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Bisphenol A (BPA) as a Contributing Factor to Decreased Fertility in Humans : a Review of the Latest Evidence

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ABSTRACT

Introduction

Bisphenol A (BPA) is a synthetic compound widely used in producing consumer plastics like polycarbonate and epoxy resins. Recognized as an endocrine-disrupting chemical (EDC), BPA has been linked to various adverse health effects, including impacts on human fertility. Exposure to BPA has been associated with infertility risks not only through direct mechanisms but also by causing transgenerational effects, potentially compromising fertility in future generations.

Aim of the Study

This review aims to summarize recent evidence identifying BPA as an environmental contributor to infertility in humans. We explore mechanisms through which BPA disrupts the endocrine system, focusing on its effects on the hypothalamic-pituitary-gonadal (HPG) axis, oogenesis, spermatogenesis, and embryo implantation. Additionally, we discuss research on BPA's potential long-term reproductive risks across generations and assess strategies for reducing BPA exposure.

Materials and Methods

We reviewed epidemiological, clinical, and experimental studies published over the past decade, with a search conducted in PubMed and Google Scholar. Both human and animal model studies were considered to provide a comprehensive perspective. Search terms

included "Bisphenol A," "fertility," "endocrine disruptors," "spermatogenesis," "oogenesis," and "transgenerational effects."

Conclusions

BPA, an EDC ubiquitous in the environment, is shown to disrupt male and female fertility. Expanding research and regulatory measures are needed to reduce the reproductive health risks posed by BPA exposure to protect current and future generations.

Key words: Bisphenol A, endocrine disruptors, reproductive health, environmental exposure, estrogen receptors

Introduction

Bisphenol A (BPA) is a synthetic compound popularly used in the production of plastics such as polycarbonate plastics and epoxy reisins. These are widely used in manufacturing many consumer products, particularly food and beverage containers, but also medical tubing, reciepts, and toys. Its annual production in 2023 has been estimated to 6.4 million tons and is anticipated to grow due to growing industrial demands. (1) BPA has been recognized as an endocrine-disrupting chemical (EDC), meaning it interferes with the endocrine system by mimicking, blocking or altering levels of natural hormones, disrupting hormonal balance and signaling. (2) Due to health concerns its use has been restricted in many countries, predominantly in baby bottles and food-contact materials. (3) Despite the ban of BPA use in many products, manufacturers are oftentimes using substitutes like Bisphenol AF, Bisphenol S, and Bisphenol F to abide restrictions, which carry similar risks and avoid many health regulations regarding production of everyday use products. (4) (Table 1) It is crucial to emphasize that BPA remains a legal compound of numerous everyday-use products, including textiles and clothing. (5) As a result, BPA has become a chemical which is so ubiquitous in the environment that it is being found even on fresh produce, since crops are irrigated with water polluted with BPA. (6) This proves the fact that despite regulations, BPA remains prevalent in numerous consumer goods, posing ongoing risks to human health, especially among vulnerable populations. (7) While the prevalence of fertility issues increases worldwide, new data points out BPA not only as a risk factor post direct exposure, but also

as a chemical capable of having transgenerational effects, influencing fertility in future generations. (8) There is also data supporting the fact, that maternal-fetal transfer of BPA is possible. (9) This makes understanding the way BPA impacts reproductive health in both men and women crucial.

Environmental Leaching and Bioaccumulation of BPA: Pathways and Health Implications

The leaching of BPA into the environment can be caused by heat, pH fluctuations and the presence of sodium chloride and vegetable oils. This phenomenon occurs during manufacturing, use and disposal of plastic products. (10) The spread of BPA into the environment increases human exposure, primarily through ingestion of contaminated food and water, as well as inhalation of dust and dermal absorption. (11) Post ingestion, BPA conjugates with glucuronic acid in the liver, which enhances its stability and promotes its accumulation in various body tissues, especially the adipose tissue. (12) BPA has been linked to an increased risk of obesity by promoting lipid accumulation and cytokine release in the adipose tissue. Those processes contribute to obesity, which itself is associated with reduced fertility. (13) BPA is widely used in the textile industry, with textiles made from recycled polyester often containing higher concentrations of this chemical. This is an important contributing factor to human exposure through skin contact. (14)

Mechanisms of BPA's Endocrine Disruption.

BPA affects the human reproductive system mainly due to it's structural similarities to natural hormones, particularly estrogens, allowing it to interfere with normal hormonal signaling. (15) BPA's chemical structure enables it to bind to and activate estrogen receptors (ERα and ERβ), modulating estrogen-responsive gene expression. This results in mimicking or antagonizing natural estrogen effects, depending on the receptor site and concentration, altering reproductive and developmental processes. (16) BPA can also bind with androgen and progesterone receptors. (17) This contributes to its broad interference with endocrine function, disrupting both male and female reproductive pathways. Additionally, BPA can interact with thyroid hormone receptors and glucocorticoid receptors. (18) These disruptions extend to thyroid dysfunction and altered stress responses, which are associated with metabolic disorders that may indirectly impact fertility. (19) BPA's interaction with androgen receptors is a critical factor in its effect on reproductive health. This interference results in reduced

testosterone levels, which is detrimental to spermatogenesis and other testosterone-dependent reproductive functions in males, while also causing hormonal imbalances in females. (20) Additionally, BPA affects the hypothalamic-pituitary-gonadal (HPG) axis. This is a critical regulatory system in reproductive health, and impairing the release and regulation of gonadotropins, specifically follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion, impacts folliculogenesis in females and spermatogenesis in males, further contributing to infertility risks. (21,22) Emerging research also points to the correlation between BPA exposure and obesity, where BPA promotes adipocyte differentiation and cytokine release, increasing lipid accumulation within adipose tissue. Obesity itself is a known risk factor for infertility, suggesting a complex correlation where BPA exposure may indirectly intensify infertility risks through metabolic disruptions. (Table 1) This connection highlights the complex and far-reaching consequences of BPA exposure, emphasizing the importance of understanding and reducing its impact on both direct endocrine disruption and related health issues that influence fertility. (23)

Impact of BPA on Male Fertility

Numerous studies indicate that BPA exposure leads to significant reductions in sperm concentration, motility, and normal morphology. A study involving 514 men from an infertility clinic found that higher urinary BPA levels were associated with a 23% decrease in sperm concentration and a 10% reduction in sperm motility. (24) BPA is also linked to increased DNA fragmentation in sperm cells, which compromises the sperm's ability to fertilize the egg. (25) Additionally, BPA disrupts Leydig cells in the testes, leading to decreased testosterone production, impairing spermatogenesis – in an animal study male rats exposed to BPA exhibited increased proliferation in testicular cells comparing to a control group. Within ten days of exposure, testosterone levels were significantly reduced, likely due to damage of Leydig cells. (26) Experimental studies on rodents have demonstrated that chronic BPA exposure decreases the number of Sertoli cells, which are essential for nourishing developing spermatozoa. (27) Epidemiological data supports the notion that BPA exposure is correlated with poor semen quality. A study on Chinese factory workers found that those exposed to BPA had a 35% reduction in total sperm count and a 30% reduction in sperm motility compared to non-exposed workers. (28) These findings are consistent across multiple geographical regions, underscoring the global relevance of BPA exposure to male infertility. (29) Another study involving male rats exposed to various concentrations of BPA

and BPA-related compounds for 28 days has also proven, that BPA-exposure causes oxidative stress, impairing fertility. The exposure led to elevated oxidative stress markers and a notable activation of antioxidant enzymes, along with a significant drop in testosterone levels, underscoring the damaging impact on male reproductive cells. (30) (Table 1)

Impact of BPA on Female Fertility

BPA has been shown to disrupt ovarian function and the production of female gametes. Studies in animals indicate that BPA exposure alters folliculogenesis, leading to fewer viable oocytes. (31) In human studies, BPA has been implicated in ovarian dysfunction, reducing the number of antral follicles, and impairing ovulatory cycles. (32) Additionally, BPA mimics estrogen and disrupts the HPG axis, which leads to hormonal imbalances affecting the menstrual cycle. (33) A study involving 200 women undergoing IVF treatment found that higher serum BPA levels were associated with irregular menstrual cycles, lower estradiol levels, and reduced ovarian response during stimulation. (34) BPA exposure also negatively affects the uterine environment, impacting endometrial receptivity and embryo implantation. (35) In vitro studies suggest that BPA disrupts progesterone receptor signaling, which is crucial for preparing the endometrium for implantation. Additionally, higher BPA levels in women undergoing assisted reproductive technologies (ART) have been associated with reduced implantation success rates and a lower likelihood of clinical pregnancy. (36) Polycystic Ovary Syndrome (PCOS) has become increasingly prevalent, with recent animal studies indicating a possible link between BPA exposure and an elevated risk for the condition. (37) It has been proven that neonatal exposure to BPA in female rats resulted in higher testosterone and estradiol levels and disrupted secretion of gonadotropin – releasing hormone (GnRH) in adulthood. (38) It is suggested that BPA exposure during critical phases of brain development may alter the hypothalamic-pituitary-gonadal axis, a disruption strongly associated with PCOS pathogenesis. (Table 1) While these findings provide insight into how BPA might contribute to PCOS, further research is needed to establish this effect in humans and to determinate specific exposure levels that may be toxic. (39) Similarly, endometriosis, another condition linked to infertility, has been associated with higher BPA levels in affected individuals. (40)

Transgenerational Effects of BPA on Fertility

Emerging evidence suggests that BPA exposure may have transgenerational effects, meaning that its impact on fertility may be passed down to future generations. Research on animal suggests that maternal BPA exposure results in lasting changes in reproductive health across generations, including reduced fertility and altered sperm quality in offspring. (41) In a study, juvenile male rats, whose mothers were exposed to BPA exhibited decreased sperm production, abnormal sperm morphology and compromised cellular structure, all of which contributed to reduced sperm motility. (42) These findings raise concerns about the long-term consequences of widespread BPA exposure on human fertility. (Table 1)

Table 1. (24, 27, 33, 35)

Health Impact	**Evidence type**	**Key findings**
Endocrine Disruption	Animal and Human Studies	Mimics estrogen, interferes with hormone signaling, impairs reproductive functions
Male Reproductive Health	Animal and Epidemiological Studies	Decreased sperm quality, testosterone production, and testicular function
Female Reproductive Health	Animal and Human Studies	Alters folliculogenesis, irregular menstrual cycles, impaired ovarian response
Obesity and Metabolic Health	Animal and Epidemiological Studies	Promotes lipid accumulation in adipose tissue, associated with obesity, further impacting fertility
Transgenerational Effects	Animal Studies	Maternal exposure impairs offspring fertility, including sperm quality and motility
Developmental Toxicity	Animal Studies	Impaired fetal development, potential impacts on neurodevelopment and pregnancy outcomes

Recent Regulatory and Public Health Responses on BPA and BPA-substitutes

In response to growing concerns over BPA's health effects, regulatory bodies such as the European Union and Canada have taken significant steps to limit BPA exposure. (5) Despite this fact, many consumer goods still contain BPA or its substitutes, raising questions about the effectiveness of current regulations. (Table 2) Many studies highlight the comparable, if not heightened, endocrine-disrupting potential of BPA alternatives, like Bisphenol S (BPS) and Bisphenol F (BPF) particularly in terms of reproductive and developmental impacts. (6) Systematic reviews and cohort studies indicate that BPS and BPF can also disrupt endocrine functions, impact reproductive health, and cross the placental barrier, with possible links to adverse pregnancy outcomes, neurodevelopmental delays, and metabolic disorders. (7) Despite the "BPA-free" labeling, these substitutes act as endocrine disruptors by mimicking estrogen and androgens, suggesting comparable risks to human health. Regulatory agencies have not yet fully addressed these analogs, which are increasingly found in everyday products, continuing consumer exposure without adequate warnings. (8) Given the complexity of BPA's effects, there is a need for comprehensive regulations that address both the chemical itself and its alternatives. (9)

Table 2. Global BPA regulation and Concerns Regarding Substitutes (6, 43-50)

Region/Country	BPA Regulations	Regulations on substitutes (BPS, BPF)	Key Notes
European Union	BPA is completely banned in baby bottles and materials that come into contact with infant food	No specific regulations on substitutes	strong BPA regulations, but substitutes like BPS and BPF remain largely unregulated, posing potential risks
Canada	BPA is prohibited in	No comprehensive	Similar approach to

	baby bottles and some food-contact materials	laws addressing BPA substitutes	the EU with BPA regulations, but substitutes are not fully regulated
United States	The FDA restricts BPA use in infant products, but considers it safe at low levels for adults	No specific bans on substitutes	Stance is considered lenient, substitutes are used without thorough scrutiny of potential risks
Japan	BPA is banned in baby bottles and certain food packaging	No regulations specifically targeting BPA substitutes	Focus on protecting infants and vulnerable populations, but there's no substantial control over BPA alternatives
China	BPA is not banned in consumer goods; awareness is rising	The use of BPA substitutes is growing without sufficient regulation	Approach to BPA is less stringent, and substitutes are being used without clear safety guidelines
Australia	BPA is banned in infant products and food-contact materials for babies	No specific regulations for substitutes like BPS and BPF	Limited regulation on substitutes, similar to other regions, allowing continued exposure to potential risks

Strategies for Mitigating BPA Exposure and Its Effects

Efforts to mitigate the adverse effects of BPA on fertility should focus on both reducing environmental exposure and exploring therapeutic interventions: Individuals can limit BPA exposure by avoiding plastic containers marked with recycling codes 3 and 7, using glass or

stainless steel for food storage, and minimizing the consumption of canned foods. (10) Since BPA induces oxidative stress in reproductive tissues, antioxidants such as vitamin C, vitamin E, and coenzyme Q10 have been proposed as potential therapies to mitigate BPA's damaging effects on sperm and oocyte quality. (11) Apart from individuals taking action, public health initiatives could further reduce BPA exposure. These might include mandatory BPA-free labeling on products, stricter regulations on plastic manufacturing, and public education campaigns to raise awareness about the potential risks of BPA substitutes like BPS and BPF. (12)

Conclusion

In conclusion, BPA is a ubiquitous synthetic compound commonly found in consumer products, with significant implications for reproductive health in animals and humans. As an endocrine disruptor, BPA interferes with hormonal pathways critical to both male and female fertility, impairing processes such as spermatogenesis, oogenesis, and hormone regulation. Evidence indicates that BPA reduces sperm quality and testosterone levels in men, whereas in women contributes to ovarian disfunction and impaired egg quality. Furthermore, BPA exposure is linked to reproductive disorders such as polycystic ovary syndrome and endometriosis. The compound’s estrogen-mimicking properties disrupt estrogen, androgen, and thyroid hormone pathways, leading to adverse reproductive outcomes, including infertility and developmental disorders. BPA’s pervasive presence in food packaging, textiles, and even products labeled "BPA-free" raises significant concerns, particularly as many BPA substitutes (like BPS and BPF) exhibit similar or even heightened endocrine-disrupting potential. The global rise in infertility underscores the urgent need for stricter regulatory measures to limit BPA and its substitutes across all consumer products, especially those with direct human contact. Additionally, the potential transgenerational effects of BPA exposure highlight the need for continued research to fully understand these risks and identify safer alternatives. Public health initiatives should prioritize raising awareness about BPA exposure risks and promote the adoption of safer materials. Addressing the full scope of BPA’s effects will require coordinated efforts in research, policy, and public education to mitigate its impact on human fertility and protect future generations.

generations.

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2. Data were obtained from
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