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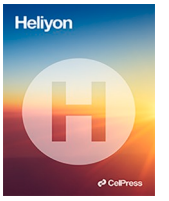

Review article

Fine particulate matter and ovarian health: A review of emerging risks

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ABSTRACT

Fine particulate matter ($PM_{2.5}$) pollution has raised significant public concerns, especially for vulnerable populations. Studies have indicated the association between $PM_{2.5}$ and ovarian disorders, although the mechanisms underlying the effects have not yet been fully elucidated. In this review, we elucidated three main conditions pertaining to ovarian function that may result from exposure to $PM_{2.5}$: diminished ovarian reserve, polycystic ovary syndrome, and infertility. Specific effects of ovarian disorders caused by $PM_{2.5}$ are discussed, including reactive oxygen species, apoptosis, DNA damage, and inflammation.

1. Introduction

Infertility has emerged as a significant public health issue, particularly as global fertility rates continue to decline [1,2]. Since the mid-1960s, global indicators have shown a consistent decline in total fertility rates (TFR). Between 1990 and 2019, the global TFR dropped by 0.7 births [3], driven by both decreased fertility desire and rising infertility rates [4]. While multiple biological, socioeconomic, and environmental factors contribute to infertility, air pollutants have recently been recognized for their potential to disrupt reproductive health, potentially exacerbating the ongoing fertility crisis.

The impact of air pollution is receiving increasing attention globally, particularly regarding fine particulate matter pollution ($PM_{2.5}$), which affects the largest number of people. $PM_{2.5}$ originate from natural sources such as desert dust, as well as anthropogenic activities like residential heating, second-hand smoke, and fossil fuel combustion [5,6], and these particles can penetrate the air-blood barrier, contributing to systemic health issues [7–9]. This systemic impact may extend to ovarian function, with growing evidence linking $PM_{2.5}$ exposure to reproductive health disorders and potentially impair female reproductive health and contributed to the

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growing epidemic of infertility [10].

It is well documented that ovarian disorders such as diminished ovarian reserve (DOR) and polycystic ovarian syndrome (PCOS) are key contributors to infertility. The cyclic development of primordial follicles into primary follicles, regulated by gonadotropins and ovarian hormones, is a critical process that is vulnerable to disruption by harmful external substances. Ovarian function can be assessed through several serum markers, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and anti-Mullerian hormone (AMH), all of which are linked to folliculogenesis and follicle quantity [11,12]. Antral follicle count (AFC), measured via sonography, provides a direct estimate of follicle numbers [13]. These markers reflect overall ovarian function and help maintain menstrual cycle regularity. Recent studies have explored the relationship between $PM_{2.5}$ exposure and ovarian function, suggesting a potential association between elevated $PM_{2.5}$ levels and alterations in ovarian markers such as AMH, FSH, and AFC [9,14,15]. Unfortunately, there has yet to be a systematic review that summarizes previous findings, making it difficult for the recent researchers and the public and recent researchers to gain a comprehensive understanding of the current state of research on the effects of $PM_{2.5}$ on ovarian function in a short period.

The aim of this review is to critically evaluate the current body of research on $PM_{2.5}$'s impact on ovarian disorders, with a particular focus on key reproductive markers and potential biological mechanisms. This review is based on a comprehensive literature search conducted on PubMed, using keywords such as 'ovary' and 'fine particulate matter,' to summarize and synthesize relevant studies from 2013 to Jan 1, 2014. By synthesizing these findings, this review seeks to emphasize the need for targeted public health interventions and policies aimed at reducing air pollution to protect reproductive health, particularly in regions with high $PM_{2.5}$ exposure.

2. DOR and $PM_{2.5}$

DOR refers to a decline in both the quantity and quality of oocytes, accounting for approximately 10 % of female infertility cases [16]. DOR is defined as AFC $<$ 5–7 in both ovaries, elevated level of basal FSH $>$10 IU/L on cycle day 2–4, or decreased AMH $<$1.1 ng/mL [16]. While studies have investigated the association of DOR with endocrine-disrupting chemicals (EDCs) or persistent organic pollutants, research on the relationship between DOR and $PM_{2.5}$ is limited [15,17]. The evidence for the relationship between $PM_{2.5}$ and DOR can be illustrated by two aspects in existing investigations: (1) decreased AMH or FSH, and (2) decreased AFC.

2.1. Ambient $PM_{2.5}$

Several studies have demonstrated a negative association between $PM_{2.5}$ exposure and AMH levels. For instance, in a cohort of 2276 Korean women, 1 and 12-month increases in the interquartile range (IQR) of outdoor $PM_{2.5}$ resulted in respective decreases of 3 % and 10 % in the AMH levels [18]. Similarly, a large-scale study in Shandong, China, involving approximately 20,000 women, found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 2.1 % reduction in AMH levels [19]. This suggests that even relatively small increases in $PM_{2.5}$ can have measurable effects on ovarian reserve. Furthermore, a cohort study of 5189 women in Hubei province in China showed that during secondary to antral follicle stage and 1-year exposure to $PM_{2.5}$ was linked with 1.99%–3.99 % decreased AMH per 10 $\mu g/m^3$ increases in $PM_{2.5}$, which may be the sensitive window of exposure [14]. Another study revealed that the sensitive window of $PM_{2.5}$ was during follicle development from the primary to preantral follicle stage with AMH changes of -0.21 (95 % CI: 0.48, 0.06) each 10 $\mu g/m^3$ increase in $PM_{2.5}$ though with no statistical significance [9]. A study from Massachusetts General Hospital Fertility Center (2004–2015) found that every 2 $\mu g/m^3$ increase in $PM_{2.5}$ was related to a -7.2 % (95 % CI: -10.4 %, -3.8 %) lower AFC among 632 women [15]. Above all, not only $PM_{2.5}$ exposure was associated with DOR but the sensitive window may be primary to preantral follicle stage biologically.

2.2. Living environment and lifestyle related-$PM_{2.5}$

The living environment and lifestyle are also important factors. A study recruited 67 women in Sabzevar showed that the shorter length of major roads in 100 m buffer and the higher surrounding greenness were associated with a higher AMH level, and per IQR increase in $PM_{2.5}$ was associated with an 11 % drop in AMH level [20]. Meanwhile, a study at the Massachusetts General Hospital Fertility Center (2004–2014) observed that 565 women aged 18–45 years, who were exposed to higher levels of greenness around their homes, showed an increased AFC, although this association was not statistically significant. In contrast, higher $PM_{2.5}$ levels were significantly associated with reduced AFC [21]. Residential heating practices and environmental factors also play a role. For example, a study from the Sister Study Cohort, involving 913 premenopausal women in the U.S., showed that using indoor heating sources such as wood or artificial fire logs more than 10 times per year was associated with lower AMH levels [22]. These studies indicated that the higher the accessibility of $PM_{2.5}$ pollution sources, the more harmful to women's ovaries.

2.3. Occupation-related $PM_{2.5}$

Occupational exposure to $PM_{2.5}$ has also been shown to affect folliculogenesis and ovulation. In a study conducted in Urumqi, female road cleaning workers exposed to $PM_{2.5}$ had lower LH and FSH levels during the follicular phase compared to government and logistics workers, potentially disrupting folliculogenesis [23]. Besides, $PM_{2.5}$ compromises estrogen synthesis, which is also related to menopause. A randomized controlled trial showed that among female traffic police, in follicular and luteal phases, mean 17-beta-estradiol levels were significantly lower in traffic police compared to controls, which can induce the delay of ovulation [24]. The NHS II

cohort study spanning 1,059,229 person-years of follow-up, conclusively demonstrates that women aged 40 years old exposure to $PM_{2.5}$ leads to earlier natural menopause [25], also in support of a 20-year European study [26].

2.4. Animal evidence

In summary, both population-based studies and animal models strongly suggest that $PM_{2.5}$ exposure adversely affects ovarian reserve, with evidence pointing to specific biological mechanisms such as apoptosis, inflammation, and hormonal imbalance. Cigarette smoke exposure reduced AMH and estradiol while increasing FSH [27]. This hormonal imbalance led to DOR and impaired preantral and antral follicular development, ultimately reducing the number of metaphase II oocytes [28]. Parallelly, exposure to fuel-related $PM_{2.5}$ in mice resulted in decreased counts of primordial, primary, and antral follicles, with antral follicles being the most sensitive to $PM_{2.5}$ [29]. Mice exposed to traffic-related $PM_{2.5}$ (mean concentration of 27.5 $\mu g/m^3$ daily) experienced a 36 % decrease in antral follicles compared to those exposed to filtered air [30]. Exposure to $PM_{2.5}$ alone increased the percentages of apoptotic antral follicles and the recruitment of primordial follicles. This led to a significant depletion of the ovarian reserve, with a 45 %, 40 %, and 17 % decrease in the numbers of primordial, primary, and secondary ovarian follicles, respectively, as demonstrated by a study using a versatile aerosol concentration enrichment system in mice [31]. Moreover, chronic exposure to $PM_{2.5}$ resulted in follicular dysplasia, characterized by increased atretic follicles and the apoptosis of granulosa cells [32]. Above all, cigarette-, fuel-, and traffic-related $PM_{2.5}$ exposure was exactly related to DOR.

Experimental animal studies have shed light on the molecular mechanisms underlying $PM_{2.5}$'s effects on ovarian function. In a study using the Institute of Cancer Research (ICR) mouse model, aerosolized $PM_{2.5}$ exposure was shown to increase apoptotic markers (Bax/Bcl-2 and caspase-3), inflammatory cytokines (IL-6 and TNF-α), and DNA damage indicators (8-OHdG), leading to decreased serum AMH levels [33]. $PM_{2.5}$ exposure has also been shown to induce systemic inflammation, marked by elevated levels of IL-6 and TNF-α, which in turn can cause morphological changes in ovarian tissue, including mitochondrial structural alterations, vascular congestion, and hemorrhage [32,34]. In a randomized study of female Wistar-albino rats, offsprings exposed to room air exhibited lower levels of apoptosis and DNA damage in granulosa cells compared to those exposed to artificial smoke [35]. Furthermore, maternal exposure to $PM_{2.5}$ has been found to accelerate the activation of primordial follicles in offspring through the PI3K/AKT/-FoxO3a pathway, which can induce the imbalance of ovarian reserve, and the high level of oxidative stress leading to ROS-dependent NF-κB pathway induces the atresia of follicles [36]. The reference to specific pathways strengthens the mechanistic insight, offering plausible biological explanations for ovarian dysfunction.

3. PCOS and $PM_{2.5}$

PCOS is a common ovarian disorder and endocrinopathy that accounts for a significant proportion of infertility cases in women [37]. It is diagnosed by the presence of at least two of the following symptoms: polycystic ovaries ($\geq$12 follicles in each ovary measuring 2–9 mm), oligomenorrhea/anovulation, or hyperandrogenism, either clinically or biochemically [38]. Its prevalence has increased in countries experiencing high levels of $PM_{2.5}$ pollution over the last decade [39].

Several studies have explored the relationship between PCOS and $PM_{2.5}$ exposure. A cohort study comprising approximately 240 thousand participants from the Korean population revealed that 3-year exposure to $PM_{2.5}$ increased the risk of PCOS by 32 % compared to 1-year exposure, and 28 % increased risk was presented when compared to the first quartile [40]. Analogously, a Chinese study based on a 12-year follow-up of 91,803 women found that compared with the first-quartile levels of exposure to $PM_{2.5}$ (mean concentration is 30.85 ($\pm$6.16) $\mu g/m^3$) increased the risk of PCOS by 3.56 times [41]. Additionally, a Boston longitudinal cohort with 6 thousand women using electronic medical ultrasonographic records data showed insignificant association between increasing $PM_{2.5}$ concentrations and the risk of polycystic ovary morphology, one of the important aspects of the diagnosis of PCOS [42].

Research on the biological mechanisms linking $PM_{2.5}$ exposure to PCOS is limited. A study showed that exposure to $PM_{2.5}$ may activate the hypothalamus-pituitary-adrenal (HPA) axis potentially worsening hyperandrogenism, a hallmark of PCOS [43]. A longitudinal panel study of 43 college students in Shanghai, China, observed that short-term $PM_{2.5}$ exposure elevated levels of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol—indicating activation of the HPA axis [44]. Further support comes from a cohort study of 179 women, where $PM_{2.5}$ exposure during early pregnancy and prenatal period was associated with higher cortisol levels, suggesting HPA axis activation and its potential impact on ovarian function [45].

4. Infertility and $PM_{2.5}$

Infertility is characterized by the inability to conceive after 12 months of consistent, unprotected sexual intercourse [46]. Studies have estimated the association between $PM_{2.5}$ exposure and infertility. Several studies have demonstrated a similar association between exposure to $PM_{2.5}$ and decreased pregnancy and live birth rates in populations from different countries and regions. A study relied on a census in Barcelona, Spain revealed that $PM_{2.5}$ exposure was associated with a significant decrease in fertility rates [47]. In Teplice, a highly industrial city, Rémy Slama et al. discovered that for 1916 couples, every 10 $\mu g/m^3$ increase in $PM_{2.5}$ levels during one month corresponded to a 22 % reduction in fertility (95 % CI: 6%–35 %) [48]. In China, each 10 $\mu g/m^3$ in a 1-year average $PM_{2.5}$ exposure was related to a decreased level of fertility by 11 % of 10,211 couples [49]. Furthermore, each 10 $\mu g/m^3$ rise in cumulative average $PM_{2.5}$ exposure was associated with a 1.15-fold increase in the hazard ratio for infertility (95 % CI: 1.01–1.30) [50]. A 1-year follow-up enrolled 1,0183 women in Demark showed that residential exposure to $PM_{2.5}$ was linked with infertility [51].

Infertility patients generally require assisted reproductive therapy (ART) to conceive, therefore more research has also noted the

impact of $PM_{2.5}$ exposure on ART outcomes. During embryo culture, elevated levels of $PM_{2.5}$ in the in vitro fertilization (IVF) lab were linked to decreased conception rates (OR 0.90, 95 % CI 0.82–0.99) among 7403 women in the USA [52]. Embryo transfer failure rates were lowest when PM concentrations were lowest among 18,478 female infertile patients [53]. $PM_{2.5}$ exposure was associated with low litter size and low birth weight involving ROS and uterine blood flow modeled by Sprague–Dawley rats [54]. In *Caenorhabditis elegans* (*C. elegans*), exposure to high doses of $PM_{2.5}$ (1000 mg/L) decreased the brood size and the number of fertilized eggs in utero [55]. However, the specific biological mechanism remains to be systematically studied.

5. Potential mechanism of $PM_{2.5}$ related ovarian dysfunction

Although an increasing amount of evidence suggests that $PM_{2.5}$ may lead to ovarian dysfunction, the mechanism by which $PM_{2.5}$, once inhaled and reaching the terminal bronchioles, further mediates pathological changes in ovarian remains far from elucidated. Studies have revealed that $PM_{2.5}$ induces substantial levels of apoptosis, DNA-related impairment, and inflammation upon entering the lungs, all of which are associated with reactive oxygen species (ROS) (Fig. 1). The use of the antioxidant N-acetyl cysteine has been shown to mitigate $PM_{2.5}$-induced cell damage, confirming that toxicity from $PM_{2.5}$ can be attributed to oxidative stress mainly, possibly linked to mitochondrial [56] and aryl hydrocarbon receptor damage [57].

ROS may play a substantial role in $PM_{2.5}$-related ovarian dysfunction [58]. ROS modify nucleic acids, proteins, and membrane lipids [10], which is related to mitochondrial structural abnormalities, dysregulating the functional activity of the mitochondrial respiratory chain and ROS production, resulting in mitochondrial damage [56]. Additionally, excessive ROS-mediated mitochondrial apoptotic signaling pathways can even enable the apoptotic procedure of granulosa cells in ovaries [59,60]. Apoptotic granulosa cells elevate ovarian oxidative levels, pro-apoptotic, and apoptotic factors, ultimately bringing out oocyte apoptosis [36,61,62]. The apoptotic debris of cells can stimulate ROS accumulation, exacerbating a vicious spiral [63]. Oocyte apoptosis reduces ovarian reserve, which directly impacts the reproductive outcomes of diverse mammalian species [59].

$PM_{2.5}$-related ROS may also induce DNA damage in a dose-dependent manner [56,64]. $PM_{2.5}$ exposure increased the proportion of primary and secondary follicles exhibiting DNA damage, potentially leading to apoptosis in growing follicles [31]. Overproduction of ROS and RNS occurs as a byproduct of oxidative metabolism, which serves as potent inflammatory stimuli, initiating an inflammatory cascade, triggering the production and release of proinflammatory cytokines as well as the activation of inflammatory signal transduction pathways [65].

$PM_{2.5}$ is well-documented to induce inflammation in vivo. The establishment of a $PM_{2.5}$ exposure model in mice revealed noticeable aggregation of inflammatory cells and secretion of inflammatory cytokines (IL-6, IL-1β, IL-8, TNF-α, and IL-17) following exposure to $PM_{2.5}$ for 8 and 16 weeks [66]. This inflammation was mediated by the NF-κB/IL-6 pathway in the ovary [67]. In the respiratory system of rats or mice, exposure to $PM_{2.5}$ increased inflammatory cytokines production with inflammatory cell infiltration via trashing autophagic flux or induced by the NF-κB pathway [66,68–71]. Additionally, $PM_{2.5}$ exposure has been shown to trigger inflammation in various organs, including the eyes, kidneys, spleen, central nervous system, liver, and heart. Although limited, existing studies suggest the potential for $PM_{2.5}$-induced inflammation in the ovary [72–76].

6. Discussion

Despite advancements in reproductive healthcare, infertility continues to affect millions worldwide, indicating that environmental factors, particularly air pollution, may play a role in this overlooked risk. After reviewing the literature in this field, we found that most population-based studies demonstrate a consistent relationship between increasing $PM_{2.5}$ levels and ovarian dysfunction, particularly in the phenotype of DOR, PCOS, and infertility [14,15,18,19,40,41,47–49,51]. Furthermore, the evidence reviewed in the paper suggests lifestyle and occupational factors exacerbate these effects. In the meanwhile, there is limited evidence on the specific biological mechanisms through which $PM_{2.5}$ affects ovarian function. Most studies cite evidence found in other organs [77,78]. $PM_{2.5}$ exposure leads to excessive production of ROS, causing mitochondrial dysfunction, granulosa cell apoptosis, and DNA damage within ovarian tissues [31,56,59,60,66]. This oxidative damage disrupts folliculogenesis, depletes ovarian reserves, and impairs hormonal regulation, including alterations in AMH, FSH, and estradiol levels. Additionally, $PM_{2.5}$ triggers chronic inflammation, as evidenced by

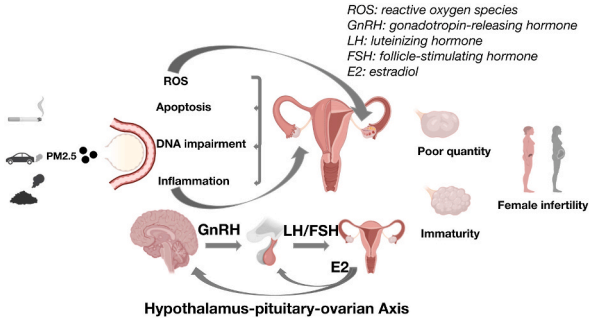

Fig. 1. Fine particulate matter ($PM_{2.5}$) and female fertility.

increased proinflammatory cytokines, contributing to ovarian structural damage and accelerating ovarian aging.

Therefore, prevention is urgently needed. From a general perspective, addressing the potential impact of $PM_{2.5}$ on female reproductive health requires coordinated action at both individual and governmental levels. On an individual level, people can take protective measures by using air purifiers in their homes and wearing masks when air quality is poor to reduce direct exposure [79]. Additionally, adopting cleaner energy sources for household heating and cooking, such as natural gas or electricity, can further reduce indoor pollution [80]. Collaborative efforts between environmental, public health, and urban planning sectors will be essential to mitigate the broader health risks of air pollution. Furthermore, policies aimed at reducing emissions from key sectors, including industry, transportation, and residential heating, are critical [81]. This can involve stricter regulations on fossil fuel combustion, incentives for the adoption of clean energy technologies, and investments in renewable energy infrastructure. By implementing these measures, governments can not only protect reproductive health but also improve overall public health outcomes in regions with high $PM_{2.5}$ exposure.

Although we can largely infer from our review that $PM_{2.5}$ may lead to ovarian dysfunction in women, there are still many limitations in this field of research, and many specific issues remain to be addressed. First, while many studies demonstrate associations between $PM_{2.5}$ exposure and ovarian dysfunction, causality remains unclear due to the observational nature of most studies. Confounding factors, such as socioeconomic status, other environmental exposures, or lifestyle differences, may influence the observed relationships. Additionally, studies differ in their methods of $PM_{2.5}$ measurement, exposure periods, and population characteristics, making direct comparisons difficult. The lack of longitudinal studies tracking exposure over time also limits the understanding of the cumulative effects of $PM_{2.5}$ on ovarian health. Moreover, biological mechanisms derived from animal studies may not fully translate to humans, given species-specific differences in reproductive biology. Further, studies on occupational exposure often involve small sample sizes, limiting the generalizability of these findings. Finally, although several mechanisms, such as oxidative stress and inflammation, have been proposed, a comprehensive understanding of the molecular pathways linking $PM_{2.5}$ to ovarian dysfunction is still lacking, and more research is needed to elucidate these pathways and establish effective prevention strategies.

7. Conclusion

In this review, we summarize the association of $PM_{2.5}$ with DOR, PCOS, and infertility and tentatively explore the mechanisms involved, such as ROS, apoptosis, inflammation, and DNA damage to provide evidence to support further in-depth studies on ambient particulate matter and female fertility. To protect female fertility, we recommend that the government take measures to reduce air pollution, encourage personal precautions, and provide timely warnings.

CRediT authorship contribution statement

Qingqing Tao: Writing – original draft. **Zhengyang Zhao:** Visualization. **Rui Yang:** Writing – review & editing. **Qin Li:** Writing – review & editing. **Jie Qiao:** Writing – review & editing.

Data availability statement

Not applicable.

Additional information

No additional information is available for this paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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