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A Comprehensive Review on Epigenetic Changes Induced by Environmental Toxins and Their Role in Male Infertility

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Abstract: Male infertility is a growing global health concern, with environmental toxins increasingly recognized as significant contributors. Among the many mechanisms through which these toxicants exert their detrimental effects, epigenetic modifications—heritable changes in gene expression without alterations in DNA sequence—are emerging as critical mediators. This review provides a comprehensive examination of current evidence linking environmental toxins to epigenetic disruptions in the male reproductive system. Specifically, it explores how exposures to heavy metals, endocrine-disrupting chemicals (EDCs), air pollutants, and pesticides can alter DNA methylation patterns, histone modifications, and non-coding RNA expression in sperm and testicular tissue. These epigenetic changes have been associated with impaired spermatogenesis, reduced sperm quality, hormonal imbalances, and even transgenerational reproductive effects. Additionally, the review discusses the molecular pathways affected by these modifications, potential biomarkers for exposure and infertility, and the reversibility of some epigenetic damage through lifestyle changes and medical interventions. Understanding these interactions is crucial for developing effective public health strategies and personalized approaches to diagnose, prevent, and manage environmentally induced male infertility.

Keywords: Male infertility, Epigenetics, Environmental toxins, DNA methylation, Histone modification, Air pollution, Sperm quality.

Introduction - Male infertility affects approximately 7% of the male population worldwide and contributes to nearly half of all infertility cases in couples (Eisenberg et.al., 2023). While genetic factors play a role, there is a growing body of evidence implicating environmental toxins as major contributors to the decline in male reproductive health. Epigenetics, which includes modifications such as DNA methylation, histone modification, and RNA-associated silencing, provides a key link between environmental exposures and changes in gene expression that affect fertility (Rotondo et.al., 2021). This review aims to synthesize current knowledge on how environmental toxins induce epigenetic changes that influence male fertility.

Understanding Epigenetics and Male Reproduction: Epigenetics refers to a collection of regulatory mechanisms that influence gene activity without altering the underlying DNA sequence. These mechanisms play crucial roles in development, differentiation, and tissue-specific gene expression (Marzouniet.al., 2022). In the context of male reproduction, epigenetic regulation is essential for the proper progression of spermatogenesis, the maintenance of sperm DNA integrity, and successful fertilization and embryogenesis. The three primary epigenetic modifications relevant to male reproductive biology are DNA methylation, histone modification, and non-coding RNAs (Hassani et.al., 2021).

DNA methylation typically occurs at CpG dinucleotides, where the addition of a methyl group to cytosine leads to transcriptional silencing of associated genes. In spermatogenesis, this modification is vital for genomic imprinting and the silencing of repetitive elements. Research evidence showed that disruption of DNA methylation patterns can lead to improper gene expression, compromised sperm quality, and infertility (Shacfeet.al., 2023).

Histone modifications involve the post-translational alteration of histone proteins, around which DNA is wrapped. These changes include acetylation, methylation, phosphorylation, and ubiquitination, each influencing chromatin structure and gene accessibility. During spermatogenesis, the transition from histones to protamines is essential for chromatin condensation and DNA protection. Experimental studies reveal that aberrant histone modifications can result in poor sperm morphology and

reduced fertilization capacity (Zhou et.al., 2021).

Non-coding RNAs, especially microRNAs (miRNAs), also regulate gene expression by targeting messenger RNAs for degradation or translational inhibition. In the male reproductive system, miRNAs are involved in testicular development, germ cell differentiation, and hormonal signaling. Altered miRNA expression profiles have been associated with oligospermia, asthenospermia, and other forms of male infertility (Aliakbariet.al., 2021).

Together, these epigenetic processes form a complex regulatory network crucial for male fertility. Emerging evidence suggests that environmental toxins can interfere with each of these mechanisms, leading to subtle yet significant changes in reproductive outcomes (Gunes, S., & Esteves, S. C. 2021). Understanding these pathways is key to unraveling the molecular basis of male infertility and identifying potential targets for intervention and therapy.

Environmental Toxins and Their Sources: Environmental toxins encompass a broad range of chemical substances that are introduced into the environment through industrial, agricultural, and domestic activities. These toxins, many of which persist in the ecosystem, pose significant health risks, including adverse effects on male reproductive health. Understanding the nature and origin of these toxicants is crucial for identifying exposure risks and formulating appropriate regulatory and preventative strategies (Krzasteket.al., 2020).

1. Heavy metals: One major class of environmental toxins affecting male fertility is heavy metals, including cadmium, lead, mercury, and arsenic (Han, X., & Huang, Q., 2021). These metals are commonly released from industrial processes such as mining, battery production, smelting, and waste incineration. Once in the environment, they can contaminate air, water, and soil, subsequently entering the human body through inhalation, ingestion, or dermal contact. Cadmium, for example, is found in cigarette smoke and industrial emissions, and has been linked to impaired spermatogenesis and hormonal disruption via epigenetic mechanisms such as DNA hypermethylation (Selvaraju et.al., 2021).

2. Endocrine-disrupting chemicals (EDCs): Endocrine-disrupting chemicals (EDCs) represent another significant group of environmental toxins. These substances interfere with hormonal signaling and are found in numerous consumer products, including plastics, personal care items, and food packaging. Common EDCs include bisphenol A (BPA), phthalates, parabens, and polychlorinated biphenyls (PCBs). These chemicals can leach into food and water supplies or be absorbed through skin contact, leading to widespread human exposure. EDCs are known to cause epigenetic alterations that disrupt the hypothalamic-pituitary-gonadal axis and adversely affect sperm development and function (Sharma et,al., 2020; Stukenborg et.al., 2021).

3. Pesticides and herbicides: Pesticides and herbicides, extensively used in agriculture to increase crop yields, also pose a significant threat to male fertility. Organophosphates, organochlorines, and pyrethroids are among the most commonly studied pesticides with known reproductive toxicity. These compounds can persist in the environment and bioaccumulate in the food chain (Moreira et.al., 2021). Agricultural workers and individuals living near farms are particularly at risk. Research indicates that exposure to these chemicals can lead to altered DNA methylation and histone modification patterns in germ cells (Giulioniet.al., 2022).

4. Air pollutants: Air pollutants constitute an increasingly recognized source of reproductive toxicants. Major pollutants include particulate matter (PM2.5 and PM10), nitrogen oxides, sulfur dioxide, carbon monoxide, and volatile organic compounds (VOCs). These pollutants are primarily emitted from vehicle exhaust, industrial activities, and fossil fuel combustion (Kumar et.al., 2021). Inhalation of polluted air has been associated with oxidative stress in the testes and sperm, potentially mediated by epigenetic changes such as altered microRNA expression and disrupted histone acetylation (Kumar, N., & Singh, A. K., 2022).

5. Plasticizers and flame retardants: Plasticizers and flame retardants, such as polybrominated diphenyl ethers (PBDEs), are widely used in manufacturing to enhance product durability and fire resistance. These substances are found in electronics, furniture, textiles, and building materials (Hales, B. F., &Robaire, B., 2020). Due to their persistence and lipophilicity, they accumulate in human tissues and are increasingly linked to male reproductive disorders through mechanisms involving DNA methylation and hormone receptor dysregulation (Caporossi et.al., 2022). These toxicants can enter the body through ingestion, inhalation, or dermal contact, and accumulate in reproductive organs .

Overall, environmental toxins originate from a wide array of sources and can exert their effects through complex biological pathways. Their pervasiveness in modern life and the emerging understanding of their epigenetic impacts on male fertility underscore the urgent need for stricter environmental policies, improved exposure assessment tools, and greater public awareness (Mariæ et.al., 2021).

Epigenetic Changes Induced by Environmental Toxins: Environmental toxins exert their effects on male fertility primarily through epigenetic mechanisms that alter gene expression profiles in germ cells and reproductive tissues. These changes can disrupt spermatogenesis, compromise sperm integrity, and impair hormonal signaling pathways. Three major classes of epigenetic modifications—DNA methylation, histone modifications, and non-coding RNA regulation—are particularly susceptible to environmental influences.

1. DNA Methylation Alterations: DNA methylation involves the addition of methyl groups to cytosine residues, particularly at CpG sites. This modification can silence gene

expression and is crucial for genomic imprinting and germ cell differentiation. Environmental toxicants such as bisphenol A (BPA), cadmium, and phthalates have been shown to induce hypermethylation or hypomethylation at key regulatory regions in sperm DNA (Sujit et.al., 2020). For instance, cadmium exposure can result in global DNA hypermethylation, leading to the suppression of genes essential for spermatogenesis (RashkiGhalenoet.al., 2021). Conversely, hypomethylation of imprinted genes can impair sperm motility and increase the risk of developmental abnormalities in offspring.

2. Histone Modifications and Chromatin Remodeling: Histones are proteins around which DNA is wrapped, forming a structure called chromatin. Modifications such as acetylation, methylation, phosphorylation, and ubiquitination of histone tails affect chromatin accessibility and gene expression. Environmental toxins can disrupt normal histone modification patterns (Zhou et.al., 2021). For example, exposure to dioxins and polychlorinated biphenyls (PCBs) can reduce histone acetylation levels, resulting in a closed chromatin conformation and transcriptional repression of spermatogenesis-related genes. Additionally, incomplete histone-to-protamine transition during sperm maturation, a process known to be affected by toxins like BPA, can compromise DNA packaging and increase sperm DNA fragmentation (Shacfeet.al., 2023).

3. Non-Coding RNAs and Post-Transcriptional Regulation: Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and piwi-interacting RNAs (piRNAs), play essential roles in regulating gene expression post-transcriptionally (Joshi, M., & Rajender, S., 2020). Environmental toxicants can alter the expression of specific miRNAs in testicular tissue and sperm, affecting mRNA stability and protein synthesis. For example, phthalates and heavy metals like arsenic have been associated with altered miRNA profiles that regulate pathways involved in cell cycle, apoptosis, and hormone receptor signaling (Aliakbariet.al., 2021). Dysregulation of ncRNAs can lead to impaired testicular development, germ cell apoptosis, and hormonal imbalances.

4. Oxidative Stress and Epigenetic Crosstalk: Many environmental toxins induce oxidative stress, which in turn influences epigenetic regulation. Reactive oxygen species (ROS) can oxidize DNA and histones, alter methylation patterns, and disrupt ncRNA expression (Krzasteket.al., 2020). This creates a feedback loop where oxidative damage exacerbates epigenetic dysregulation, further impairing sperm quality. For instance, air pollutants like particulate matter and ozone can increase ROS production in the testes, resulting in both DNA damage and aberrant epigenetic marks (Selvaraju et.al., 2021).

5. Reversibility and Therapeutic Potential: Unlike genetic mutations, epigenetic changes are potentially reversible. Studies have explored the use of dietary interventions, antioxidants, and pharmacological agents to restore normal epigenetic patterns. Nutrients such as folate and zinc, which serve as cofactors in methylation reactions, can help mitigate the effects of toxicant-induced DNA methylation changes (Yahaya et.al., 2022). Antioxidants like vitamin C and E may reduce oxidative stress and its epigenetic consequences. Furthermore, inhibitors of histone deacetylases (HDACs) are being investigated for their potential to restore histone acetylation levels and reactivate suppressed genes (Barati et.al., 2020).

Overall, the interplay between environmental toxicants and the epigenome is complex and multifaceted. These epigenetic disruptions have significant implications for male fertility, not only by impairing reproductive function in exposed individuals but also by potentially influencing the health of future generations. A deeper understanding of these mechanisms can aid in the development of diagnostic biomarkers and therapeutic interventions aimed at preventing or reversing environmentally induced infertility.

Mechanistic Pathways and Molecular Targets: Understanding the mechanistic pathways through which environmental toxins induce epigenetic modifications is essential to unraveling their impact on male fertility. These mechanisms involve complex interactions between toxicants and molecular targets within reproductive tissues, resulting in disruptions to spermatogenesis, hormonal regulation, and testicular function.

1. Disruption of the Hypothalamic-Pituitary-Gonadal (HPG) Axis: Environmental toxins can interfere with the hypothalamic-pituitary-gonadal (HPG) axis, a critical regulator of male reproductive function. Toxins such as phthalates and BPA have been shown to reduce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, which are essential for testosterone production and spermatogenesis (Plunk, E. C., &Richards, S. M., 2020). Epigenetic mechanisms mediate these disruptions by altering gene expression in the hypothalamus and pituitary gland, often through DNA methylation and histone deacetylation of hormone receptor genes. This results in impaired signal transduction and hormonal imbalances that compromise fertility (Di Nisioet.al., 2023).

2. Regulation of Genes Involved in Spermatogenesis: Several genes are directly involved in the process of spermatogenesis, including those that regulate meiosis, chromatin remodeling, and germ cell differentiation. Environmental toxins can target these genes via epigenetic alterations (Kumar, N., & Singh, A. K., 2022). For instance, histone methylation changes at promoters of protamine and transition protein genes can impair chromatin condensation during spermiogenesis. DNA methylation of the c-Kit receptor gene, crucial for germ cell proliferation, has been observed in cases of toxicant exposure, leading to reduced sperm production (Mima et.al., 2018).

3. Oxidative Stress-Activated Signaling Pathways: Oxidative stress serves as both a consequence and a

mediator of toxicant-induced epigenetic modifications. Reactive oxygen species (ROS) activate stress-responsive signaling pathways, such as the MAPK and NF-êB pathways, which can influence chromatin structure and gene expression (Shi et.al., 2021). Environmental pollutants that elevate ROS levels indirectly modify the epigenome through these signaling cascades. This can result in persistent activation of inflammatory genes and apoptosis-related factors in testicular tissue.

4. Mitochondrial Dysfunction and Epigenetic Interplay: Mitochondria play a pivotal role in cellular energy metabolism and redox balance. Environmental toxins such as lead and mercury disrupt mitochondrial function, leading to altered ATP production and increased ROS generation. These mitochondrial disturbances can influence nuclear epigenetic mechanisms (Arya et.al., 2022). For example, decreased NAD+ levels impair sirtuin activity—a class of histone deacetylases—affecting chromatin structure and transcriptional regulation in germ cells. Additionally, mitochondrial-derived non-coding RNAs may be involved in cross-talk with the nuclear genome, adding another layer to toxicant-induced epigenetic regulation.

5. Modulation of Epigenetic Enzymes: Environmental toxicants can alter the expression or activity of key epigenetic enzymes such as DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs). For example, cadmium exposure upregulates DNMT expression, promoting hypermethylation of promoter regions in fertility-related genes. Similarly, PCBs and dioxins can suppress HAT activity, leading to decreased histone acetylation and gene silencing. These enzyme-mediated changes provide a direct route through which environmental exposures impact gene regulation. These interactions can alter gene expression profiles critical for testicular function and sperm quality (Han, X., & Huang, Q., 2021).

In summary, the mechanistic pathways through which environmental toxins exert epigenetic effects on male fertility involve hormonal dysregulation, oxidative stress, mitochondrial damage, and modulation of epigenetic machinery. These pathways intersect at multiple levels, creating a web of molecular interactions that ultimately compromise reproductive health. Greater insight into these mechanisms may offer new targets for therapeutic intervention and risk assessment in affected populations.

Transgenerational Epigenetic Inheritance: Emerging evidence suggests that some epigenetic changes induced by environmental toxins can be inherited across generations. Animal studies have shown that paternal exposure to toxins like vinclozolin can lead to reproductive abnormalities in offspring via altered sperm epigenomes. Transgenerational epigenetic inheritance refers to the transmission of epigenetic modifications and their associated phenotypic effects across multiple generations, without direct exposure of the subsequent offspring to the original environmental toxicant. In the context of male infertility, this phenomenon is especially concerning as it implies that damage incurred from environmental exposures may have enduring consequences on reproductive health for generations.

Environmental toxins such as vinclozolin, BPA, and dioxins have been shown in animal studies to induce epigenetic changes—particularly DNA methylation alterations and histone modifications—in germ cells. These changes can evade the global epigenetic reprogramming that typically occurs during gametogenesis and embryogenesis, allowing aberrant marks to persist in offspring (Nilssonet.al., 2022). As a result, descendants may exhibit altered gene expression patterns associated with reduced sperm count, abnormal testicular development, and increased susceptibility to reproductive disorders.

Furthermore, these inherited epigenetic alterations may interact with environmental factors encountered by future generations, compounding the risk of infertility. This underlines the need for preventative strategies and regulatory measures to limit toxicant exposure, not only for current reproductive health but for safeguarding the reproductive capacity of future generations.

Clinical Implications and Biomarkers: Understanding these epigenetic alterations provides opportunities for developing biomarkers to assess exposure and predict fertility outcomes. Techniques such as methylation-specific PCR and next-generation sequencing are increasingly used to study epigenetic changes in clinical settings.

The epigenetic effects of environmental toxins on male reproductive health have significant clinical implications, particularly in the diagnosis, prognosis, and potential treatment of infertility (Jeremias et.al., 2020). The identification of reliable biomarkers that reflect these epigenetic alterations is crucial for early detection and intervention. One of the primary clinical concerns is the silent nature of epigenetic damage. Many men may remain unaware of their compromised reproductive health until attempting to conceive. By that time, cumulative epigenetic insults—such as aberrant DNA methylation or altered histone acetylation—may have already impaired spermatogenesis or sperm function. Clinical screening for epigenetic biomarkers could enable earlier diagnosis and personalized treatment strategies. DNA methylation patterns in sperm are emerging as promising biomarkers. Aberrant methylation of specific gene promoters, such as H19 and MEST, has been associated with poor sperm parameters and assisted reproductive technology (ART) failure (Alam et.al., 2021). Similarly, changes in the expression of certain microRNAs (e.g., miR-34c and miR-449) have been linked to testicular dysfunction and male infertility. These markers can potentially serve as non-invasive indicators of underlying epigenetic dysregulation. Histone modifications also hold diagnostic value. Altered acetylation and methylation profiles of histones in sperm

chromatin are indicative of abnormal chromatin remodeling, which can compromise DNA integrity and fertilization capacity. Clinical assays assessing these modifications could help identify men at risk of infertility and guide decisions about ART (Schrott et.al., 2022).

Beyond diagnostics, understanding epigenetic changes offers therapeutic insights. Epigenetic alterations are often reversible, opening avenues for interventions such as antioxidant therapy, dietary modifications, and lifestyle changes aimed at restoring normal epigenetic profiles (Han, X., & Huang, Q., 2021). Additionally, the development of epigenetic drugs, such as histone deacetylase inhibitors and DNMT inhibitors, may offer future treatment options, although their application in reproductive medicine remains experimental. From a public health perspective, identifying epigenetic biomarkers of toxicant exposure can inform regulatory policies and risk assessments. Population-level screening could help detect at-risk groups and implement targeted interventions. Moreover, counseling men on potential environmental risks and recommending preconception care based on epigenetic profiles can improve reproductive outcomes (Svoboda et.al., 2022).

Prevention and Reversibility: While some epigenetic damage may be long-lasting, studies suggest that interventions such as antioxidant supplementation, lifestyle changes (e.g., reduced exposure, improved diet), and medical treatments can partially reverse these changes and improve fertility outcomes.

Understanding that epigenetic modifications are, to some extent, reversible provides a hopeful outlook for mitigating the impact of environmental toxins on male fertility. Preventative strategies and potential reversibility of epigenetic changes are central to both individual health and broader public health initiatives (Iurato, G., &Igamberdiev, A. U., 2022). One of the most effective prevention strategies is minimizing exposure to known environmental toxins. Public health policies aimed at reducing pollutants—such as banning harmful pesticides, regulating industrial emissions, and promoting the use of safer alternatives—are foundational. On a personal level, individuals can reduce their risk through lifestyle changes: choosing organic food to limit pesticide intake, avoiding plastics with BPA, reducing exposure to tobacco smoke and heavy metals, and using protective gear when handling chemicals. Occupational health regulations and community awareness campaigns also play a critical role in reducing exposure. Men in high-risk industries such as agriculture, manufacturing, and waste management should be particularly vigilant and undergo regular reproductive health assessments (Ruden et.al., 2023).

In terms of reversibility, evidence suggests that some epigenetic changes induced by environmental toxins can be reversed through behavioral and therapeutic interventions. Antioxidant-rich diets—comprising vitamins C and E, zinc, selenium, and omega-3 fatty acids—have been shown to counteract oxidative stress and improve sperm quality. Lifestyle modifications such as regular exercise, adequate sleep, and stress reduction also contribute to restoring healthy epigenetic profiles (Hodjat et.al., 2020). Pharmacological interventions are also under investigation. Epigenetic drugs like DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) offer promising avenues, although their use in fertility treatments is still experimental and must be approached cautiously due to potential off-target effects (Le Goff et.al., 2021).

Furthermore, preconception care for men is gaining recognition as a vital step in reproductive planning. By assessing and modifying environmental exposures and lifestyle factors before conception, men can enhance their fertility potential and reduce the risk of transmitting epigenetic abnormalities to offspring.

Conclusion: The relationship between environmental toxins and male infertility is a growing area of concern in reproductive health, with epigenetic alterations emerging as a central mechanism through which toxic exposures impair fertility. This review underscores that environmental agents—ranging from heavy metals and endocrine-disrupting chemicals to pesticides and air pollutants—can significantly modify the male reproductive epigenome. These epigenetic changes, including aberrant DNA methylation, altered histone modifications, and dysregulated non-coding RNAs, disrupt the expression of genes essential for spermatogenesis, sperm function, and hormonal balance.

Moreover, the evidence for transgenerational inheritance of epigenetic marks raises the alarming possibility that these adverse effects may extend beyond the directly exposed individual to impact the health and fertility of subsequent generations. This adds urgency to the need for comprehensive research, public health awareness, and policy interventions aimed at minimizing environmental exposures.

The identification of epigenetic biomarkers holds promise for early diagnosis and risk assessment in affected individuals, while emerging therapeutic strategies—such as antioxidant supplementation and lifestyle modification—offer potential for partial reversal of toxin-induced epigenetic damage. Ultimately, advancing our understanding of epigenetic mechanisms in the context of environmental toxicity will be pivotal in developing more effective prevention, diagnostic, and treatment strategies for male infertility.

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