STM JOURNALS

Emerging Trends in
Personalized Medicines

ISSN: 3049-1347
Volume 3, Issue 1, 2026
January–June
DOI (Journal): 10.37591/ETPM

https://journals.stmjournals.com/etpm

Review ETPM

Paternal Pre-Pubertal Smoking: Small RNAs, Lasting Marks, and the Hidden Legacy of Early Exposure

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Abstract

While the negative effects of maternal smoking during pregnancy are well-established, the lasting and transgenerational impact of paternal pre-pubertal smoking remains a critical, underexplored area. Emerging evidence in sperm epigenetics suggests that cigarette exposure during early male development may create persistent molecular imprints that can affect the health of future offspring. This phenomenon is rooted in the fact that heredity extends beyond the DNA sequence. Sperm carry a complex epigenetic cargo, including small non-coding RNAs (like microRNAs and piRNAs) and DNA methylation marks, which regulate gene expression without altering the underlying genetic code. The period of adolescence, when spermatogonial stem cells are undergoing rapid proliferation, represents a particularly sensitive developmental window. Exposure to cigarette smoke constituents during this time – including nicotine and reactive oxygen species – can disrupt germ cell maturation and permanently modify the epigenetic "blueprint". The proposed transgenerational pathway involves three steps: toxicants from cigarette smoke reach the developing testes (Exposure); germ cells respond by altering their DNA methylation and small RNA expression (Epigenetic alteration); and these altered marks modulate gene expression in the zygote upon fertilization, leading to long-term physiological changes (Embryonic influence). Human epidemiological studies support this, showing that children of men who began smoking before puberty have higher risks of obesity, asthma, and accelerated epigenetic aging. This body of work challenges the traditional view that only maternal factors shape the next generation. If validated, these mechanisms underscore the urgency of tobacco-control efforts targeting adolescents and highlight the need for sperm epigenetic biomarkers to assess exposure history and counsel prospective fathers.

Keywords: Biological, DNA, obesity, paternal pre-pubertal smoking, RNA, transgenerational transmission

INTRODUCTION

Cigarette smoking remains one of the world's leading preventable causes of disease, disability, and premature death. While the respiratory, cardiovascular, and carcinogenic risks of tobacco use are well documented, a growing body of scientific research is uncovering its more subtle and far-reaching biological effects–particularly those that extend beyond the individual who smokes. Increasingly, evidence suggests that a father's lifestyle choices, environmental exposures, and health behaviors may influence not only his reproductive potential but also the long-term health trajectory of his future children. This shift in understanding challenges the long-held assumption that paternal contributions to offspring health are limited to genetic information alone [1].

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Received Date: October 11, 2025
Accepted Date: October 28, 2025
Published Date: November 10, 2025

Citation: Aayush Goyal. Paternal Pre-Pubertal Smoking: Small RNAs, Lasting Marks, and the Hidden Legacy of Early Exposure. Emerging Trends in Personalized Medicines. 2026; 3(1): 1–5p.

Historically, studies of smoking-related inheritance have focused either on the direct effects of tobacco exposure in adult males or on maternal smoking during pregnancy, which can directly

influence the developing fetus. However, researchers are now paying closer attention to adolescence, a life stage marked by significant biological transformation. During puberty, spermatogonial stem cells–precursors of mature sperm–undergo rapid division and epigenetic programming. This developmental window may, therefore, be uniquely vulnerable to environmental toxins such as those found in cigarette smoke [2].

When smoking begins during adolescence, harmful chemicals can interact with germ cells at a time when their epigenetic landscape is still being established. These exposures may induce changes in DNA methylation patterns, small RNA expressions, and other regulatory mechanisms within the sperm. If such alterations persist as these cells mature into functional spermatozoa, they could potentially be passed on to future offspring [3]. This raises the possibility that early-life paternal smoking may contribute to transgenerational health effects, including increased risks of respiratory disorders, metabolic diseases, and immune dysregulation in children [4].

Taken together, emerging findings highlight the importance of recognizing paternal adolescence as a critical window of susceptibility. Understanding how lifestyle behaviors during this period shape reproductive biology and influence offspring outcomes may help guide future public health strategies, encourage early preventive interventions, and broaden our appreciation of the intergenerational consequences of tobacco exposure [5].

SPERM BEYOND DNA: THE EPIGENETIC CARRIERS

Historically, heredity was viewed through a purely genetic lens–DNA as the sole carrier of information [6]. This perspective has evolved dramatically in recent years. Sperm are now known to transport a complex cargo of epigenetic regulators, including small non-coding RNAs (such as microRNAs, piRNAs, and tRNA fragments), DNA methylation marks, and histone modifications. These molecular features do not change the DNA sequence but can profoundly influence how genes are expressed after fertilization [7]. Small RNAs, in particular, play a role in early embryonic development, guiding cellular differentiation and gene silencing. Environmental exposures that alter these RNA profiles can, therefore, reprogram developmental pathways in subtle yet enduring ways [8].

THE BIOLOGICAL IMPACT OF PRE-PUBERTAL SMOKING

During puberty, the testicular environment undergoes extensive hormonal and cellular reorganization. The spermatogonial stem cells that will sustain sperm production throughout adult life are established during this time [9]. Exposure to cigarette smoke constituents–including nicotine, reactive oxygen species, and aromatic hydrocarbons–can generate oxidative stress, disrupt Sertoli cell function, and alter the signaling networks that regulate germ cell maturation. In animal studies, paternal exposure to cigarette smoke prior to conception has been linked with changes in sperm DNA methylation and small RNA expression, alongside altered metabolic profiles in offspring. These findings suggest that smoke-induced stress during critical developmental windows may permanently modify the epigenetic “blueprint” of germ cells [10].

HUMAN EVIDENCE AND EMERGING HYPOTHESES

Human data investigating the influence of paternal pre-pubertal smoking on offspring health are still limited, yet the patterns emerging from existing studies are both compelling and difficult to ignore. Epidemiological analyses have repeatedly shown that children of men who began smoking before puberty tend to exhibit higher rates of obesity, asthma, and signs of accelerated epigenetic aging when compared with children whose fathers initiated smoking in later adolescence or adulthood [11]. Although these associations do not establish direct causality, they are consistent with the broader hypothesis that early-life environmental exposures can leave durable molecular marks on the germline. Such marks may persist for years–even after smoking cessation–and potentially shape developmental pathways in the next generation.

One plausible mechanistic link involves the disruption of sperm small RNA populations, which play essential roles in regulating gene expression during early embryonic development. Research has

demonstrated that cigarette smoke can modify levels of specific small RNAs associated with oxidative stress responses, metabolic regulation, and immune function. These changes may reflect the body's attempt to cope with the toxic burden of smoke exposure, but in doing so, they could unintentionally encode stress-related signals into germ cells.

If such alterations occur during pre-pubertal development–a period when germ cell lineages are being established and their epigenetic programming is particularly malleable–their impact may be especially profound. Modified small RNAs could influence how key genes are activated or silenced during fertilization and early embryogenesis, thereby altering developmental trajectories in subtle but meaningful ways. This concept strengthens the argument that paternal adolescence represents a sensitive window in which environmental factors can have long-term, multigenerational consequences. As research advances, understanding these mechanisms may offer not only insight into the biological origins of certain childhood conditions but also opportunities for early intervention and prevention.

POSSIBLE PATHWAYS OF TRANSGENERATIONAL TRANSMISSION

The proposed pathway unfolds across three interconnected levels:

- *Exposure:* Cigarette smoke introduces toxicants and reactive oxygen species that reach the developing testes.
- *Epigenetic Alteration:* Germ cells respond by adjusting DNA methylation patterns and RNA expression, some of which persist into mature sperm.
- *Embryonic Influence:* Upon fertilization, these altered epigenetic marks modulate gene expression in the zygote, leading to long-term physiological changes in the offspring.

The resulting effects may not manifest as congenital anomalies but as subtle metabolic or neurodevelopmental differences–outcomes often attributed to complex gene-environment interactions.

IMPLICATIONS FOR PUBLIC HEALTH AND PREVENTION

If further validated, these mechanisms hold substantial and far-reaching public health implications. They suggest that the consequences of adolescent smoking may extend far beyond the well-recognized immediate health risks, potentially creating an intergenerational echo of exposure that affects individuals who were never directly exposed to tobacco themselves. This possibility reframes smoking not only as a personal health issue but also as a societal and multigenerational concern. It underscores the need to prioritize tobacco-control policies that specifically target adolescents–an age group that is often underemphasized in discussions about reproductive health, despite being a period of critical biological development.

Strengthening prevention initiatives during adolescence may help reduce not only the early onset of nicotine addiction but also the likelihood of passing on harmful molecular signatures to future generations. School-based programs, community awareness campaigns, and stricter regulations of youth-oriented tobacco marketing could play essential roles in mitigating these risks. Public health agencies may also need to broaden their messaging to highlight that smoking during puberty can have long-term reproductive consequences, thereby motivating earlier behavioral changes.

Additionally, the identification of sperm-based epigenetic biomarkers opens new possibilities for clinical practice. These molecular indicators could allow healthcare providers to evaluate a man's exposure history, even years after he quit smoking, and offer personalized reproductive counseling. Such biomarkers may also help identify subtle, heritable changes that could influence offspring health before conception occurs. In the future, integrating epigenetic screening into preconception care could support more informed family-planning decisions and enable early interventions aimed at minimizing transmittable risks. Collectively, these advancements emphasize the growing recognition of paternal health as a key component of public health and disease prevention.

FUTURE DIRECTIONS

To clarify causality, future research should integrate longitudinal human cohorts with experimental models. Ideal studies would involve multi-omic profiling–combining small RNA sequencing, DNA methylation mapping, and chromatin accessibility assays of sperm from individuals who began smoking at different ages. Correlating these findings with epigenetic and metabolic markers in offspring will be essential to understanding the true heritability of these effects.

CONCLUSION

The concept of paternal pre-pubertal smoking influencing offspring health represents a significant paradigm shift in our understanding of heredity and intergenerational biology. Traditionally, scientific and public health discussions have focused almost exclusively on maternal exposures during pregnancy as the primary drivers of developmental risk. However, growing evidence now suggests that a father's early-life environment–particularly during the critical window of puberty–may leave molecular imprints on germ cells that contribute to the health outcomes of future children. This realization broadens the scope of reproductive responsibility and highlights the importance of considering paternal factors long before conception takes place.

By positioning sperm as a biological messenger capable of carrying not only genetic information but also epigenetic traces of past environmental exposures, this emerging field challenges long-standing assumptions about the limits of inheritance. It underscores the profound reach of lifestyle choices made during adolescence, a developmental phase often marked by experimentation and risk-taking. If harmful behaviors, such as smoking leave measurable and potentially heritable marks on sperm cells, then the implications for public health, prevention strategies, and personal decision-making become far more expansive. Ultimately, this perspective invites a more comprehensive, balanced view of parental contributions to offspring health and emphasizes the need to include young males in early preventive and educational efforts aimed at safeguarding the well-being of future generations.

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