100 μg/d	For 30 and 44 days	[26]
Induced inflammatory responses	PS-MPs	5.0–5.9 μm	100 μg/d	For 30 and 44 days	[26]
		5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		0.5, 4, 10 μm	10 mg/mL	For 28 days	[29]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]

Table 1. (*Continued*).

Hazardous effects	Type of NPs/MPs	Particles size	Dosage	Duration	References
Destroyed the integrity of the blood-testis barrier (BTB)	PS-MPs	0.5 μm	0.015, 0.15, and 1.5 mg/day	For 90 days	[24]
		0.5, 4, and 10 μm	10 mg/mL	For 28 days	[29]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Reduced testosterone levels	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]

3.2. Overview of the screened literature

In the current work, 15 preclinical investigations were identified and included. Only one study reported the negative influence of PS-MPs on both male and female reproduction [26]. Among the other included studies, eight studies examined the detrimental impact of PS-NPs/MPs on male reproductive health [21–25,27–29], three on female reproduction [30–32], and three on offspring health [33–35]. Of the 12 studies on male or/and female reproduction, only one work disclosed the hazardous effect of PS-NPs (50 nm) on male reproduction with the dosage ranging from 1 to 10 mg/kg/d for five weeks [33]. The other studies reported that PS-MPs exposure (diameters ranging from 0.5 μm to 10 μm) with distinct doses could also impair reproduction of male and/or female experimental animals. Additionally, male and female reproductive lesions took place after PS-MPs (0.1 mg/d) exposure for 30 days, accompanied by a marked dose-dependent relationship between plastic particle exposure and reproductive damage. PS-NPs were mainly employed to evaluate the harmful effect of plastic particles on offspring health.

3.3. Unfavorable influence of NPs/MPs on male reproductive health

In nine studies on male reproduction, eight studies uncovered that after treatment with PS-NPs/MPs for more than one month, the sperm count, viable epididymis sperm count, and spermatogenic cell count were all decreased [21–28]. Six studies disclosed that PS-MPs exposure could elevate the sperm deformity rate [21,22,25,26,28,29]. Four studies observed that the integrity of BTB was impaired by PS-MPs [24,25,28,29]. Moreover, five investigations revealed that PS-MPs interfered with the hormonal synthesis and secretion and thereby reduced the testosterone level [21–23,27,28] (**Table 1**).

Mechanically, PS-MPs triggered oxidative stress and inflammatory responses [22,23,25,26,28,29]. The abnormal sperm quality and quantity in mice may be attributed to the PS-MPs-induced JNK and p38 MAPK pathways [22,24], or related to the NF-κB pathway caused by Nrf2 suppression [24,25]. Meanwhile, Nrf2 depletion and NF-κB stimulation also destroyed the integrity of BTB and then motivated the spermatogenic cell apoptosis [24,25,28]. Furthermore, PS-MPs could inhibit StAR expression through the LHR/cAMP/PKA signaling pathway mediated

by LH, thereby reducing the testosterone level [27] (**Figure 2**).

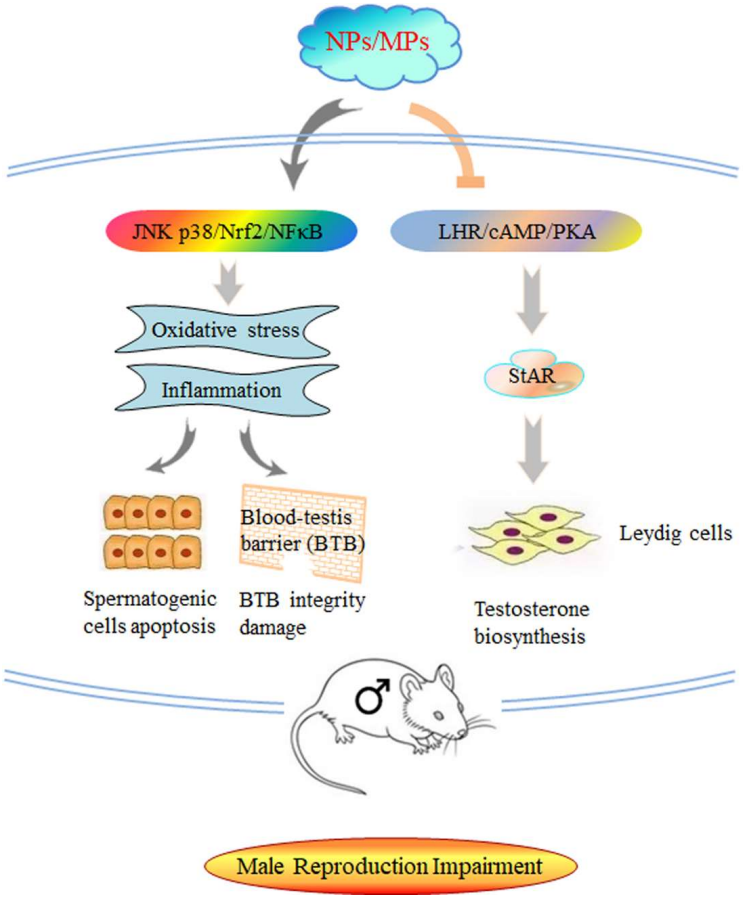

Figure 2. The unfavorable influence of NPs/MPs on male reproductive health and underlying mechanisms.

3.4. Unfavorable influence of NPs/MPs on female reproductive health

PS-MPs exposure could disturb female hormone balance by downregulating levels of estradiol and anti-Müllerian hormone [26,31] and upregulating levels of follicle-stimulating hormone, luteinizing hormone, as well as testosterone in ovarian tissue [26]. Additionally, PS-MPs restrained the survival rate of superovulated oocytes, the first polar body extrusion rate [32], and the growing follicle number [30,31], thereby reducing ovarian reserve capacity as well as the pregnancy rate (**Table 2**). Likewise, it has suggested that inflammatory responses and oxidative stress also contribute to the adverse influence of PS-MPs on female reproduction [26,30–32], such as the study revealing that PS-MPs brought about ovarian fibrosis via triggering oxidative stress and inducing the Wnt/β-Catenin pathway, finally bringing about ovarian granulosa cell apoptosis [30]. Similarly, another study also uncovered that PS-MPs induced the NLRP3/caspase-1 pathway via oxidative imbalance and then mediated ovarian granulosa cell death, including pyroptosis and apoptosis [31] **(Figure 3**).

Table 2. The unfavorable influence of NPs/MPs on female reproductive health.

Authors	Type of NPs/MPs	Particles size & dosage & duration	Species	Unfavorable influence and underlying mechanisms
Wei et al. [26]	PS-MPs	0.1 mg/d PS-MPs with 5.0–5.9 μm diameter administrated by gavage for 44 days	C57BL/6 female mice	**Decreased:** the estradiol levels; GSH levels in ovarian tissue; the corpora lutea count; the pregnancy rate and embryo count. **Increased:** the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone; ROS and MDA contents in ovarian tissue.
An et al. [30]	PS-MPs	0.5 μm PS-MPs at 0, 0.015, 0.15, and 1.5 mg/d for 90 days	Female Wistar rats	PS-MPs entered into granulosa cells (GCs). **Decreased:** the growing follicles number; the anti-Müllerian hormone (AMH) level. **Increased:** oxidative stress, granulosa cell apoptosis, and ovary fibrosis (transforming growth factor-β, fibronectin, α-smooth muscle actin); the protein expression of the Wnt/β-Catenin pathway (Wnt, β-catenin, and p-β-catenin). **Mechanism:** PS-MPs triggered oxidative stress and the Wnt/β-Catenin pathway, then led to apoptosis of GCs and ovary fibrosis, and finally contributed to the decline in ovarian reserve capacity.
Liu et al. [32]	PS-MPs	0.8 μm PS-MPs (1.0% and 2.5% w/v) for 35 days	CD-1 female mice	PS-MPs bioaccumulated in different organs or biological samples of exposed mice, such as the liver, kidney, brain, uterus, ovary, as well as blood. **Decreased:** the rate of the first polar body extrusion and the survival rate of superovulated oocytes; glutathione content; mitochondrial membrane potential (MMP), and endoplasmic reticulum calcium level. **Increased:** the levels of IL-6 and malondialdehyde in mouse ovaries; the ROS level in oocytes.
Hou et al. [31]	PS-MPs	0.5 μm PS-MPs (2.5% w/v) dispersed in deionized drinking water at 0, 0.015, 0.15, 1.5 mg/kg/d for 90 days	Female Wistar rats	**Decreased:** the number of growing follicles; the thickness of the granulosa layer of secondary follicles; the glutathione peroxidase, catalase, and superoxide dismutase activity in ovary tissue; the content of anti-Müllerian hormone (AMH). **Increased:** the ovarian MDA content; the expression of NLRP3 and cleaved caspase-1 in granulosa cells; the level of IL-1β and IL-18; the expression of NLRP3/Caspase-1 pathway-associated factors and cleaved caspase-3. **Mechanism:** PS-MPs activated the NLRP3/Caspase-1 pathway via oxidative stress and then triggered ovarian granulosa cell pyroptosis and apoptosis.

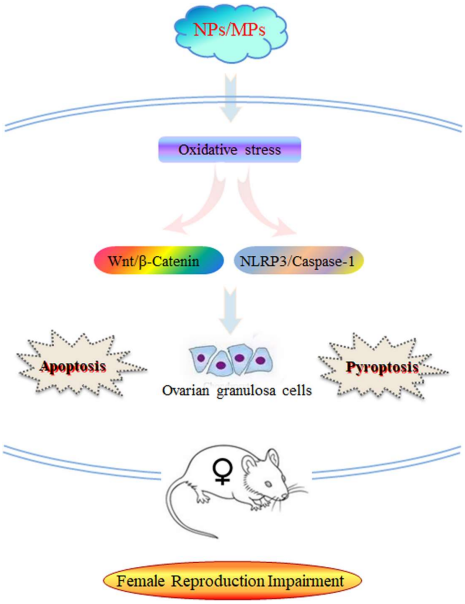

Figure 3. The unfavorable influence of NPs/MPs on female reproductive health and underlying mechanisms.

3.5. Unfavorable influence of NPs/MPs on offspring health

Three studies conducted in rodent models verified that PS-NPs exposure restricted fetal growth to varying degrees [33–35]. The possible reasons for the fetal growth retardation might be the decrease in the feto-placental weight ratio (FPWR) and umbilical cord length, which limited the nutrient transfer capacity and thereby retarded fetal growth [33] **(Table 3)**. Furthermore, previous studies discovered that PS-NPs exposure could elicit inflammatory responses, disorder glycolipid metabolism, perturb testicular development and function of male mouse pups, and impede the normal formation of muscle tissue and skin of fetuses [34,35] (**Figure 4**).

Table 3. The unfavorable influence of NPs/MPs on offspring health.

Authors	Type of NPs/MPs	Particles size & dosage & duration	Species	Unfavorable influence and underlying mechanisms
Chen et al. [34]	PS-NPs	Maternal PS-NP exposure (100 nm; 1 and 10 mg/L) via drinking water for 18 days	C57 BL/6 female mice	**Decreased:** fetal weights to cause fetal growth restriction. **Outcomes:** PS-NPs brought about inflammatory reactions, impeded the formation of muscle tissue and skin, and perturbed cholesterol metabolism of fetuses.
Aghaei et al. [33]	PS-NPs/MPs	Dams treated with 5 μm and 50 nm PS-NPs/MPs in drinking water (0.1, 10, and 1000 μg/L)	Adult CD-1 female mice	**Decreased:** the feto-placental weight ratio (FPWR), suggesting the insufficiency of the nutrient transfer capacity; a 30% decline in the umbilical cord length and a 12% decline in fetal weight in the high concentration group, demonstrating the fetal growth retardation.
Huang et al. [35]	PS-NPs	Maternal PS-NP exposure (100 nm) during gestation and lactation (0.1, 1, and 10 mg/L)	Female Kunming mice	**Decreased**: in birth; the weight of body, liver, and testes; sperm count; testicular CAT and SOD activities of offspring. **Increased:** inflammatory cell infiltration and proinflammatory cytokine expression (Il-1β, IL-6, and TNFα); testicular oxidative damage; testicular MDA content of offspring. **Outcomes:** PS-NPs exposure during gestation and lactation disordered hepatic glycometabolism and gave rise to testicular inflammatory and oxidative impairment of offspring.

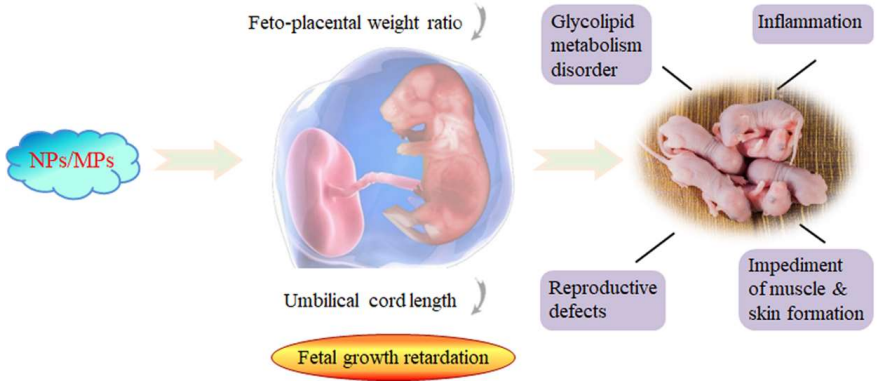

Figure 4. The unfavorable influence of NPs/MPs on offspring health.

4. Discussion

Mounting literature has indicated that reproductive health injury is associated with widespread exposure to environmental contaminants, such as NPs/MPs [21,26,30], which could interfere with reproductive health by regulating steroid hormone biosynthesis, apoptosis, and pyroptosis of germ or granulosa cells, etc. NPs/MPs as an emerging environmental pollutant could contribute to the impairment of male and female reproduction, as well as offspring health.

In male animal models, PS-MPs exposure not only decreased numbers of active

epididymis sperms and spermatogenic cells in testes but also increased the rate of sperm deformity. Meanwhile, serum LH, FSH, and testosterone contents were downregulated, while E2 was upregulated in experimental animals [26]. Another study reported that PS-MPs accumulated in mouse testes and then led to male reproductive dysfunction, abscission and malalignment of spermatogenic cells, decline in sperm quality and T levels, disruption of BTB, and so on [27]. Similar hazardous impacts of PS-MPs on male reproduction were also displayed in the study by Li et al. [24]. Further research has indicated that oxidative stress and subsequent oxidative damage are one of the common mechanisms by which NPs/MPs mediate the detrimental effect on male reproduction, such as the work demonstrating that after treatment with PS-MPs for six weeks, PS-MPs not only inhibited the sperm metabolism-associated enzyme activity, including succinate dehydrogenase and lactate dehydrogenase, but also activated the p38/MAPK pathway via oxidative stress to facilitate sperm damage and testosterone secretion suppression in mice [22]. Nevertheless, these pernicious effects mediated by PS-MPs could be antagonized and alleviated by the antioxidant NAC or p38-specific inhibitor SB203580. Similar findings were uncovered in the investigation, which exhibited that PS-MPs exposure impaired seminiferous tubules, destroyed the integrity of BTB, and brought about spermatogenic cell apoptosis via activating the MAPK-mediated Nrf2 pathway in rat testes [24]. In addition, the inflammatory response is also considered another important mechanism of PS-NPs/MPs-mediated reproductive lesions. In PS-MPs-exposed mice, inflammatory factors were significantly enriched in mouse testes, as evidenced by the increase in mRNA levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), MCP-1, and CXC chemokine ligand 10 (CXCL10), which finally gave rise to reproductive dysfunction in male animals [27]. Furthermore, the alteration of gut microbial abundance, especially the elevation of Bacteroides and Prevotellaceae_UCG-001 abundance, activated the IL-17A signaling pathway, and gut microbial dysregulation was positively correlated with PS-MPs-induced reproductive damage and testicular dysfunction, proposing that gut microbial might be significantly involved in PS-MPs-mediated male reproductive injury [28].

It is well-known that exposure to environmental hazardous factors will give rise to a number of female reproductive diseases and even cause infertility in women [36], but compared with male reproduction, the unfavorable impacts of PS-NPs/MPs on female reproduction and offspring health have received less attention. Nevertheless, growing evidence has suggested that female reproduction is also an underlying target of NPs/MPs, and in comparison with male mice, the female is more vulnerable to NPs/MPs in reproduction [26]. Ovary is an important organ for female reproduction and endocrine regulation, whose predominant roles are to generate oocytes, synthesize, and release related reproductive hormones. In animal studies, PS-MPs restrained ovarian reserve function and interfered with fertility by perturbing sex hormone secretion and reducing follicle number and quality [26,30–32]. Further research revealed that excessive activation and maintenance of inflammatory pathways or their dysregulated resolution may partially account for NPs/MPs-mediated female reproductive disorder or impairment.

With the detection of NPs/MPs fragments in human placentas [37], the underlying unfavorable influence of NPs/MPs on offspring health is receiving

increasing attention and gradually reported. The study conducted in 43 pregnant women declared that in patients with intrauterine growth restriction (IUGR), MPs exposure was significantly negatively associated with the birth outcome in terms of birth weight, height, head circumference, and 1-minute Apgar score, suggesting that plastic particles might interfere with the interaction between the placenta and the fetus [38]. The harmful influence of NPs/MPs on offspring health mainly represented fetal growth restriction [33–35] and the decrease of umbilical cord length [33] in animal models. In humans, maternal NPs/MPs exposure would give rise to fetal growth retardation, which was closely associated with the insufficient transfer of placental nutrition and short umbilical cord [39]. In summary, evidence from population epidemiological studies and experimental research indicates that NPs/MPs have an underlying negative impact on the health of the next generation, which should be paid more attention to in future research.

Because of the mounting concern about the potential reproductive influence of plastic particles, several studies also reviewed the possible impact of NPs/MPs on reproductive health. Marcelino et al. [40] reviewed and synthesized the risk of PS-NPs/MPs on reproductive organs in mammals; however, they were more concerned about the influence of PS-NPs/MPs on offspring health. Another review only confined the concern regarding the impact of PS-NPs/MPs on male reproductive health [1]. Therefore, it is quite necessary to outline the unfavorable influence of PS-NPs/MPs on reproductive health of male and female reproduction and offspring health, as our present work did.

Given the critical interpretation of current evidence, none of the studies met all the methodological standards. Methodological quality assessments indicated that the aspects of animal allocation sequence, intervention design blinded, data collection blinded, and the outcome assessor blinded were critical bias elements in the selected research. Nevertheless, the other aspects such as random housing of animals, baseline features, etc. were eligible. Remarkably, the declaration of the risk of bias could objectively provide clear evidence for the influence of plastic particles on reproduction rather than highlight the flaws in the experimental protocols of the included studies.

5. Conclusion and perspective

With the extensive usage of plastics in production and daily life, humans and animals are ubiquitously exposed to nano/microplastics (NPs/MPs) via inhalation, ingestion, dermal exposure, etc. As the frequent detection of NPs/MPs in a variety of biological samples such as testicular tissue, semen, amniotic fluid, etc., the potential health risk, especially reproductive risk, elicited by NPs/MPs has aroused great public concern and worry. In recent years, a large amount of epidemiological data and toxicological investigations have clearly indicated that NPs/MPs exposure will impair both male and female reproduction and fertility, as well as offspring health, and the underlying modes of action of NPs/MPs-mediated reproductive damage are dominantly consisted of the direct histological injury, oxidative stress, inflammation, immune response, mitochondrial impairment, endoplasmic reticulum stress, apoptosis and pyroptosis of reproductive cells, and so on. Nevertheless, it should be

noted that human studies are relatively sparse in terms of quantity and scale, and even so, the limited population studies have dominantly looked at the correlation between NPs/MPs exposure and negative reproductive health outcomes, lacking in-depth mechanism-based exploration. In addition, the vector-like effect of NPs/MPs implies that further cohort studies and experimental research are warranted to evaluate the cumulative effect of environmental hazardous pollutants carried by NPs/MPs. Furthermore, it is a cruel fact that global accumulation of plastic particles will continuously exacerbate NPs/MPs exposure of ecosystems and organisms. As a result, there is a great need to conduct scientific and systematic risk assessments and then identify the feasible risk mitigation strategies in future work.

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