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Review Article

Transgenerational reproductive risks of BPA: epigenetic mechanisms and biomarker applications. A critical review

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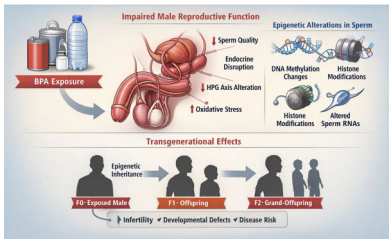
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Abstract

Bisphenol A (BPA), which is a common ingredient of plastics and epoxy resins, is among the most commonly found endocrine-disrupting chemicals in the human environment. Chronic human exposure has raised concerns over its effects on reproductive health. There is growing evidence showing that BPA causes epigenetic changes, primarily DNA methylation, histone changes, and non-coding RNA changes that result in hormonal imbalances, a disruption in gametogenesis, and fertility impairment. This review summarizes current understanding of how BPA alters male reproductive performance in exposed individuals, including impaired spermatogenesis and sperm quality, endocrine imbalance, and disruption of hypothalamic–pituitary–gonadal (HPG) signaling, often in concert with oxidative stress and altered steroidogenesis. We then discuss evidence that BPA exposure, especially during critical developmental windows, can reprogram the paternal germline, such that epigenetic alterations carried by sperm, such as DNA methylation changes, abnormal histone acetylation (H3K9ac, H3K27ac, H4K12ac), disrupted histone-to-protamine transition, and altered sperm small RNAs/miRNA profiles, can contribute to fertility defects in subsequent generations. Moreover, various therapeutic methods, like epigenetic drugs and natural products such as resveratrol, naringenin, and genistein, are being studied to reverse or alleviate the impact of BPA. Given BPA's ubiquity, these findings also highlight the necessity of stricter regulation, health education to the general population, along with research into potential safer alternatives. Learning the ways BPA is remodeling the epigenome and fertility through generations is essential to protecting reproductive health and the basis of policy intervention.

Keywords **bisphenol A (BPA), epigenetic, fertility health, hormone regulations, transgenerational inheritance**

Graphical abstract



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Lists of abbreviations

PGC	primordial germ cells
PCOS	polycystic ovary syndrome
BPA	bisphenol A
HPG	hypothalamic–pituitary–gonadal
ART	assisted reproductive technology
MDS	myelodysplastic syndromes
SAM	S-adenosylmethionine
DNMT	DNA methyltransferase
VPA	valproic acid
TSA	trichostatin A
HDACs	histone deacetylases
RISC	RNA-induced silencing complex
SIRT1	sirtuin 1
EDC	endocrine-disrupting chemicals
AMP	adenosine monophosphate

Introduction

Bisphenol A (BPA) was first synthesized by an industrial chemist in 1890 and is most known for its use in the manufacture of polycarbonate plastics and epoxy resins [1]. Due to its remarkable qualities, including length and clarity, BPA allows for its extensive use in consumer items, specifically water bottles, as well as food containers paired with dairy linings [2]. The great use of BPA in common products led to thorough studies on its probable negative effects. Scientific studies have shown that human contact can occur when BPA leaks from the containers of food and drink goods [2]. In particular, research by Krivohlavek *et al.* [3] shows how BPA moves from food packaging to residential items in the Croatian market, thus urging quick legislative action. Ongoing discussions surround the impact of BPA exposure on health; data point to its possible endocrine-disrupting properties that can cause problems with development and reproduction [4]. New studies relate BPA exposure to greater illness risks, especially cardiovascular diseases and diabetes, thereby raising the challenge of assessing its safety status [5, 6]. The regulatory difficulties persist despite concerning studies on the health hazards associated with BPA. Many nations have set rules and standards to restrict the use of BPA, especially in items meant for young children and newborns. However, the industrial interests connected to BPA's manufacture complicate the regulatory procedure and can cause extended discussions on its safety criteria. The regulatory authorities handle the difficulty of balancing public health issues along with the financial consequences of restricting a widely used substance. Furthermore, a challenge to the shift to safer substitutes is the great frequency of BPA in consumer products [2]. The effects of BPA extend to broader influences on public policy, as well as behavioral shaping. People who are aware of the possible risks associated with BPA are increasingly demanding a complete view of which items use these chemicals. While some manufacturers have started seeking BPA substitutes for their goods, continuous scientific research casts doubt on the safety profile of such substitute compounds [4].

Epigenetics is the study of hereditary changes in gene expression that do not entail changes to the underlying DNA sequence [7]. Different processes regulate these phenomena, notably the methylation of DNA, the alteration of histones, and the interactions of non-coding RNA, which significantly control gene expression [8, 9]. Usually occurring at the bases of cytosine in the CPG islands, DNA methylation results in transcriptional silencing. Depending on the particular circumstances they arise under, changes in histones via both methylation and acetylation either tend to stimulate or repress gene transcription [10]. Furthermore, research on epitranscriptomics is broadened by looking at chemical changes on RNA molecules linked to these activities, thereby generating greater regulatory complexity [9]. Deep implications for development, disease, and inheritance have been identified in epigenetic mechanisms. These frameworks ensure the appropriate expression of the genes controlling the differentiation and the function of the cells during development. For processes like stem cell differentiation, for instance, where particular gene models must be activated or silenced at specific phases of development, epigenetic regulation is essential [11]. Multiple diseases share a link with epigenetic alterations, particularly chronic conditions including obesity and cancer, because deregulated epigenetic marks trigger uncontrolled cell proliferation [12]. The inheritance of epigenetic markers creates complex scientific inquiries about heredity because these alterations move through generations to impact characteristics without altering DNA sequencing [7]. For example, environmental factors like food and stress trigger epigenetic modifications that get transmitted to offspring and lead to modifications of their health and behavioral outcomes [13]. Furthermore, the interaction between life factors and epigenetic regulation suggests that interventions targeting epigenetic mechanisms can mitigate the risks of various diseases. This perspective has sparked growing interest in therapeutic strategies that aim to modulate epigenetic marks, which can potentially reverse or prevent pathological states [14]. In the end, epigenetics seems to be a central actor in the orchestration of gene expression, development, and pathogenesis of diseases, justifying continuous research in this rapidly evolving field [15]. Recent work by Lombó *et al.* [16] and Deng *et al.* [17] indicates that BPA can impair male fertility directly in exposed individuals (F0), largely by disrupting endocrine signaling and spermatogenesis, and also contributes to transgenerational effects by inducing epigenetic alterations in sperm (e.g. DNA methylation changes and abnormal histone retention) that can be transmitted to offspring. BPA remains a pervasive endocrine-disrupting chemical (EDC) with continuing concern for male reproductive health, and various researches indicate that its effects extend beyond endocrine disruption to epigenetic reprogramming of testicular cells and sperm. However, the evidence is dispersed across DNA methylation, histone remodeling during spermiogenesis, and sperm non-coding RNAs, with inconsistent endpoints across exposure windows and doses, making it difficult to extract a coherent mechanistic model and identify robust biomarkers. This review is timely because recent epigenetic-focused studies have strengthened mechanistic links and raised biomarker and heritability questions. Therefore, this work synthesizes direct effects in exposed males and the sperm-borne mechanisms potentially underlying transgenerational outcomes, emerging opportunities for epigenetic biomarkers and intervention strategies relevant to risk assessment and prevention.

Bisphenol A (BPA)

The growing concern about the number of environmental toxins and their impact on the reproductive health of men has been a subject of great interest over the past few years [18]. One such chemical is BPA [19]. It is one of the most outstanding EDCs that are recognized to be

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detrimental to the reproductive system of both human beings and animals [5]. It is a typical industrial chemical, which can be found in thermal sheets, food containers, and plastics [20]. Plastics or polycarbonates start leaching chemicals into food at around 25°C (77°F), and the process accelerates when heated above 50°C (122°F). Specifically, BPA leaches into food 55 times faster when the temperature increases from room temperature to 70°C (158°F), leading to chronic human exposure [21]. Low doses of BPA may lead to damage to the testicles, disruption of hormones, oxidative stress, and epigenetic alteration, particularly during critical periods of development [22, 23]. Human exposure to BPA primarily occurs through ingestion, inhalation, or skin contact [20]. Literature reports indicate that foods and beverages that are acidic or basic, stored for longer periods, frequently used, and enclosed in cans or polycarbonate plastics can leak BPA [24]. Food and beverages eventually hydrolyze the leached BPA, exposing humans primarily through dietary consumption [25]. González-Casanova *et al.* [26] observed that the lipophilic nature and extended half-life of BPA lead to its bioaccumulation in adipose tissue.

Dose–response relationship and critical windows of exposure

The impact of BPA exposure on reproductive health is a complex phenomenon that depends on both the dose and timing of exposure [27]. Studies on low doses of BPA have revealed notable impacts, especially during important windows of vulnerability, including prenatal development, neonatal life, and puberty [28]. Exposure during these sensitive periods can lead to long-term reproductive effects, showing the importance of understanding the dose–response relationship and finding ways to reduce BPA exposure during these critical developmental phases.

Low-dose vs high-dose BPA exposure effects

High-dose BPA exposure is typically reported in micrograms per liter, which is a level far exceeding those in consumer products, while low-dose exposure is generally reported in the nanograms-per-liter range. The non-monotonic nature of BPA dose–response relationships complicates the evaluation of physiological effects, as low doses of BPA may elicit biological responses that are diminished or not observed at higher BPA exposure doses [29]. This phenomenon highlights the need for ongoing research to define exposure levels and challenge conventional toxicological paradigms.

Evidence in animal models points to low-dose BPA having major impacts on several organ systems. For instance, studies by Prins *et al.* [23] indicate that low doses can interfere with reproductive health, therefore affecting the estral cycle in women and spermatogenesis in men. In murin's models, the exposure throughout adolescent development has also been demonstrated to disturb immunological responses, hence aggravating allergic respiratory tract inflammation [30, 31]. These results contradict the previously held view that low levels of BPA would be physiologically neutral, highlighting the prospect of significant physiological changes elicited by low levels. High-dose BPA effects are more likely than low-dose BPA effects to be associated with a more well-documented range of unwanted physiological effects than low-dose effects [32]. High dosages in mouse studies have changed body weight and fat distribution; thus, they reflect a more direct association with severe metabolic dysfunction than low levels. Low-dose exposure has detrimental effects on liver function, as demonstrated by Linillos-Pradillo *et al.* [33], whose studies reveal that low levels of BPA cause oxidative stress, inflammation, and liver cell death. In low-dose and high-dose models, the effects of BPA have been clear during development. Studies on prenatal BPA exposure have demonstrated that BPA interferes with normal neurodevelopmental processes, which in turn affects cognitive and motor performance in postnatal life [34]. Low-dose BPA exposure, particularly during critical developmental windows, can alter learning and memory capacity in offspring by modifying neurotransmitter levels and neuromorphology [34].

Long-term reproductive consequences of BPA exposure

The widespread use of BPA and its analogs has raised concerns about their adverse biological effects, mainly because these compounds can imitate or interfere with natural hormones, thus exerting endocrine-disrupting effects. The capacity of BPA to disrupt hormonal pathways determines mostly how it affects reproductive health. Exposure to the BPA was demonstrated to change hormonal profiles by binding to estrogen receptors, therefore modifying gene expression and impacting reproductive physiology [32]. Since normal reproductive activities depend on hormonal balance, this hormonal disturbance might cause several reproductive health issues. For instance, Santoro *et al.* [28] noted that neuroendocrine modulation of gonadal activities is much influenced by BPA exposure. Based on significant documentation from animal research, this disruption can cause problems with infertility in men and women. In wildlife, the reproductive consequences of BPA exposure were illuminated by several studies. The research has shown that even low BPA doses can profoundly affect reproductive capacities in numerous species. Nevoral *et al.* [35] found that long-term exposure to BPA, even at minimal concentrations, negatively affected female reproductive health, causing changes in ovarian function and a decline in fertility rates. BPA transfer from maternal sources to children during critical development periods has been associated with long-term reproductive issues in progeny, highlighting the transgenerational risks of BPA exposure [36].

Not confined to animal research, BPA-linked reproductive issues have human epidemiological support. Ma *et al.* [37] indicated that BPA might cause problems like polycystic ovarian syndrome (PCOS) and endometriosis in women. In addition, male reproductive health was adversely affected, as evidenced by the reduced quality of sperm and testosterone levels in exposed individuals [38]. Changes in reproductive hormones can cause persistent female and male fertility issues, therefore influencing population dynamics in animals. Chianese *et al.* [39] found alterations in DNA methylation patterns that might help to explain noted developmental abnormalities and raise lifetime vulnerability to reproductive problems. These deviations have consequences beyond personal health that influence genetic diversity in animals and population viability. The propensity of the chemical to accumulate in biological tissues and its persistence in the surroundings aggravate the consequences for the health of BPA exposure. Santos-Silva *et al.* [40] found that its endocrine deviation potential can cause permanent changes in endocrinological and biochemical profiles. The findings emphasize the need to assess long-term exposure to BPA, especially during sensitive development stages such as breastfeeding, where babies are mostly susceptible.

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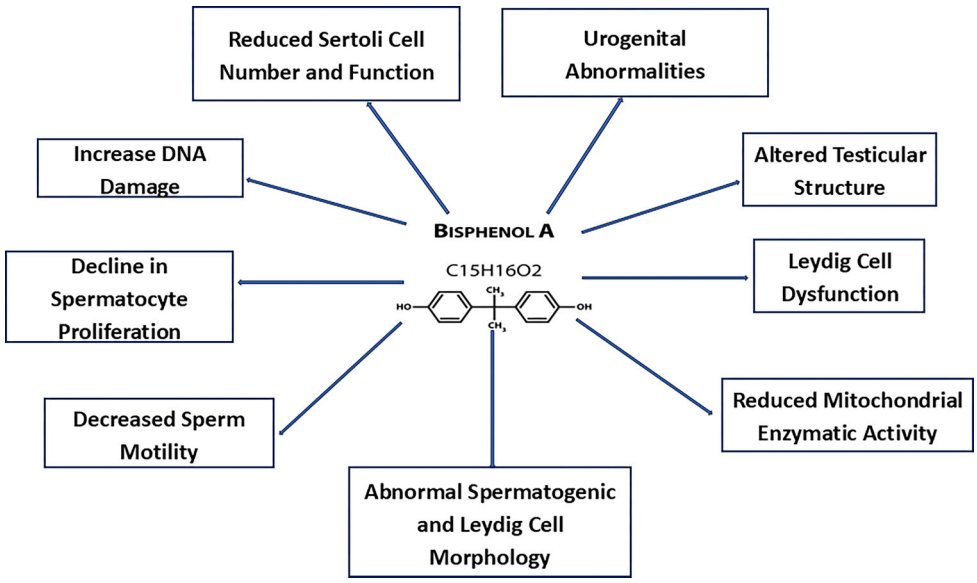


Figure 1 Showing the effects of bisphenol A on male fertility. Schematic representation of BPA-induced reproductive toxicity, including impaired spermatogenesis, hormonal disruption, oxidative stress, and germ cell apoptosis.

BPA and epigenetic alterations in male fertility

The wide distribution of BPA creates significant health risks that particularly impact male reproductive functions [41]. BPA induces its reproductive toxicity based on its effect as xenoestrogen, targeting estrogen receptors (ERα and ERβ), the G-protein-coupled estrogen receptor (GPER), and more marginally, androgen and thyroid hormone receptors [5]. These interactions disrupt the hypothalamic–pituitary–gonadal (HPG) axis, alter feedback regulation of gonadotropins, and impair steroidogenesis within the testes and ovaries [28]. Exposure of BPA in males suppresses the synthesis of testosterone by downregulating the activity of major steroidogenic enzymes, including CYP11A1, CYP17A1, and StAR, and upregulating the synthesis of estradiol, providing a feminizing hormonal phenotype [28]. In men, there have been experimental studies indicating that exposure to BPA lowers the count of sperm, reduces motility, enhances fragmentation of DNA, and alters abnormal morphology, all of which are key predictors of male infertility [42]. The pathways responsible for these sperm changes are oxidative stress, mitochondrial malfunction, and impaired chromatin remodeling throughout spermatogenesis [43]. In animal models, BPA exposure during critical developmental windows has been linked to Sertoli cell dysfunction, blood–testis barrier disruption, and apoptosis of germ cells, processes that collectively compromise spermatogenic efficiency, as shown in Fig. 1 [44]. Sertoli cell number is largely established during fetal and early postnatal life, when Sertoli cells actively proliferate and set the adult testicular capacity for spermatogenesis [45]. Therefore, BPA exposure during these critical developmental windows has been shown in experimental models to interfere with Sertoli cell proliferation and survival, likely through disruption of estrogen and androgen signaling, oxidative stress, and altered expression of cell-cycle and differentiation regulators [46]. Such early-life exposure can therefore reduce the final Sertoli cell complement in adulthood, indirectly limiting sperm output. Also, exposure to BPA after Sertoli cell proliferation has ended can disrupt Sertoli cell function, compromising blood–testis barrier integrity and the support of germ cell development [47].

Oxidative stress represents another major pathway through which BPA contributes to infertility [48]. BPA exposure increases the generation of reactive oxygen species (ROS) in testicular tissue by disrupting mitochondrial function, impairing electron transport, and activating pro-oxidant signaling pathways, while simultaneously weakening endogenous antioxidant defenses such as superoxide dismutase, catalase, glutathione peroxidase, and DNA breakage. Elevated ROS levels cause lipid peroxidation of sperm membranes, which are particularly vulnerable due to their high polyunsaturated fatty acid content, leading to reduced membrane fluidity, compromised motility, and impaired fertilization capacity [49]. Oxidative DNA damage in sperm, particularly at CpG-rich promoter regions, can exacerbate epigenetic instability and reduce fertilization success [50]. Beyond direct cellular damage, BPA-induced oxidative stress interacts with endocrine and epigenetic pathways that regulate male fertility. Excess ROS disrupts steroidogenesis by impairing Leydig cell function and downregulating key enzymes involved in testosterone synthesis, thereby exacerbating HPG axis dysregulation. In Sertoli cells, oxidative stress compromises metabolic and structural support to developing germ cells and destabilizes the blood–testis barrier [51].

Current research on BPA concentrates on epigenetic alterations as inheritable gene expression modifications that do not alter DNA sequences. According to Cariati *et al.* [52], long-lasting epigenetic changes brought on by BPA exposure during the crucial development windows may affect male reproductive ability. These modifications might include DNA methylation, histone modification, alterations in the expression of the non-coding genes, which, taken together, modify the transcriptional nature of the essential genes for reproductive purposes [16, 53]. Knowing these epigenetic modifications helps one to understand how environmental toxins like BPA cause male reproductive toxicity through their mechanism. Han and Huang [54] affirm that harmful substances create lasting epigenetic changes that are passed on between generations. Such transgenerational epigenetic inheritance leads to reproductive discomfort through decreased fertility rates and elevated reproductive disorder risks affecting male offspring. Furthermore, BPA exposure during crucial development win-

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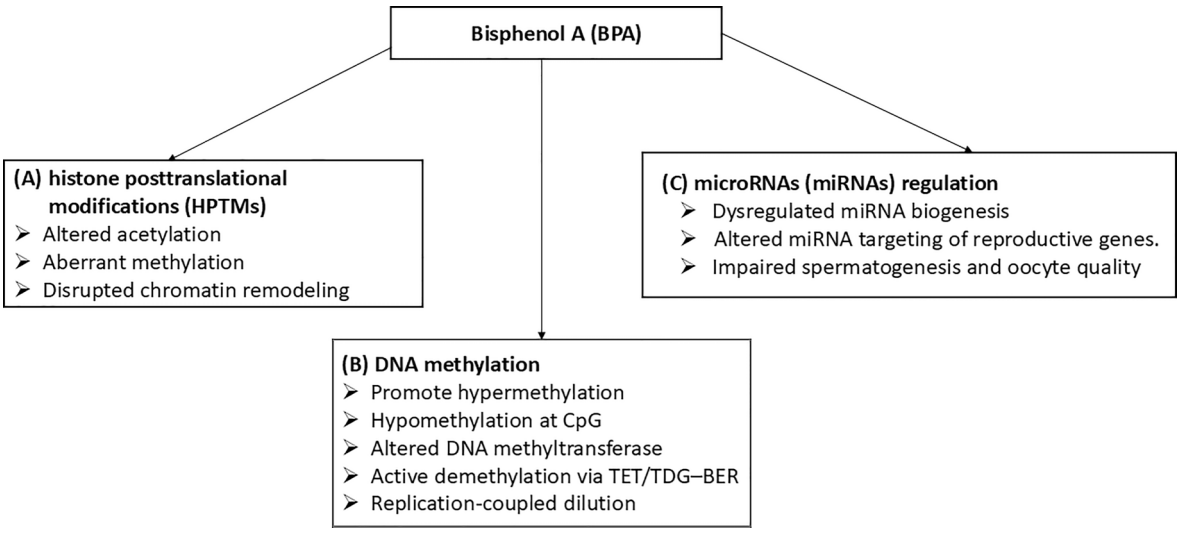


Figure 2 Epigenetic regulation mechanisms caused by BPA. An overview of BPA-induced epigenetic pathways, including DNA methylation, histone post-translational modifications, and non-coding RNAs (miRNAs, lncRNAs).

dows such as those in prenatal and peripubertal can produce permanent epigenetic modifications that compromise the reproductive capacity later in life. Lombó *et al.* [16] indicate that the degree of epigenetic modifications starts to depend critically on the timing and duration of BPA exposure.

Mechanism of epigenetic regulation

A fundamental feature of gene expression that goes beyond traditional genetic coding is epigenetic regulation. It involves several processes, notably DNA methylation, modifications in histones, and the action of non-coding RNAs, which together help to control gene activity and cellular functions as illustrated in Fig. 2. These epigenetic changes are essential not only for normal development but also in the context of diseases, including cancer and cardiovascular conditions [55].

DNA methylation

This process implies that the addition of a methyl group to the DNA molecule can alter the way genes are expressed. In general, DNA methylation is involved in various biological processes such as gene silencing, meaning that the gene is turned off or its expression is reduced, genomic imprinting, genome stability, and regulation of epigenetic gene expression [56]. Methylation models are established and maintained by enzymes called DNA methyltransferases (DNMTs) [56]. This enzyme is responsible for DNA methylation, which transfers a methyl group from the S-adenosylmethionine (SAM) to the 5′-site of the cytosine ring in DNA (Fig. 2). DNA methylation is a key epigenetic change in mammals and is primarily performed at CpG dinucleotides, where cytosine is enzymatically changed to 5-methylcytosine (5mC) [57]. This change is defined by the de novo DNA methyltransferases (DNMT3A and DNMT3B) and maintained during DNA replication by the UHRF1–DNMT1 maintenance axis, which ensures the accurate replication of methylation patterns throughout cell generations [58]. There are two complementary pathways for removing methyl marks, such are TET dioxygenases (TET1/2/3), which actively oxidize 5mC to 5-hydroxymethyl-, 5-formyl-, and 5-carboxyl-cytosine, which thymine DNA glycosylase (TDG) removes before repair by base-excision repair, replacing base-excision repair with unmodified cytosine [59]. Passively, methylation may be lost when the DNMT1–UHRF1 maintenance machinery fails to copy the parental CpG methylation pattern onto the nascent DNA strand during replication [60]. Recent mechanistic analyses have indicated that the E3 ligase activity of UHRF1 and the ubiquitin recognition of DNMT1 are essential in copying the methylation in these areas, and interference in this area selectively results in hypomethylation [60]. In addition, the MOF-dependent acetylation of UHRF1 at K670 increases its activity and leads to the recruitment of DNMT1 to chromatin, which illustrates that histone-reader crosstalk optimizes maintenance efficiency [61].

Genome-wide analysis of tissues all exhibit a two-pronged epigenetic signature of focal CpG island (CGI) hypermethylation, especially in the promoters of regulatory genes, and broad hypomethylation in CpG-poor regions [62]. These modifications tend to be concomitant in the same sample, indicating both a deviant presence of DNMT3A/3B at CGIs and abnormal UHRF1–DNMT1 activity at partially methylated domains (PMDs) [62]. Hypermethylation functionally silences genes, whereas hypomethylation destabilizes chromatin and deregulates repetitive elements. For instance, in the gastric mucosa, noncancerous tissue after *Helicobacter pylori* eradication shows positively correlated CGI hypermethylation and non-CGI hypomethylation, supporting early co-emergence of both directions [63]. Placenta presents a useful comparator because it naturally harbors extensive PMDs and exhibits global DNA hypomethylation compared with most somatic tissues [64, 65]. These methylation programs overlap with endocrine disruptors, such as BPA.

Human cohort epigenome-wide association studies indicate that exposure to bisphenol in the prenatal period correlates with different CpG methylation in cord blood and placenta, and the most tissue-specific changes were found in placental tissue [65]. In experimental studies, BPA has been shown to induce promoter methylation changes in loci like JUN in placental trophoblasts, which results in the epigenetic remodeling of placental steroid metabolism [66]. In men, repeated measurements of urinary Bisphenol F (BPA/BPF) are associated with increased sperm DNA damage, suggesting disrupted DNA

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methylation maintenance and progressive methylome instability [67]. Collectively, contemporary evidence supports a model in which DNA methylation is dynamically balanced by DNMT-driven deposition, UHRF1–DNMT1 copying, and TET–TDG–BER removal; environmental disruption by BPA can yield locus-specific hypermethylation (e.g. promoter JUN) together with broader hypomethylation in CpG-poor domains, echoing the dual signature seen across development and disease [61].

Histone modifications

Chromatin structure and gene accessibility are regulated in part by histone post-translational modifications, which alter nucleosome–DNA interactions and create binding sites for chromatin "reader" proteins, thereby modulating transcription [68]. As part of the histone octamer, these proteins undergo various post-translational modifications, including methylation, acetylation, phosphorylation, and ubiquitination [56]. These changes serve as signals that either promote or inhibit the recruitment of transcription factors and transcriptional co-regulators (co-activators/co-repressors) to specific loci [69]. The N-terminus of H3 and H4 histones in lysine positions becomes primarily targeted for acetylation events in the process. The modification occurs through the balance activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [70]. HATs catalyze the transfer of an acetyl group to a lysine site, hence promoting histone acetylation. The HATs function through three primary categories, which comprise P300 and cyclic adenosine monophosphate (AMP) response element-binding protein (CBP) complex together with MYST (including MOZ, Ybf2/Sas3, Sas2, and Tip60) and GCN5-related *N*-acetyltransferase [56].

Animal and available cell data provide direct evidence of BPA-induced disrupted histone exchange and Post-Translational Modification (PTMs) in the male germline. Oral BPA induces histone-to-protamine substitution during spermiogenesis in mice, including retention of histone/transition proteins, abnormal Protamine (PRM) ratios, and reduced fertility, which shows that the histone exchange program itself is a BPA target [71]. To supplement this, studies on rat testes indicate that long-term exposure to low doses of BPA causes changes in histone acetylation and methylation, resulting in the loss of H3K9ac, H3K27ac, and H4K12ac, as well as an increase in SIRT1 (class IIIHDAC), which suggests enhanced deacetylase activity and chromatin compaction. Secondly, other models report HAT-biased hyperacetylation (H3K9ac/H3K14ac/H4K12ac) and altered H3K27me3, indicating disrupted HAT/HDAC balance rather than a unidirectional effect [72].

Mechanistic cell-and-mouse studies also position histone methyltransferase/demethyltransferase circuitry downstream of BPA: DPY30, the critical cofactor of SET1/MLL H3K4 methyltransferase complexes, mediates BPA-induced testicular toxicity and transcriptional repression and directly links Lysine Methyltransferase (KMT) activity to exposure to BPA [73].

These chromatin findings observed in fetal and perinatal paradigms, as well as earlier developmental windows, indicate that prenatal BPA suppresses meiosis (causing zygotene–pachytene arrest), impairs sperm concentration, and induces transcriptional repression programs in the testes of offspring phenotypes, which is consistent with chromatin condensation and lowered transcription [66]. Collectively, these empirical data on mouse testes, germ cell lines, and complementary fish testis models converge on a common picture, such as BPA disrupting the exchange of histones for protamines and reprogramming the functions of HAT/HDAC and Lysine Demethylase (KMT/KDM), including the SIRT1/HDAC and DPY30/KMT axes. This disruption results in abnormal acetylation of H3/H4, altered H3-methyl marks, chromatin condensation defects, and downstream spermatogenic failure and subfertility [71].

Non-coding RNAs (ncRNA)

Non-coding RNA has played a significant role in the regulation of epigenetic processes over the last few years. MicroRNAs (miRNAs) are short non-coding RNAs that bind to messenger RNA (mRNA), thus inhibiting the translation process and regulating gene expression. In addition to their role in post-transcriptional control, miRNAs affect epigenetic processes in response to their interactions with DNA methylation and the processes that mediate the alteration of histone protein modification. Indeed, some miRNAs can call upon HDACs or DNA methyltransferase (DNMT), thus modulating the epigenetic landscape of the cell [15]. Furthermore, non-coding long regulatory RNAs are shown to recruit complexes altering chromatin to certain genomic areas, thereby either enhancing or inhibiting the expression of genes in response to cell signals [74]. This regulatory ability emphasizes the complicated function of non-coding RNAs in epigenetic-level regulation of gene expression. The evidence from emerging ncRNA studies supports the idea that BPA disrupts reproductive microRNA programs that are part of steroidogenesis and granulosa cell survival that complement DNA methylation and histone modifications. BPA triggers the expression of miR-146a-5p in murine Leydig cells, which directly targets Mta3 and suppresses the expression of steroidogenic genes. Gain- and loss-of-function experiments indicate that forced expression of miR-146a-5p exacerbates BPA-induced steroidogenic failure, while forced expression of MTA3 restores output, thereby establishing a causal miRNA node in BPA-stressed testicular steroidogenesis [75]. Seminal-plasma BPA concentrations are converged with human data: small-RNA sequencing (15 miRNAs that are associated with embryogenesis pathways) reveals that BPA-related effects on the sperm miRNA milieu involve remodeling of the miRNA milieu focused on fertilization and early development. BPA disrupts the miR-regulated apoptotic control in granulosa cells. Experimental studies involving miR-21 knockdown and perturbation in bovine granulosa cells reveal that miR-21 is a crucial anti-apoptotic regulator. Additionally, BPA reduces the pro-apoptotic target PDCD4, along with further upstream effects on STAT3 and VMP1 that activate miR-21, leading to the deregulation of the PDCD4/PTEN axis and inducing apoptosis. Complementary studies indicate that BPA-induced apoptosis in granulosa cells can still occur [76]. Experimental studies involving miR-21 knockdown and perturbation in bovine granulosa cells reveal that miR-21 is a crucial anti-apoptotic regulator [76]. Additionally, BPA reduces the pro-apoptotic target PDCD4, along with further upstream effects on STAT3 and VMP1 that activate miR-21, leading to the deregulation of the PDCD4/PTEN axis and inducing apoptosis [77]. Complementary work shows BPA-triggered GC apoptosis can proceed even when miR-21 protection is bypassed, underscoring BPA's multi-pathway toxicity [77]. In addition to miRNAs, BPA perturbs ovarian lncRNA circuits that interact with steroidogenesis: in pubertal mice, BPA disrupts ERα-regulated lncRNA Fhad1os2–RUNX3 interactions in granulosa cells, disrupting estrogen synthesis and accelerating ovarian maturation; in parallel, BPA reshapes mRNA/lncRNA m^6A methylation landscapes in granulosa cells and engages m^6A-dependent autophagy programs in Leydig cells, extending BPA's epigenetic reach to the ncRNA epitranscriptome [78]. Collectively, these empirical findings spanning across

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rodent testis, bovine/human granulosa systems, and human sperm fit into a paradigm in which BPA-induced ncRNA signatures (miR-146a-5p in Leydig cells; miR-21/PDCD4 signatures in granulosa cells; more general sperm-wide miRNA signatures) combine with methylation and histone-level imbalances to further propagate defects in steroidogenesis, gametogenic quality, and implantation [75].

Transgenerational and developmental impacts

With evidence pointing to BPA causing epigenetic modifications passed on by subsequent generations [52], research conducted by Bansal *et al.* [79] has proven that exposure to BPA has transgenerational and developmental effects. This, therefore, poses possible hazards to future generations.

Evidence of BPA-induced epigenetic inheritance in male rodents

There is emerging research on rodent studies that suggests that information is imprinted in the paternal germline by BPA, thereby affecting descendants that were not exposed directly. BPA reduces fertility and alters sperm functionality in offspring when adult F0 males are treated and then mated with unexposed females. Additionally, molecular changes in sperm persist into the F1 generation, even after exposure has ceased, meeting the criteria for intergenerational (F1) effects and, in some cases, transgenerational (F2–F3) effects, where F3 is not continuously exposed [80].

A groundbreaking mouse experiment exposing adult males to BPA has reported dose-related defects in sperm functionality and spermatogenesis in F1 and F2, with certain endpoints being observed in F3. More importantly, the exposed lines had sperm methylomes bearing differentially methylated regions (DMRs), which tracked the reproductive phenotypes across generations, supporting a germline mechanism rather than transient systemic toxicity [80].

BPA also disrupts chromatin packaging in testes and sperm, a likely vehicle for hereditary information. In male mice exposed for 6 weeks, BPA disrupted the histone-to-protamine transition, altered transition proteins and PRM1/PRM2 balance, and reduced fertility; these changes point to defective chromatin condensation at spermiogenesis, a stage at which retained histones and their post-translational modifications can be delivered to the zygote [71]. To complement this, an independent experiment demonstrated that hyper-acetylated histones (H3K9ac and H3K27ac) were observed in the sperm of BPA-exposed adult zebrafish males, and hyper-acetylation was also evident in the early embryos that were fathered by those males, indicating direct evidence that BPA-altered sperm chromatin states are transmitted at fertilization [16].

Although fewer studies have mapped BPA-specific sperm small RNAs, contemporary frameworks highlight sperm-borne small RNAs (miRNAs, tRNA fragments) as key paternal vectors capable of reprogramming early embryonic gene expression; environmental stressors remodel these small RNAs in mammals, and recent syntheses directly place endocrine disruptors within this inheritance logic. Combined with DNA methylation and histone modifications, altered sperm RNAs provide a multilayer convergent model for BPA's heritable effects [81].

The paradigms of gestational BPA exposure (dams treated during pregnancy) contribute convergent evidence relevant to the male line: male offspring exhibit defects in reproductive characteristics with generation-specific sperm methylation and proteomic remodeling throughout F1–F3, which aligns with the hypothesis that BPA is capable of leaving marks that can be detectable in male germ cells of the unexposed generations. While these designs involve maternal exposure, the persistence of male-line sperm epimutations strengthens the inference that BPA can leave durable germline marks compatible with epigenetic inheritance [82].

Across studies, effect magnitude varies with dose, exposure window, and route (gavage vs diet), but several themes are consistent: (i) paternal BPA exposure impairs male reproductive phenotypes in descendants; (ii) sperm carries corresponding molecular alterations such as DMRs, abnormal histone retention/acetylation, and (by inference from broader paternal-exposure literature) remodeled small RNAs; and (iii) some endpoints persist into F2–F3 without continued exposure, fulfilling a conservative definition of transgenerational inheritance in rodents [70, 80, 83]. Recent state-of-the-field reviews synthesize these lines of evidence and emphasize integrating sperm DNA methylation, chromatin marks, and small RNAs in the same animals across generations to resolve mechanism and causality [57, 80, 84].

Epigenetic biomarkers and translational implications

Recent research has linked BPA exposure to certain epigenetic modifications that might act as biomarkers for health outcomes. Epigenetic biomarkers like DNA methylation and histone modification provide insights into how environmental exposures can influence gene expression without altering the DNA sequence [85]. Early diagnosis and prognosis of metabolic illnesses depend much on these markers [56]. Table 1 lists several important biochemical and epigenetic biomarkers associated with BPA exposure and reproductive dysfunction.

One of the critical results is the identification of specific epigenetic biomarkers that can serve as health risk indicators associated with exposure to BPA [89]. Furthermore, the inclusion of epigenetic biomarkers into environmental health assessments would help to clarify the chemical hazards associated with BPA [90]. These biomarkers can help to clarify individual vulnerability to BPA and enable more approaches to prevention and intervention. For example, lifestyle changes such as dietary adjustments, weight control, and an increase in physical activity can mitigate the effects of the BPA on health, in particular among susceptible populations [91]. On the other hand, Table 2 outlines epigenetic pathways and molecular mechanisms implicated in BPA-induced reproductive toxicity, emphasizing how alterations in chromatin structure, DNA methylation machinery, and microRNA regulation contribute to disrupted reproductive function and increased fertility risk.

Future directions

The growing concern surrounding the implications for the health of exposure to BPA has led to an increased concentration on understanding its absorption mechanisms, its health effects, and potential alternatives to reduce plastic exposure. Major knowledge gaps still exist today, requiring further study to help define public health policies and regulatory procedures. One of the main issues is the mechanism by which BPA is absorbed into the human body. Studies show that the gastrointestinal tract is the major route through which BPA may be absorbed; however, oral, dermal, and inhalation routes can also be essential [106]. The details of these absorption mechanisms, especially

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Table 1 Overview of epigenetic and biochemical biomarkers linked to BPA exposure and male reproductive outcomes.

Biomarker (assay)	Model/tissue	Exposure or BPA measure	Direction of change	Reproductive readout	References
Histone acetylation (H3K9ac, H3K27ac; also H4K12ac) in sperm and embryos	Zebrafish (paternal exposure; sperm and F1 embryos)	Adult males exposed during spermatogenesis (100–2000 μg/l)	Increased H3K9ac/H3K27ac in sperm and embryos (dose/window-dependent)	Reduced embryo survival; increased apoptosis/DNA damage in embryos	[16, 86]
Histone-to-protamine transition; testis H3 marks; sperm DNA methylation	Mouse testis + sperm	In vivo BPA (adult; multiple doses)	Abnormal histone replacement; increased testis H3 marks; changes in sperm DNA methylation	Decrease in fertility; spermiogenesis defects	[71]
Sperm DNA methylation (DMRs) with multigenerational outcomes	Mouse sperm (paternal design)	F0 males dosed 5–50 mg/kg/day BPA	DMRs in sperm across generations	Multigenerational decrease in fertility; partial transgenerational effects	[80]
Seminal-plasma miRNAs (increase in let-7a/7c, decrease in miR-518f) vs measured BPA	Human seminal plasma	Clinical cohort with BPA quantified in seminal plasma	Increase in let-7a/7c, and decrease in miR-518f with BPA; BPA correlated negatively with semen quality	Lower sperm concentration and morphology with higher BPA	[87]
Sperm miRNA profile (small-RNA-seq) vs measured BPA	Human sperm	102 men; BPA in seminal plasma; small-RNA-seq in subset	15 sperm miRNAs correlated with BPA	Target enrichment for embryogenesis/early development	[88]

Table 2 Summary of epigenetic mechanisms and pathways underlying BPA-associated reproductive toxicity.[a]

Category	Drug/compound	Mechanism of action	Potential in infertility treatment	References
DNA methylation modifiers	5-Azacytidine (5-AzaC)	DNA methyltransferase (DNMT) inhibitor	Restores normal DNA methylation in sperm and oocytes, improving fertility outcomes	[92]
	Decitabine (DAC)	DNMT inhibitor	Reverses hypermethylation of reproductive genes (e.g. Hoxa10, Igf2, Esr1)	[92]
	Folic acid and choline	Methyl donors	Prevents abnormal DNA methylation, protecting against BPA-induced epigenetic changes	[92]
Histone modification modulators	Trichostatin A (TSA)	Histone deacetylase (HDAC) inhibitor	Restores normal histone acetylation, improving sperm and oocyte development	[93–95]
	Valproic acid (VPA)	HDAC inhibitor	Enhances chromatin accessibility, improving embryo implantation	[96]
	Curcumin	Histone acetylation modulator	Restores histone modifications and reduces oxidative stress in reproductive tissues	[97, 98]
microRNA (miRNA) modulators	Antagomirs (miRNA inhibitors)	Suppress specific miRNAs	Downregulates BPA-induced overexpression of infertility-related miRNAs (miR-29, miR-146a)	[75, 84, 99]
	miRNA mimics	Restore normal miRNA function	Corrects BPA-induced downregulation of fertility-related miRNAs (miR-141, miR-10b)	[100, 101]
Natural epigenetic modulators	Resveratrol	DNMT and HDAC inhibitor	Improves sperm quality and ovarian function	[102, 103]
	Genistein (phytoestrogen)	DNA methylation modulator	Restores normal estrogenic signaling in BPA-exposed females	[104]
	Naringenin	Epigenetic antioxidant	Reduces oxidative stress and DNA methylation errors in reproductive tissues	[105]

[a]This table gives an overview of pharmacological and natural compounds targeting DNA methylation, histone modifications, and microRNA dysregulation with potential therapeutic relevance.

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with relation to the way BPA interacts with cellular and molecular structures in the human body, remain poorly known. For example, studies exploring the biodistribution and metabolism of BPA are limited, leaving critical gaps in our understanding of its initial absorption and subsequent modifications after exposure [107]. Enhanced understanding, including human epidemiological research and advanced techniques for investigating BPA's epigenetic impacts, might help to clarify the ways to reduce future BPA exposure and hence lower related health concerns.

Advanced techniques for studying BPA's epigenetic effects

Recent advances in molecular and computational biology have enabled more precise characterization of the epigenetic mechanisms underlying BPA-induced reproductive toxicity. Next-generation sequencing (NGS)-based epigenomic profiling techniques, such as whole-genome bisulfite sequencing (WGBS) and reduced representation bisulfite sequencing (RRBS), allow high-resolution mapping of DNA methylation changes across the genome, facilitating the detection of low-dose and non-monotonic BPA effects at single-base resolution [108]. These approaches have proven particularly valuable for identifying exposure-sensitive loci in germ cells and reproductive tissues. To interrogate chromatin-level regulation, chromatin immunoprecipitation followed by sequencing (ChIP-seq) is increasingly used to map BPA-induced alterations in histone modifications and transcription factor binding [109]. Complementary chromatin accessibility assays, including ATAC-seq, provide insights into BPA-driven changes in chromatin architecture and gene regulatory potential, enabling integration of epigenetic marks with transcriptional activity. Advances in single-cell epigenomics, such as single-cell RNA sequencing (scRNA-seq) combined with single-cell DNA methylation and chromatin accessibility profiling, now permit the investigation of cell-type-specific epigenetic responses to BPA exposure [110]. These techniques are particularly relevant for reproductive tissues, which are highly heterogeneous and sensitive to developmental timing. In addition, high-throughput non-coding RNA profiling, including small RNA sequencing and long non-coding RNA (lncRNA) analyses, has enhanced understanding of BPA-induced post-transcriptional regulatory disruption. These approaches allow systematic identification of microRNA networks and regulatory RNAs associated with altered spermatogenesis, oocyte maturation, and implantation processes. Finally, integrative multi-omics and systems biology approaches, combining epigenomic, transcriptomic, and metabolomic datasets with bioinformatic modeling, are increasingly applied to elucidate the complex regulatory networks affected by BPA. Such approaches improve mechanistic inference, support biomarker discovery, and strengthen exposure-risk assessment by capturing coordinated molecular responses rather than isolated endpoints.

Conclusion

Through DNA methylation, histone changes, and non-coding RNA control, the study emphasizes the important epigenetic impacts of BPA on fertility, therefore disturbing male reproductive health. BPA exposure has been linked to reduced sperm quality, impaired spermatogenesis/spermiogenesis (including chromatin remodeling), and endocrine imbalance, which cause infertility and reproductive disorders. Additionally, BPA-induced epigenetic changes are heritable, affecting not only exposed individuals but also future generations, raising concerns about its long-term impact on population health. The discovery of epigenetic biomarkers, together with studies on natural compounds and epigenetic drugs, gives hope to tackle BPA-related reproductive toxicity. However, the widespread presence of BPA in consumer products underscores the urgent need for strategies to minimize human exposure and prevent adverse reproductive outcomes. The strong effects of BPA exposure on fertility, together with public health, warrant enhanced regulatory measures for minimizing its usage primarily within food packaging, along with plastics and everyday consumer products. Public safety needs policymakers to enact robust BPA-free regulations supported by educational initiatives that will warn individuals about the harmful effects of endocrine disruptors. Furthermore, complete research about BPA's mechanisms through epigenetics needs to advance so that we can understand both health impacts and any available intervention methods. Large-scale human epidemiological studies and advanced molecular research should be prioritized to assess the full scope of BPA's impact and inform effective regulatory policies. Addressing these challenges is essential to safeguarding reproductive health and ensuring the well-being of future generations.

Author contributions

Okon Michael Ben (Conceptualization [lead], Data curation [equal], Investigation [equal], Project administration [equal], Validation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Olorunnisola Sinbad Olubukola (Formal analysis [equal], Methodology [equal], Project administration [equal], Validation [equal]), Ifie Josiah Eseoghene (Data curation [equal], Validation [equal], Writing—review & editing [equal]), Ugwu Okechukwu Paul-Chima (Data curation [equal], Formal analysis [equal], Validation [equal]), Alum Esther Ugo (Investigation [equal], Methodology [equal], Writing—review & editing [equal]), Mounmbegna Philippe (Conceptualization [supporting], Data curation [equal], Project administration [equal], Validation [equal]), and Aja Patrick Maduabuchi (Conceptualization [equal], Formal analysis [equal], Project administration [equal], Supervision [equal], Validation [equal])

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Data availability

This article is a viewpoint review of published literature. Consequently, there is no new data relevant to this article.

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