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BISPHENOL- A INDUCED OXIDATIVE STRESS AND ITS FERTILITY ASPECTS

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ABSTRACT: Bisphenol-A (BPA), 2,2-bis(4-hydroxyphenyl) propane is an emerging environmental toxicant with endocrine disrupting properties and toxic effects on living organisms. BPA is ubiquitously present in consumer products current in our daily lives. As it is released from consumer products and deposited in the environment, thus creating the potential for human exposure through oral, inhaled, and dermal routes. BPA exposure might be able to cause oxidative damage by disturbing the balance between reactive oxygen species (ROS) and the antioxidant defense system of eukaryotic cells, resulting in the development of oxidative stress-related diseases. From the available information, it can be inferred that a wide variety of BPA intake through any mode results into a generation of reactive oxygen species (ROS), altering the antioxidant balance of eukaryotic cells, induces mitochondrial dysfunction, and affects cell signaling pathways related to oxidative stress. BPA induced oxidative stress might be able to cause sperm damage, mitochondrial dysfunction, and impairment of the structure and function of spermatozoa resulting in male infertility. Here, a review of the current literature examining literature related to BPA exposure, induction of ROS or oxidative stress and concludes that it alters reproductive system functions through induced oxidative stress pathways and negatively affects the fertility of male and females.

INTRODUCTION: Endocrine disrupting chemicals (EDCs) are both synthetic and natural compounds known to mimic natural hormones. Global industrialization has increased population exposure to EDC's. EDC's has found to have detrimental health effects on the living organisms by negatively disrupting their endocrine system functions. They are attracting high attention during the past two decades.

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Endocrine disruptors because of their structural similarity, interfere with several processes of natural hormones as a result, they may found to be associated with different kinds of diseases [1].

Among potential EDCs, Bisphenol-A (BPA) [4, 4'-isopropylidenodi -phenol, 2, 2-bis (4- hydroxy phenylo-propane); CAS # 80 b5-7] is synthetic organic compound firstly synthesized by A.P. Dianin in 1891. BPA is an anthropogenic compound mainly used as a precursor in the production of consumer products, including polymer synthesis (polycarbonate plastics and epoxy resins) thermal paper and non-polymer additives [2]. Now it is one of the most used and produced synthetic compound all over the world. Every year, more than 8 billion lbs (1 lb= about

0.45 kg) of BPA is produced worldwide but strongest growth in production of BPA is seen in Asia [3]. Predominant BPA product, polycarbonate used in the manufacture of food containers and epoxy resins are using for coating in, food and beverage cans [4].

BPA is a solid matter, insoluble in water but well soluble in alcohols, ethers, and fats. The molecular weight of BPA is 228.28 g cm^{-3}. Melting temperature of BPA is 156 °C; boiling temperature is 220 °C and the combustion temperature is 79.4 °C. BPA used in the production of safety helmets, sunglasses, road signs, baby bottles and dishes, food containers, lenses, infant incubators, fridges, hair dryers, CD and DVDs, cell phones, and computers; due to its properties of thermo-resistance and transparency. Epoxy resin containing BPA also used as protective films for automotive and marine applications [5].

In recent years BPA is a subject of concern because of its harmfulness. It is found to be present in different animate matters such as urine, human milk, and blood. The United State Environmental Protection Agency (USEPA) provided much information that about 400,000 kilograms of BPA are leached into our ecosystem per year [6]. A study designed by Center for Disease Control and Prevention (CDC) confirmed a detectable concentration of 92.6% of BPA in ranging from 0.4 to 149 ng/mL and an average of 2.6 ng/Ml in urine of 2517 Americans (≥6 years of age) from the year 2003-2004 National Health and Nutrition Examination Survey (NHANES) [7]. Recently, a study on BPA correlates relationships between urinary BPA concentrations and semen quality parameters and reproductive hormone levels were examined and found that BPA was detectable in 95.3% of the urinary samples [8]. Studies also confirmed that during the development of embryo there is a high risk of vulnerability to BPA exposure and it has been found in eight weeks human embryos after fertilization [9].

BPA is commonly present in different food-related products that are commercially used, such as baby bottles, metal food cans, and food contact paper. BPA was banned in the production of baby bottles in the European Union in 2011, due to report, adverse effects on health. Primarily food is thought to be a predominant source of exposure to BPA, because it migrates from food containers into water or food, at high temperatures and by repeated use [10]. Its maximum detectable concentration in canned based food is 842 ng/g. It is estimated that BPA exposure from food is 0.01-13 μg kg^{-1} BW day^{-1} and less than 4.2 μg kg^{-1} b.w day^{-1} for children and adults respectively [4, 7, 11, 12, 13, 14, 15]. BPA can also be released from epoxy resin lining leading to an increase of BPA levels in drinking water and has been found in drinking water at concentrations ranging from 0.014 to 0.317 μg/L and in water bottles at concentrations from 0.07 to 4.21 μg/L [16, 17]. BPA also reported being found in detectable level in amniotic fluid, umbilical cord, placenta and fetal serum [18].

Human exposure to BPA is low since BPA does not bioaccumulate in the body; chronic exposure of BPA is dependent on routine exposure from different sources. Many studies predict that BPA acts as an endocrine disrupting compound (EDC) even in low doses [19, 20, 21]. Low doses experiments on BPA predicts that it quickly metabolized into bisphenol A glucuronide (BPAG) or bisphenol A sulfate, (BPAS) and eliminated through urine in the relatively short period - virtually all administered BPA leaves the body within 48 h without any significant amount of retention in bodily tissues [22]. But studies demonstrated that free BPA also to be found circulating throughout the body [23, 24, 25, 26].

The presence of free BPA in maternal and fetal serum and breast milk may result in long-term exposure to BPA during the fetal and neonatal period that results long-term harmful effects on the fetus and neonate.

BPA is regarded as estrogenic EDC or xenoestrogen compound after its observed effects on different hormonal regulated processes. Xenoestrogens are compounds that may disturb several processes of endogenous estrogens, such as synthesis, transport, and activity of natural estrogen. BPA has structural similarity to the synthetic estrogen diethylstilbestrol (DES) and consequently has estrogenic activity but substantially weaker than DES and natural estrogen [27, 28]. BPA is capable of mimicking like endogenous estrogens and interacting with their receptors in a variety of fashions, and because of this, adverse

neuro-developmental, reproductive, cancerous, and metabolic outcomes have been reported in various studies [29, 30, 31]. Recently, studies reported that BPA believed to disturb bone metabolism. BPA exerts estrogen antagonistic effect on bone cells by binding to the non-classical ERγ receptor which reduces the differentiation and increases the apoptosis in the osteoblasts and osteoclasts [32].

Experimental and epidemiological studies confirmed that the estimated daily intake of BPA by humans ranges from < 1 to 5 μg/kg body weight (BW)/day [4, 9, 12, 33]. It is very difficult to precisely estimate whether these levels of BPA can cause endocrine disruptive or toxic effects in humans. However, several studies have reported adverse endocrine disruptive or toxic effects of BPA in animal models in the range of < 1 μg/kg b.w/day. The free form of BPA in biological samples is of concern because animal and human studies have identified adverse health effects, many of these reported effects on neurodevelopment, male and female reproductive systems alterations, metabolic diseases and oxidative stress [34, 35, 36].

The United States Environmental Protection Agency (EPA) has established, after toxicological testing studies, a reference dose of 50 μg/kg/day. The Canadian equivalent of this reference dose is known as, the tolerable dose intake (TDI), and was established at 25 μg/kg/day. The European Food Safety Authority (EFSA) has establish a TDI of 4 μg/kg/day [37]. After an analysis of different exposure sources to BPA, EFSA stated that at current levels of exposure below the tolerable daily intake (TDI), BPA does not constitute any threat to consumers [38]. These doses mentioned above are approximately 1000-fold lower than the lowest used dose at which effects were noted in preliminary animal testing, and are well above to most estimates of the daily day today routine human exposure [37].

Scientists provided much attention to find out the molecular mechanism by which BPA shows its susceptibility to a wide range of disorders, and there is numerous evidence suggests that BPA exposure causes induction of Reactive oxygen species (ROS) and contributes to the predisposition to a variety of toxicity [28, 38]. A plethora of evidence suggested that increased BPA exposure is associated with increased oxidative stress, which could be one of the possible mechanisms causing reproductive, hepatotoxicity and genetic toxicity [6, 38]. In a eukaryotic cell, reactive oxygen species (ROS) form as a result of normal physiological conditions in which molecular oxygen is reduced partially. ROS that is, superoxide anions ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2), peroxyl ($ROO^{\bullet}$), and hydroxyl ($OH^{\bullet}$) radicals, arise in many ways, as a product of the respiratory chain in mitochondria during aerobic respiration by enzymatic reactions. These highly reactive molecules including reactive oxygen species (ROS) and reactive nitrogen species (RNS) are most widely studied species and play essential roles in cell death or to acceleration in aging and age-related diseases [39].

A cells ability to keep balance in the pro-oxidant and antioxidant levels is essential for the normal cellular metabolism, cell survival, and cell proliferation [40, 41]. But as a result of the exposure to UV light, ionizing radiation, EDC (*e.g.*, BPA) or heavy metal ions, this balance is disrupted and leading to a predisposition to a wide range of diseases including accelerated aging, cardio-vascular problems, neuronal disorders, and the onset of cancer [6]. The health issues resulting from BPA exposure have been widely studied; however, the safety of BPA in consumer products is evaluated, and studies indicate that BPA is not only widely spread in the environment due to its wide uses, but also toxic even in low doses level. Several lines of evidence suggest that BPA-induced cytotoxicity caused by oxidative stress occurs in both cell culture studies and an animal model. Various doses and durations of BPA exposure through an imbalance of pro-oxidants/antioxidants in cultured cells and rodents observed increased oxidative stress in multiple tissues [42, 45].

Furthermore, Bindhumol *et al.*, demonstrated that BPA induced oxidative stress in the liver of rats by decreasing antioxidant enzymes and increasing hydrogen peroxide and lipid peroxidation and co-administration of antioxidant vitamin C reversed this BPA-induced oxidative stress [46]. In the body, BPA also processed enzymatically by cytochrome P450, and as similar to natural estrogen metabolism BPA converted into quinone form that is reactive to DNA that is lethal to the viability of eukaryotic cells [47]. BPA is structurally similar to estradiol and

thus interferes with steroid signaling with different possible outcomes on reproductive health depending on doses, life stage, mode, and timing of exposure. BPA exerts its epigenetic effects in both male and female reproductive system. In males, BPA affects spermatogenesis and sperm quality and possible trans-generational effects on the reproductive ability of the offspring. In females, BPA affects ovary, embryo and gamete development. It is now investigated that BPA induced oxidative stress as a result of an imbalance between oxidants and antioxidants in the semen can lead to sperm damage, mitochondrial dysfunction [48], impairments of the structure and function of spermatozoa eventually lead to male infertility [49, 50, 51]. In this review, we will address BPA-induced oxidative stress and its possible role in fertility problems in humans by animal studies.

Dose Level of BPA: Affecting the dose level of BPA is highly controversial. Both *in-vitro* and *in-vivo* data also has contradictory health effects of BPA and create problems for regulatory agencies in evaluating the adverse health effect of BPA [52]. A plethora of evidence indicates that adverse effects of BPA on health are varying with duration, doses, exposure route and sex difference [53]. A cut-off for lowest observable adverse effect level (LOAEL) is 50 μg/kg b.w/day (*in-vivo*) and 50 ng/ml or 2.19×10^{-7}M (*in-vitro*) BPA [25, 29, 38, 54, 55].

The European Food Safety Authority (EFSA) defined the maximum tolerable daily intake (TDI) for BPA at 4 μg/kg of body weight per day, and FDA established the "no observed adverse effect level" (NOAEL) of 5 mg/kg of body weight per day [56, 57]. Based on these data Gassman, 2017 conclude in their review of 2017 that doses that are mostly used in experiments for animal studies range from 0.2 to 50 μg/kg/bw and in cell culture studies it ranges from 10^{-15} to 10^{-4} M [38]. Based on these doses used in experiments on BPA it is predicted that a variety of BPA doses induced oxidative stress studies says that these doses affect differently in inducing oxidative stress.

BPA Induced Oxidative Stress and Generation of ROS: From the last decade, oxidative stress has become the most interesting research topic of many scientists working in the field of biology because of its role in the initiation of various diseases. Oxidative stress describes the condition in which levels of oxygen and oxygen-derived free radicals overwhelm the natural antioxidant defenses naturally present in the cell and results in the damage of cellular components, inactivate essential metabolic enzymes and disrupt signal transduction pathways. Chemically, oxidative stress is associated with increased production of reactive oxidizing species (ROS) or a significant decrease in the effectiveness of antioxidant defenses [41, 58, 59].

The eukaryotic cell has a variety of natural antioxidant defenses, such as reduced glutathione, ascorbic acid, thioredoxins, and α-tocopherol, and enzymes, like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), play critical roles in redox reactions in the cell. Oxidative stress induces modifications of cellular proteins, thereby altering their functions and causes a state of susceptibility to a wide range of disorders. It causes damage to biomolecules including DNA, lipids and proteins and contributes to the pathology of many diseases including neuronal degeneration, autoimmune diseases, cardiovascular dysfunction, accelerated aging, the progression of cancer and conditions of the reproductive system including both male and female infertility [41, 60].

Reactive oxygen species (ROS) are cytotoxic agents causing oxidative damage by disrupting cell membrane and cause harm to DNA [43, 60]. Reactive oxygen species (ROS) are highly reactive oxidizing free radical agents represent a broad category of molecules including organic (hydroxyl ion, superoxide, NO, peroxyl, *etc*.) and non-radical (ozone, singlet oxygen, lipid peroxide, hydrogen peroxide) and oxygen derivatives. ROS play important roles in cell signaling, a process termed redox signaling. Thus, to maintain proper cellular homeostasis, a balance must be struck between reactive oxygen production and consumption. Free radical scavengers are involved in the defense mechanism of the organisms against the pathologies associated with the attack of free radicals. Free radicals in the body have a physiological as well as the pathological role, antioxidant molecule due to its free radical scavenging activity sometimes may act as disease promoter, by neutralizing the physiologically desired ROS molecules, and as disease mediator by removing the excessive levels of ROS species [41].

ROS also have been shown to play an important role in the defense mechanisms against pathological conditions, but the excessive generation of free oxygen radicals may damage tissues and also damage proteins, leading to the structural alteration and functional inactivation of many enzymes and receptor proteins involved in cell signaling. From some recent studies, it is now clear that this generation of ROS by BPA exposure depends on cell types and which hormone receptor is being found in that particular cell type. Koong and Watson work on androgen-dependent and -independent (LAPC-4 and PC3) prostate cell lines made it clear that the same dose shows a difference in generation of ROS in both cell lines [38, 61]. Some tests are available to measure the extent of oxidative stress, and these generally involve quantification of ROS levels, total antioxidant capacity (TAC) and levels of biomarkers associated with oxidative damage to biomolecules [45].

Environmentally persist low level of BPA exposure might be able to cause oxidative damage by disturbing the balance between reactive oxygen species and antioxidant defense system, resulting in the development of oxidative stress-related diseases **Table 1**. Experimental data have shown BPA can induce the generation of ROS through the enzymatic and non-enzymatic formation of radicals [61, 62]. Doses of BPA below the NOAEL induce mitochondrial dysfunction in the liver, and this is thought to be caused by an increase in oxidative stress and inflammation [63]. Cell death, DNA mutation, replication errors, and genomic instability can occur if the oxidative DNA damage is not repaired before DNA replication [64, 65]. Recently, it has been reported that BPA exposure significantly induced DNA damage in zebrafish, with a significant increase in ROS production [66].

BPA exposure to adult male and female rats below the NOAEL dose (5.0 mg) and even at 10 mg, which is very close to environmental exposure, led to a significant increase in the chromosome breaks and fragments in bone marrow cells as well as DNA fragmentation in blood lymphocyte thereby showing genotoxic effects [67]. ROS thought to create stable base lesions and basic sites in genomic DNA. The base excision repair (BER) is the main repair system responsible for removal of modified bases [such as 8-oxo-guanine (8-oxoGua) and 2, 6-diamino -4 -hydroxy -5 -formamide-pyrimidine (FapyGua)] that formed upon oxidative stress [68, 69].

Several studies also suggest that BPA exposure causes an increase in oxidative stress biomarker, such as 8-OHdG, white blood cell count, and C-reactive protein, as well as malondialdehyde (MDA) [70]. Eid *et al.*, found that early life exposure to BPA significantly increased oxidative/nitrosative stress, decreased antioxidant enzyme activities, inducing DNA damage and severe chronic inflammation in the hepatic tissue of female rat offspring in a time-dependent manner [71]. Tiwari and Vanage, predicts in their study that both low and high doses (0.01 and 5.0 mg/kg/b.w) of BPA exposure generate excess of ROS by decreasing the levels of SOD, CAT, reduced GSH and increasing LPO in bone marrow cells, blood lymphocyte, and reproductive organs, thereby causing oxidative stress [72]. *In-vivo* and *in-vitro* studies of BPA observed the formation of BPA-DNA adducts after high dose exposure of BPA [73, 74].

About the effects of BPA on metabolism studies demonstrate exposure to low or high doses of BPA induces abnormal glucose metabolism and insulin resistance. Insulin resistance may be thought to be associated with induced by decreased ADP production and increased oxidative damage [75]. A study of Moghaddam *et al*., indicated that BPA dose-dependently increased the levels of blood glucose, lipid profile and MDA in the tested groups compared with the control group ($p \leq 0.001$) [76].

BPA injection increased the levels of MDA and decreased the levels of GSH and TAS, and also the activities of SOD and CAT in the pancreas of exposed mice compared with the control group ($P \leq 0.05$). Results suggest that BPA exposure might induce hyperglycemia and its complications in adult male mice by induction of oxidative stress.

Epidemiological, animal and *in-vitro* studies following BPA exposure data demonstrate that BPA promotes adipogenesis, lipid and glucose dysregulation and adipose tissue inflammation, thus contributing to the pathophysiology of obesity. Induction of oxidative stress correlated with 8-hydroxydeoxyguanosine (8-OHdG) or malondialdehyde (MDA) levels has been confirmed further by population studies [70, 77].

Recently an study of Lv Y *et al.*, observed that due to the high levels of BPA on thermal receipts and their wide applications in our daily life, some amount of BPA may be transferred to our skin that has serious health issues confirmed by urinary BPA, TCS and 8-hydroxy-2′-deoxyguanosine (8-OHdG) concentrations determined by High-Performance Liquid Chromatography / Tandem Spectrometer (LC/MS/MS) [78]. Moreover, they investigate the potential oxidative DNA damage from exposure to BPA and TCS, ninety-six urine samples of children (aged 3–6) and 57 dust samples were collected and concentrations of urinary BPA, TCS, and 8-hydroxy-2′-deoxyguanosine (8-OHdG, a biomarker of oxidative DNA damage) in urine were determined using a liquid chromatography tandem mass spectrometer. Results showed that both BPA exposures were associated with oxidative damage.

Additionally, Ferguson *et al.*, investigated an association between BPA exposure and oxidative stress and inflammation in 482 pregnant women by analyzing urine and plasma [79]. Results suggest that BPA and two biomarkers of oxidative stress (8-hydroxydeoxyguanosine and 8-isoprostane) were found in the urine of women. Besides this Inflammation markers, including C-reactive protein and cytokines were also measured in their plasma. Han and Hong in 2016 suggest effects of BPA exposure such as endocrinal disturbance, induction of oxidative stress and inflammation, epigenetic change, and links with other chronic diseases may highlight a possible association between BPA exposure, hypertension, and cardiovascular diseases [80]. It is reported that BPA has an adverse effect on the heart of rats which is mediated principally by the generation of ROS and reduction of antioxidant defenses of the heart aggravating a state of oxidative stress.

Study revealed that BPA administration induced a state of oxidative stress in the heart of rats as evident from the increase in MDA levels and decrease in catalase activity at the two tested doses (10 and 25 mg/kg) after 6 weeks and the decrease in GSH levels after the administration of the two doses of BPA at all tested time segments. Increased lipid peroxidation may indicate an increased oxygen free radical generation, and BPA induced ROS production significantly compromises mitochondrial function [81].

TABLE 1: INDUCTION OF OXIDATIVE STRESS BY BPA

S. no.	Model system	Dose (per-day)	Duration	Effects	Reference
1	Male Holtzman Rats	0.01, 5.0 mg/kg	6 days	Increased lipid peroxidation, decreased antioxidant enzyme activity	72
2	*Drosophila melanogaster*	0.1, 1.0, 2.5 and 5.0 µg/mL	4 h	Increased ROS, lipid peroxidation and depletion of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione-s-transferase (GST)	82
3	Bone mesenchymal stem cells	200 lM to 500	18 h	Increased lipid peroxidation, decreased antioxidant enzyme activity	83
4	Rats	150, 250, 500 mg/kg	14 days	Hepatotoxicity by increased lipid peroxidation	84
5	Mice	0.5, 2 mg/kg	28 days	Increased lipid peroxidation, decreased antioxidant enzyme activity	85
6	Rats	0, 2, 10, 50 mg/kg	30 days	Hepatotoxicity by increased lipid peroxidation	85
7	Sprague-dawley rats	200 mg/kg	10 days	Increased lipid peroxidation, decreased antioxidant enzyme activity and induce DNA damage	86
8	Rats (Wistar)	0.1, 1, 10, 50 mg/kg	28 days	Decresed antioxidant enzyme activity	45
9	Female mice (CD-1)	0.1, 1, 5, and 10 lg/ml	8 days	Increased ROS observed	87
10	Male mice (C57BL/6)	0.05 and 1.2 mg/kg	5 days	MDA increased at both doses, GPx decreased at both doses	63

BPA Effects on Reproduction Process and Fertility: In human populations, most of the studies point towards an association between exposure to EDCs and male and female reproductive system disorders, such as infertility, breast cancer, testicular cancer, poor sperm quality,

and function. In recent years the detrimental effects of BPA on reproductive function, following in experimental exposure, have been widely studied in laboratory animals such as rodents [88]. Humans are mainly exposed to BPA through food ingestion [89], and increasing evidence supports its association with impairment of reproductive function, as well as other health problems and diseases; such diseases include diabetes, obesity, cardiovascular diseases, and cancer [36, 90-95]. Epidemiological studies also report that BPA has a toxic effect on male and female reproductive organs at the environmentally relevant level of exposure [38]. Even at a low dose of BPA, it is supposed to disturb the semen production in men and oocyte production in women by the interrupting the synthesis of sex steroids [96]. But the effects of BPA on reproductive hormones and semen quality in different epidemiologic studies are inconsistent [97].

Association between BPA exposure and spermatogenesis is quite clear yet. BPA has been considered as a possible risk factor for fertility because it might induce testicular toxicity [98]. It is reported that a low dose of BPA impairs spermatogenesis by suppressing reproductive hormone production and promoting germ cell apoptosis in adult rats [27]. Additionally in this sense reported earlier that there is a reduction in the testosterone level after the exposure of BPA [99, 100]. BPA also reported to interrupts the process of formation and maturation of sperm [101]. The decreased sperm count at the lowest tested BPA group (25 µg/kg) is to some extent supported by other studies reporting decreased sperm count in rodents after low-dose developmental exposure to BPA [102, 103]. Salian *et al.*, performed a three-generation study to assess the effects of very low doses of BPA (1.2 or 2.4 µg/kg bw/day administered by gavage) in Holtzman rats (n = 8 litter per group/generation) [103]. Sperm count and motility were significantly reduced in the F1, F2 and F3 male offspring, with a dose-related reduction in sperm count.

Additionally, a recent study has shown that pre- and postnatal exposure of Sprague Dawley rats (n = 3) to 5 µg/kg b.w/day of BPA also decreased epididymal sperm count and motility at 70 days of age [104]. Other studies have not found significant effects of low-dose BPA on sperm count [105-108]. In 2015 Johnson *et al.*, in their experiment selected three doses of BPA (2.5, 25 and 2500 µg/kg bw/day) or a 0.5 µg/kg/day ethinyl estradiol and doses were given to Sprague Dawley dams by oral gavage on gestational days 6-21, whereas offspring were dosed directly from birth to weaning. These findings indicate that developmental exposure to BPA can disrupt aspects of spatial navigational learning and memory in a sex-dependent manner [109]. Study of Rahman *et al.*, investigated the effects of varying concentrations of BPA (0.0001, 0.01, 1, and 100 µM for 6 h) on sperm function, fertilization, embryonic development, and on selected fertility-related proteins in spermatozoa[110].

Results suggest that BPA at concentrations of 0.0001, 0.01, and 1 µM did not produce significant or partial toxic effects on spermatozoa; however, 100 µM BPA affected motility parameters, the acrosome reaction, fertilization, and early embryonic development, which are closely associated with down-regulation and phosphorylation of fertility-related proteins in spermatozoa. Other study demonstrated that BPA induces subacute toxicity in wistar rats and there was significant ($P \leq 0.05$) reduction in the epididymal sperm count in 200 mg/kg and 600 mg/kg dose group. Sperm motility percentage, dead count percentage, head, and tail abnormality percentage were found to be significantly ($P \leq 0.01$) increased in rats of BPA-treated groups as compared to rats of control groups.

About the effect of BPA on accessory reproductive organs, BPA also has been reported to affect the prostate gland. It is reported that developmental exposure to BPA has been associated with the increased susceptibility to the prostate cancer [111]. Additionally, Wu *et al.*, reported that at low dose BPA has an effect on the prostate in Sprage-Dawley rats by changing the estrogen to androgen ratio and also affect testosterone metabolism [112]. Experimental studies suggest that BPA's mechanism of action is related to life stage and that its effect on the female reproductive system may involve agonism with estrogen nuclear receptors as well as steroid biosynthesis inhibition [113]. It is already mentioned that BPA exposure is able to disturb the hormonal balance due to its endocrine disrupting effects at low doses, so it may also affect the reproductive process in women. Experimental

results of *in-vivo* and i*n-vitro* studies confirms BPA shows a significant effect on female reproduction. Earlier reported that BPA interrupts the process of meiosis and affect the development of oocyte [114]. Even at low doses, BPA is able to disturb the process of oocyte maturation [115]. Additionally, BPA exposure increased the formation of multi-oocyte follicles and caused an increase in some apoptotic oocyte [116, 117]. Another study of Zhang *et al.*, found that low dose BPA exposure causes an increase in ovarian weight, atretic follicles, and peri-nuclear oocytes [118]. Cultural oocyte experiments also suggest that BPA might disturb the process of the prophase stage of meiosis and survival of the oocytes [119]. Ganesan and Keating observed that after one-day exposure to BPA, DNA damage is also observed in rat ovaries. *In-vitro* studies also indicated the impairment of uterine cell proliferation after BPA exposure [120].

The epidemiological study confirms that BPA level was found higher in infertile females as compared to fertile, but results are often contradictory. Its effects on female reproductive organs depend upon exposure level, dose and duration, and model used in the study. Some results suggest that it has a toxic effect on female reproduction and affect female fertility by affecting reproductive organs. Studies using animal model provide evidence that BPA has effects on litter size of mice [121]. Other studies indicate at a dose of 50 mg/kg/day during gestation period BPA has no significant effect on litter size of mice [122]. BPA is in higher concentration in the blood plasma of infertile women and thought to be having hormone effect on fertility [123]. According to case studies concentration of BPA in the serum of women may be related to the onset of endometriosis, PCOS and pre-eclampsia and shows an association between BPA exposure and fertility outcomes [124-128]. Cohort studies also found as an association between urine BPA concentration and increased pre-term birth compared to full- term birth [129].

About the cohort study on male, Li *et al.* observed BPA concentration in urine of men and found significantly lower sperm count, sperm concentration, sperm vitality and sperm motility [130]. Another study of Li *et al.*, observed BPA in the urine of 427 men and evaluated the significant decrease of libido, erection problem and lower ejaculation intensity [90]. It was also observed that increased BPA concentration in urine is also found to be related to greater sperm DNA damage [50]. Viktu *et al.*, observed blood plasma and also found a correlation with BPA level in plasma and alteration in sperm parameters [131]. Recently reported that there is an interaction between BPA exposure and obesity on sperm count and sperm concentration as observed in mice confirming the toxic effect of BPA on male reproduction [132, 133].

BPA exposure induced oxidative stress, demonstrated by an increase in lipid peroxidation and a decrease in activity of various enzymatic and non-enzymatic antioxidants in bone marrow cells, blood lymphocytes, and testicular and epididymal tissues of male Holtzman rats illustrates one of the possible mechanisms causing reproductive and genetic toxicity [72]. The reproductive health effects resulting from BPA exposure due to its endocrine disrupting properties it is thought to have a pronounced effect on human reproduction even at low doses that are below the LOAEL. For example, BPA at its lower doses has been reported to induce complete degeneration of epididymal epithelium with reduction in the number of spermatozoa due to either a decrease in serum testosterone or dihydrotestosterone (DHT) or even as a result of reduction in 5α- reductase, an enzyme required to convert testosterone to DHT of male Wistar rats [88].

Studies to date have explored associations between maternal exposure to BPA in pregnancy and indicators of inflammation and oxidative stress with an increase in maternal biomarkers of oxidative stress, including indices of oxidative DNA and lipid damage [79]. About oxidative stress effects of BPA on reproductive organs, the literature shows an association between BPA exposure and its effects on reproduction. BPA at doses of 50 or 70 μm induces apoptosis by an excessive ROS generation and mitochondrial dysfunction in sertoli cells which are crucial for the development of sperm [66]. The oxidative stress caused by BPA exposure has been found to affect the fertility of rats in a study where different doses of BPA (0, 2, 10, 50 mg/kg/b.w) that induces oxidative stress in liver and epididymis of treated rats and found to affect the semen quality by decreasing sperm count and quality [51].

The study confirms that BPA exposure inhibits the reproductive function in the male rat and cause genotoxicity [134]. Histopathological findings in the testes showed necrosis of the germinal layer and spermatogonial cells in the seminiferous tubules. Thus, it appears that BPA affects the germ cells leading to impairment in the spermatogenesis and thus having its property as reproductive toxicant [135]. Hass *et al.*, reported that developmental exposure to 25 µg/kg b.w/day bisphenol A that is above the safe level described by the EFSA [136]. This exposure can cause adverse effects on fertility (decreased sperm count), neurodevelopment (masculinization of spatial learning in females) and lead to increased female body weight late in life.

Results suggest that highly exposed humans may not be sufficiently protected about endocrine disrupting effects of BPA. Spermatozoa with damaged DNA have the minimum potential of fertilizing an ovum, and the presence of high levels of DNA damage in human spermatozoa has been correlated with adverse clinical outcomes including infertility, recurrent pregnancy loss, genetic disorders, and childhood cancers. ROS generation causes DNA damage in spermatozoa that are generated by spermatozoa themselves and by leukocytes present in the seminal plasma. Study now confirmed that human exposure to BPA might be associated with reduced semen quality and increased sperm DNA damage [50].

CONCLUSION: From the available information it can be inferred that a wide variety of BPA intake through any mode results into a generation of ROS, altering the anti-oxidant balance, induces mitochondrial dysfunction, and affects a number of cell signaling pathways related to oxidative stress. Moreover, it also alters the reproductive system functions through induced oxidative stress pathways and negatively affects the fertility of mammals. BPA induced oxidative stress negatively affects fertility and probably adding to increasing infertility worldwide. Still, a more precise study of BPA intake, dose, duration, and model system to reveals that wide variety of BPA doses promote the generation of ROS and in form affect the normal reproductive system functions.

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