



Aspects of Environmental Pollutants on Male Fertility and Sperm Parameters

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Abstract

Air pollution has considerable interest because it has multiple adverse effects on human health and the male reproductive system seems to be sensitive. For male fertility, environmental pollutants are vital owing to effects on semen quality. Male infertility is increasing in industrial countries with high air pollution. This review aims to investigate the effect of air pollution on fertility in humans based on available signs. Genetic and epigenetic alterations effect on the failure of male gamete. In this paper, we reviewed the major impacts of air pollutants on male infertility as well as the role of sperm DNA damage and epigenetic changes in male gamete. The DNA molecule and epigenetic changes, transmitted to future generations, can be altered and induced, respectively by some pollutants. A good knowledge on the effects of air contaminants on the molecular mechanisms leading to infertility is helpful for clinicians to identify the cause of infertility.

Keywords: Environmental Pollutants, Male Fertility, Sperm Parameters

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1 Introduction

In industrial countries, there has been an increase in infertility from 7% - 8% to 20% - 35% from 1960 by now, respectively (1). For the World Health Organization (WHO), the important priority is decreasing infertility rate (2). Based on some studies carried out, there has been a decrease in semen quality and sperm concentrations recently in most

places in the world. In addition, there has been a noticeable decrease in human sperm concentrations from 113 to 61 million/Ml (which shows 50% reduction) during the last 50 years (3). According to available evidence, fecundity and human semen quality have been decreasing during the last decades especially in Europe and the United States (2-4). Based on an estimate provided, there has been a decline by

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1.5% each year in the sperm count in American males (5, 6). However, there has been an increase in the infertility rate in Iran for the last 20 years. Studies show that in one-fourth Iranian couples are infertile; thus, by the end of their reproductive age three-fourth will be infertile. Furthermore, the infertility and the primary infertility rate have been increased by 20% and two-fold, respectively, for the last two decades (7). On the other hand, this idea that important factors might lead to decreasing semen in quality in some areas not all of them can be supported by geographical variations effects on semen quality (8, 9) as well as other changes which are in men reproductive functions (4,5). Lifestyle and environmental factors contribute toward these changes and constant exposure to environmental endocrine-disrupting chemicals has been provided (6). According to the reports, the malfunction of male reproductive system may be a well sensitive marker for environmental danger (4). Either gonadal endocrine disruption or direct damage to the spermatogenesis may cause the changes of male reproductive system (6). Investigating the unclear results obtained from the effect lead (Pb) and cadmium (Cd) elements on some variables, including male infertility, sperm parameters and hormone concentration has been carried out by epidemiological studies. (Give reference).

Now, one of the most vital risk factors of metropolises is air pollution and it has an effect on all people, who live in urban areas. Owing to the importance of air pollution and effects, many studies have done to investigate adverse effects of it on the human health (10). Based on perinatal outcomes, there has been a correlation between air pollution and some adverse perinatal events, including reduced gestational period (11), preterm delivery (12–14) and low birth weight (15). However, the effect of air pollution on the fertility has not been clear yet, it has been interested due to multiple adverse effects, which were reported on human health (1). The impacts of air pollution on some items, including in vitro fertilization (IVF) success rates (16), mammalian fertility and semen quality (17–20) have been highlighted by some reports (21, 22). Clinical practice is tended to focus on the impacts of various air pollutants on fertility and knowing if subfertile populations are more sensitive toward these detrimental impacts. This review aims to investigate the effect of air pollution on fertility in humans based on available signs.

2 Methods of Searching

This study is a review investigating the effect of environmental air pollutants on reproductive health or fertility. The PubMed database is our source helping us to conduct the search in April 2019. In our study, there has been a combination of descriptors and terms correlated to air pollution and fertility so that every contaminant or substance such as gases, particulate matters, or volatile organic compounds in the air, which have an interference with human health or produce other harmful environmental effects, was considered as an air pollution (23). The entire search was conducted using the Advanced Search Builder and the keywords were found in 'Title OR Abstract'. We tried to filter the hits by selecting articles, which are written in English.

3 Mechanisms of action of air pollutants on fertility

There have been 4 mechanisms for air pollutants effects on fertility, as follows: i) hormonal changes caused as a result of an endocrine disruptor action, ii) induction of oxidative stress, iii) cell DNA change and iv) epigenetic modifications. Air pollutants can play a key role as endocrine disruptors through activation of the aryl hydrocarbon receptor (AhR), estrogen or androgen receptors (24). One of the common cellular mechanism caused air pollutants and used adverse effects is acting directly as pro-oxidants of lipids and proteins or as free radicals' generators, developing the inflammatory responses induction and oxidative stress (25). The DNA molecule and epigenetic changes, including DNA methylation and histone modifications transmitted to future generations, can be altered and induced, respectively by some pollutants.

3.1 Action as endocrine disruptors

All air pollutants especially the PAHs and heavy metals like Cu, Pb, Zn, PM, notably from diesel exhaust (26, 27), are discussed in the article as endocrine disruptors with either estrogenic, antiestrogenic or anti-androgenic activity (28–33).

3.2 Induction of reactive oxygen species (ROS)

The most air pollutants like NO₂ or O₃ can generate ROS; in addition, ROS is produced by particulate matters (PM) using the heavy metals and the PAHs. They are able to change by CYP450 dihydro-dehydrogenase producing quinone redox, catalyzing electron transfer reactions and hence stimulating ROS production (34–37).

3.3 Cell DNA alteration

Inducing alterations in the cell DNA is the third mechanism discussed in the paper in order to explain the pathophysiologic mechanisms, which are in fertility alteration led by air pollution. As discussed above, these DNA alterations could be related to oxidative stress, which is induced. Based on studies carried out on taxi drivers, DNA can be altered by the inflammation processes because of ROS (38). Besides, increasing annual some factors, including exposure to NO_x, inhalable particulate matter and fine particulate matter (PM_{2.5}) cause telomere length to increase (39). After forming of DNA adducts, they might occur. Since some of molecules can bind to a DNA base within covalent bonding, then change gene expression. Moreover, mutation incidence can lead to alternating the cell DNA and increasing apoptosis risk. Some of air pollutants are able to form DNA adducts in germ cells and the PAHs, which are in PM (40, 41, 42).

4 Epigenetic modifications

Epigenetic modifications, which are noticeable changes in DNA methylation, are able to cause abnormal gene expression. These abnormalities have roles in impact of air pollution upon respiratory failure (43, 44) and carcinogenesis (45). According to studies carried out by Ding et al, both hypomethylation and hypermethylation were shown in rats exposed to PM₁₀, PM_{2.5} and NO₂ (46) and mitochondrial (mt) DNA can be affected by these

changes (47). It was shown by Byun et al. blood mtDNA methylation, which is in the D-loop promoter, was accompanied with PM-2.5 levels (48). It was reported that epigenetic alterations are involved in the spermatogenesis failure (49). Based on findings of Stouder et al. (50), administration of alcohol in pregnant mice led to inducing hypomethylation of the H19 imprinted gene, in addition to the decreased spermatogenesis. Furthermore, it is proven by Park et al., (51) that exposure to butylparaben (BP) for a long time can make DNA hypermethylation from the mitotic in a post-meiotic stage in tests for adult rats. Altering microRNA (miRNA) can occur by air pollutants. According to study done by Tsamou et al, the placental expression of miR-146a, miR-21 and miR-222, which are three miRNAs affected by air pollution exposure in leucocyte blood cells and also expressed in the placenta, was inversely accompanied with PM-2.5 exposure throughout the 2nd trimester of pregnancy (52). There are some details about environmental pollutants which are effective on male fertility as follows:

5 Effects of environmental pollutants on male fertility

5.1 Environmental pollutants and epigenetic changes in male germ cells

Reliable evidence for damage to spermiogenesis, which is caused by ambient air pollution exposure notable for genotoxic impacts and epigenetic alterations is provided by experimental and clinical studies. It is needed to have more investigations on the clinical relevance of air pollution-induced impacts in male germ cells. Indeed, one of the clinical challenges has been the diagnosis of environmentally induced DNA damage or male infertility. The importance of the genotoxic impact on human spermatozoa is on both the offspring's health and the reproductive performance of the men, who were exposed. There is a negative correlation between the semen quality and percentage of DNA-fragmented spermatozoa in an ejaculation (53; 54; 55). Although fragmented DNA with a spermatozoon is able to fertilize similarly an oocyte (56). Some studies have been carried out to show that the embryo and oocyte keep the ability to make a repair to DNA damage present in the paternal genome (57). Although there has been a question if all damage can be repaired. For example, double-stranded DNA breaks seem less repairable in comparison with single-stranded breaks and; therefore, they have a stronger effect on embryo development (58).

Indeed, the oocyte is able to repair DNA, which has damage of sperm, for a certain level that damage caused in this level will lead to fragmenting low rate embryonic development and embryos. In addition, it was shown by Carrell et al, (59) that measurement of DNA fragmentation in men, with partners had pregnancy losses repeatedly, had higher levels. Therefore, some events, including impaired embryo morphology of blastocysts, fertilization failure, repeated spontaneous abortions or embryo implantation failure might happen.

According to evidence, epigenetic changes cause toxicity mediated from some environmental pollutants (60), thus, studies should be accurately carried out to investigate probable direct interactions between epigenetic alterations, air contaminants, and sperm abnormalities. By alterations in

morphology and sperm number and a male fertility impairment, epigenetic modification of sperm gene function can have an effect on the reproductive outcome. It is important to reprogram epigenome and-imprinted loci throughout gametogenesis and peri-implantation stages in order to maintain a suitable inheritance pattern, especially at imprinted loci (61). Based on data obtained from literatures such as animal and human studies, there has been an increasing concern about risk of various diseases in the offspring made using assisted reproductive technologies (62; 63). Most of abnormal conditions are correlated to epigenetic alterations, which lead into adversely affecting embryonic development and imprinting disorders, based on some strong evidence. To identify reasons of infertility and describe therapeutic and preventive protocols, clinicians need to have better information about air contaminants effects on the molecular mechanisms, which lead to male infertility (64).

5.2 Environmental pollutants and changes in sperm parameters

Air pollution as a common factor has an effect on reproductive functions in all countries for both men and women especially for sperm parameters in men. According to the results obtained from meta-analysis that air pollution, however, decreases sperm motility, it does not affect the others parameters of spermogram. Some of stages in spermatogenesis and testicular size in mice were impaired and decreased, respectively, by post-natal and prenatal exposures to ambient air pollution (65). However, air pollution does not cause any changes in sperm counts in many studies; some abnormalities in DNA, sperm motility and morphology have been seen (66-69) and there is a negative correlation between air pollution and sperm counts specially in some population (70).

A decrease in sperm counts can occur due to exposure to environmental pollution in the world (71-77). In a reported done recently, it was shown that there is progressive decrease in sperm production throughout a period due to increasing air pollution in Greece (78). Although a relationship between either exposure to increasing air pollution or residence district and declined sperm production, including sperm per sample and concentration has not been found in the Czech Republic (66).

However, there was poorer morphology (both years) and lower sperm motility from 1994 samples for men sampled at the winter after increasing pollution in comparison with those of sampled after decreasing air pollution (Teplice in the fall and Prachatice the late winter or fall). Thus, based on the evidence, it is likely to have a relation between increasing air pollution and decreasing sperm quality. In addition, fertility data are not, however, available for this group of young men, there is a correlation between normal morphology and low values for sperm motility with infertility (79-82). In study carried out by Selevan et al (66), it was found that there is highly noticeable relation between exposure to high (1993) air pollution, periods of medium (1994) and poor sperm morphology. Increasing air pollution in winter 1993 was accompanied with increasing sperm percent and abnormal chromatin structure (COMPat). In clinical studies, high COMPat (> 30) has been accompanied with spontaneous abortion and infertility (83); however, this

measure has been used recently for epidemiology studies. In another study, there was a relation between increasing COMPat and exposure to cigarette smoke such as air pollution containing genotoxic PAHs and elevated COMPat (84). Thus, it can be deduced that smoking was kept in the COMPat model. Regarding this, other measurement of genetic integrity called sperm aneuploidy noticeably increased in a subset of the same men exposed to high air pollution, including nonsmokers from the Teplice winter 1993 group in comparison with those exposed to low air pollution, including nonsmokers from the Teplice summer 1993 group, who were from Czech (84).

5.3 Environmental pollutants and changes in sperm DNA integrity and telomeres

Nowadays, it is believed, based on the available evidence, that sperm DNA integrity maybe a better factor to predict male fertility potentiality in comparison with common semen parameters (85). However, the most routine method used in a clinical setting called DNA fragmentation might not to be able to give complete information about DNA damages everyand the molecular mechanisms (85). Thus, it is needed urgently for male germ line cells to have more sensitive biomarkers of DNA integrity. Recently, there have been many studies about the effect of sperm telomeres in male infertility and reproduction (86). According to results obtained from studies, sperm telomere length could be as an extra sperm quality parameter which might add information regarding DNA damage and make a new way in evaluating infertile males (87, 88). It was shown, by a study conducted recently, that a probable relation has been between sperm telomere length and high environmental pressure, in which polluted areas (89).

Based on a study carried out recently, environmental exposure with high level might lead to increasing semen telomere length (TL) in young normospermic men, who have important effects and roles on sperm as a sensitive sentinel biomarker of environmental impactsthat was obtained for the first time (90). In addition, it has been shown tha tembro quality development sperm and sperm telomere length (STL) have been correlated and TL is higher in normozoospermic than oligozoospermic men (91). The pollutants effect on semen telomere length has been evaluated in a just one study owing to a few types of PAHs; there was a shortening in semen TL ledby an impairment in telomerase (89) and it is shown that there has been a noticeable increase in telomere length in sperm for young men who live in places with high environmental pollutants exposure than others. These results reveal that one of the sensitive sentinel biomarkers of environmental exposure is semen. To do more studies in majorpopulations, it is necessary to know the importance of telomere lengthening in places with high environmental situations.

5.4 Environmental pollutants and sperm DNA damage

Fertility can be affected by chromosomal aberrations, either structural or numerical. The chromosomal aberration sfrequency is approximately 0.6 %in the total population (92), while increaseup2%–14% in infertile males (93). There has been an increase in chromosomal aberrations due to increasing severity of infertility. In conclusion, as men, who have normal semen parameters, might have high-degree

DNA fragmentation, which can be an important reason for undiagnosed/unexplained infertility, sperm DNA integrity has been considered as a better suggestion to predict male fertility better in comparison with common semen analysis. In a study carried out by Rubes et al. (94) in 2005, it was revealed that air pollution was correlated with increasing damage of DNA in human sperm without any other changes associated with semen quality such as motility and sperm concentration. These results proved preceding evidence of sperm morphological abnormalities (95, 66) in men, who live in the Teplice District in Northern Bohemia (Czech Republic) an place in which high-levelair pollution has been annually registered (96; 97). Radwan et al. (98) observed a statistically noticeable relation between exposure to all examined air pollutants and abnormalities in sperm morphology using analyzing infertile men based on normal semen concentrations. It is probable that sperm DNA fragmentation was the most common reason of paternal DNA noticeably transmission to progeny and found in a high percentage of spermatozoa from infertile men, subfertile and also from subjects, which were exposed to toxicants (99).

In many studies, there has been a potential relation between fertility status and sperm DNA fragmentation (100-102). Rubes et al. (103,104) investigating seasonal differences in policemen worked in the center of Prague and exposed, which was verified by personal monitoring and ambient), revealed that there is notably higher DNA fragmentation in winter, that has high exposure compared to spring, that has low exposure for total non-smokers. Furthermore, it was seen a noticeable correlation between two standard indexes of DNA fragmentation, including HdFI and detDFI with% of sperm with only high DNA damage and detectable DNA fragmentation Index, respectively, and specific genetic modification on DNA repair genes. A correlation was between immature sperm and polymorphisms in GSTM1 gene codifying for one of the enzymes, which generally defend from many toxicants, and supported the genetic polymorphisms role as potential modifiers of associations between modifications in sperm quality and air pollution exposure (103,104). On the other hand, the idea for special factors, which present in some areas not all of them, might be in charge of declining semen quality, is maintained by the impact of geographical variables in the quality of semen and other alterations in men reproductive function (105-107).

5.5 Environmental pollutants and Epigenetic changes and male infertility

Heritable alterations in gene expression and in phenotype without changes in the DNA sequence are defined based on Epigenetics containing chemical changes to histone proteins related to DNA (histone modifications), the cytosine residues of DNA (DNA methylation) in addition to posttranscriptional regulation by noncoding microRNAs. Despite of the similarity of DNA sequence between humans, there has been a large epigenetic difference (108). Some diseases might be caused bychanges of epigenetic profile responding to environmental stimuli, and epigenetic modifications triggered by environmental exposure (109-111). There has not carried out any studies yet to investigate the direct impact of environmental toxicant exposure on male fertility abnormality and epigenetic stat; however, there

issome animal evidence making a suggestion that epigenome is altered by environment-induced abnormality in sperm parameters (112,113). Epigenetics mechanisms ultimately regulating the activity of gene and expression throughout differentiation and development are basic mechanisms for normal spermatogenesis and gonadal development (114-116). It has been clear that special errors, which are in the procedure of epigenetic control, might occur throughout every stage of spermatogenesis, negatively, having an effect on embryonic development and male fertility and (117).

In recent meta-analysis, alterations in miRNA profile caused sensitive indicators made from impacts of chronic and acute environmental exposure (118). There has not been published any special studies yet; however, the available data strongly makes a suggestion that air pollutants could have an impact on the miRNA signature, which are needed for normal spermatogenesis. miRNAs have an important role in meiosis, mitosis and spermatogenesis (119-121). In order to participate in every step control of male germ cell differentiation, throughout spermatogenesis, the miRNAs are stated in a cell-specific manner. The significance of miRNA paths for normal spermatogenesis has been revealed by models of genetically modified mouse, and functional studies have been conducted in order to dissect the specific miRNAs roles in different cell type (122). Based on clinical studies, spermatozoa from patients with seminal changes shows a differential miRNA profile (123,124). Therefore, on the one hand, there is a hard evidence of miRNA important role in spermatogenesis contributing to the mechanisms, which are involved in human fertility; on the other hand, the profile of miRNA expression has been offered as a new non-invasive, diagnostic biomarker of male fertility. Study conducted by Wang et al. (125), investigated samples of pooled semen acquired from infertile men and the results in comparison with normal fertile individuals as control groups. It was revealed that changes in miRNA profiles in both asthenozoospermia and azoospermia. The seven miRNAs level was noticeably lower and higher in azoospermia and asthenozoospermia, respectively, in comparison with control. Therefore, it was proposed by the authors that seven miRNAs may confirm molecular diagnostic value for infertility in males.

5.6 Impact of Environmental pollutants on the male gamete in animals

Studies conducted out on animals have revealed that different forms of air pollution have detrimental impacts on the quality of sperm. A statistically noticeable decline in spermatozoa production has been expressed which is along with increasing abnormal sperm shapes in rats and mice exposed to car exhaust, remarkably from diesel vehicles (126-130). It has been reported that there is an impact on the nuclear quality of spermatozoa (131). It was observed by Yauk et al. that there was a statistically noticeable increase in sperm DNA breakage and hypermethylation in mice which were exposed to air pollution in a Canadian city (132). There was a noticeable increase in the mutations rate, which was found in sperm DNA, particularly on the loci of DNA sequence repeats. The probability of genetic mutations in germ line cell's DNA increased by this last phenomenon such as spermatozoa, which are transmitted to descendants (133). However, Yoshida et al. reported structural alterations

in Leydig cells on the testicular level, (126); Watanabe has reported a Sertoli cells reduction in rats, which were exposed to diesel exhaust (127). It was shown by Jeng and Yuhaveon the hormonal level that prolonged exposure to PAHs leads to decreasing and increasing in blood testosterone levels and LH levels, respectively, at the end of the exposure time (46). It was found by Inyang et al. that there is a statistically noticeable decrease and increase in levels of blood testosterone and LH levels, respectively, in rats, which were exposed to a type of PAH: benzo (a) pyrene (134). According to study carried out on rats by Tsukue et al., hormonal alterations in the group, which were exposed to diesel exhaust with a statistically noticeable increase in levels of blood testosterone and LH, were correlated with modifications in the weight of the accessory sex glands such as seminal vesicles and prostate (135). It was reported by Watanabe and Oonuki that there was a statistically noticeable increase in testosterone and estrogens levels and a noticeable decrease in the levels of FSH and LH in a group of rats, which were exposed to diesel exhaust. Moreover, an increase in degenerative cells was observed between spermatid and the spermatocytostages (130).

5.7 Impact of Environmental pollutants on the male gamete in humans

In the past few decades, there was a decrease in the sperm quality in industrialized countries (136, 137). The exposure to toxic materials in ambient and the environment air pollution can be a probable cause for these changes (138-140). Indeed, it has been revealed that professions, which were exposed to exhaust like toll collectors and worked on expressways, more regularly generate sperm abnormalities (141, 142). However, this paper is rich in this subject, there have not been enough studies on it since they do not investigate the same pollutants and their methods are different based on populations studied during exposure time. Besides, results obtained are not sometimes in agreement.

Although many studies reveal modifications, after exposure to air pollution, in parameters of sperm, giving evidence for decreasing the quality of sperm. These changes have a decrease in either sperm mobility (138, 140-146), or in the movement quality (138, 140). In addition, a decrease in the percentage of normal shapes, especially head morphology, along with changed sperm morphology is regularly mentioned (66, 140, 142, 144-150, 151). Results obtained for sperm counts are not in agreement with a few studies reporting a noticeable decline in the concentration of sperm in semen after exposure to specific forms of air pollution (140, 142, 144, 149, and 152); however, others do not report noticeable impacts (66, 148, and 153). The results can be true for the proportion of alive spermatozoa such as sperm vitality, with a few studies investigating a noticeably negative impact of air pollution on these parameters (138, 146).

Guven et al. carried out a study on comparison sperm parameters at males, who were exposed to exhaust from diesel vehicles during work at toll plazas on pathways with unexposed males, who worked as official personnel in the exact company. The exposed group had a statistically noticeable decline in sperm mobility, sperm counts as well as sperm morphology especially cephalic faults (142). Selevan et al. conducted a study on parameters of sperm in

healthy young males from two areas of the Czech Republic, a coal-producing region with high levels of air pollution (Teplice) and a less-polluted region (Prachaticze).

In comparison with the low level of exposure, it was found that there is a statistically noticeable negative effect of exposure to high and medium air pollution levels on the proportion of motile sperm that they are respectively for low, medium and high exposure are as follows: $36.2\% \pm 17$; $27.9\% \pm 18.1$ and $32.5\% \pm 13.2$. Those were also true for sperm morphology, noticeably sperm heads. On the other hand, in comparison with the low level of exposure, they did not have an impact of high or medium exposure to air pollution on all sperm count which are respectively for low, medium and high exposure as follows: 113.5 ± 130.7 million/ejaculate; 100.9 ± 97.6 and 129.1 ± 103.1 (66). The same team revealed that there is a statistically noticeable increase in the percentage of spermatozoa along with abnormal chromatin such as abnormalities in DNA compaction and fragmentation in males, who were exposed to air pollution with high levels in the Teplice area of Czech Republic (153). Thus, these studies offer that air pollution might change sperm DNA (131, 154). Based on these observations, it was expressed by other authors that there is a probable impact of air pollution upon the sperm genome at the chromosomal level (144, 155). Therefore, the rate of aneuploidy in the sperm of Polish men associated with normal sperm concentrations ($> \text{or} = 15 \text{ million/ml}$), which consult for infertility was measured by Jurewicz et al. (155). It was observed that there is a noticeable relation between the rate of aneuploidy as well as exposure to sure air pollutants, significantly Y-chromosome disomy and disomy 21 and PM-10 ($\beta = 0.58$ (95% CI: 0.46–0.72)), PM-2.5 ($\beta = 0.68$ (95% CI: 0.55–0.85)) and PM-2.5 ($\beta = 0.78$ (95% CI: 0.62–0.97)), after alteration for 12 confounding factors, including smoking, age, season, alcohol consumption, abstinence interval, past diseases, distance from the monitoring station.

Recently, it was reported by some authors that there is an alteration in the circulating levels of hormones in the gonadal axis, which follows exposure to air pollution. According to study carried out by De Rosa et al., there is a comparison between a group of exposed men, who work at a toll plaza on an pathway and an unexposed group, who work as drivers, clerks, doctors and students or live in the same geographical region. According to altering sperm parameters, a noticeably higher level of FSH was observed in the group that were exposed (mean $\pm$ SE: $4.1 \pm 0.3 \text{ UI/l}$ vs 3.2 ± 0.2 ; $p < 0.05$); however, it was kept within range of normal value (138). It was also found by Radwan et al. (150) that there is a negative correlation between exposure to specific air pollutants testosterone levels (PM-10, PM-2.5, CO and NO_x).

Therefore, there is a strong evidence regarding detrimental impacts of air pollution on male reproductive parameters; in addition, a decreased in male fertility can be in interest. Although, the many studies of human are retrospective. It was found just one study on a 2-year period in the youth, who were nonsmokers with healthy sperm donors from Los Angeles, California (152). The sample was completely small ($n = 48$) and only motility and sperm concentration were investigated. Although, every sperm donor gave sample at least 10 times at the duration studied period. Only O₃ exposure revealed a noticeable effect on

parameters of sperm for the 4 air pollutants calculated at region, including PM-10, CO, NO₂ and O₃) after alteration for many factors such as abstinence period and the other air pollutants. There was a 4.22% decline in concentration of sperm per inter quartile range (IQR) of increase in O₃ ($p = 0.01$) for every exposure until before semen collection 9 days. Moreover, there was 2.92% and 3.90% declines in concentration of sperm per IQR for an increase in O₃, respectively ($p = 0.05$ in both cases) (156) for the exposure 10–14 days and 70–90 days before ejaculation.

6 Conclusion

Clinical and experimental studies provide important evidence for damage to male gamete caused by air pollution for its genotoxic effects and epigenetic alterations. Diagnosis of environmentally induced male infertility by clinicians is likely to remain a challenge. An accurate knowledge of genotoxic effect on spermatogenesis is important not only for the fertility of the men exposed, but also for the offspring's health. Indeed, the percentage of DNA-fragmented spermatozoa in an ejaculate negatively correlates with semen quality on the other hand it is now clear that also a spermatozoon with fragmented DNA can fertilize an oocyte and cause to abnormal offspring. Indeed, the effect of epigenetic modification of sperm gene function can affect the reproductive outcome.

A large amount of literature data, including human and animal studies strongly suggest that the majority of risk of different diseases in the offspring are related to epigenetic alterations leading to imprinting disorders and adversely affecting embryonic development. A good knowledge about the effects of air contaminants on the molecular mechanisms cause to male infertility could help the clinicians to identify the cause of infertility and to define preventive and therapeutic protocol.

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