Overview of the Content of Bisphenol A in the Amniotic Fluid of Pregnant Women And Its Adverse Health Outcomes

Dardan Dreshaj [1], Flaka Pasha[2]

[1]Researcher, University of Prishtina "Hasan Prishtina", Kosovo, [2]Researcher, Department of Pharmacology and Toxicology and Clinical Pharmacology, University of Prishtina "Hasan Prishtina", Kosovo

Abstract

Background: This review represents a critical and constructive analysis of literature in the content of Bisphenol A in amniotic fluid of pregnant women and its adverse health outcomes. The review is generated through summary, classification, analysis and comparison of already existing material and researches on field.

Methods : Databases as Scopus, PubMed, Medline, Web of Science, Global Health, were used to extract data for the review. Search terms like "Bisphenol A", "pregnancy", "amniotic fluid", "endocrine disruptors" were used. Out of 200 research articles screened, 70 most relevant studies are included in this review.

Conclusions: This review highlights the correlation between Bisphenol A and its endocrine disrupting potential, impacting especially fragile categories as pregnant women and their fetuses through its toxicokinetic features and its metabolites. Thus, BPA distorts important physiological processes necessary for fetal development and disease progression later in life.

We can conclude that human exposure to BPA, as one of the leading environmental contaminants, represents a major global issue and its adverse health outcomes can be debilitating for human health. Further research on field considering BPA distribution, varying exposure rates, racial disparities, inter-species differences and EDCs cumulative effects, should be conducted. Finding safer alternatives for replacing BPA in market must remain a priority.

Keywords: *amniotic fluid; Bisphenol A, pregnancy; adverse health outcomes;*

Introduction

Bisphenol A (BPA), 2,2-bis(4-hydroxyphenyl) propane (CAS No. 80-05-7), is a synthetic chemical excessively produced worldwide.[1] BPA commercial production began in the United States in 1957, followed by Europe one year later. Its global production grows consistently, varying between 0% and 5% annually, with the strongest growth occurring in China.[2] A yearly increase of 4.6% in production of BPA is envisioned to happen from 2013 to 2019.[3]

Correspondence:
Dr. Flaka Pasha,
Str: Fehmi Agani 141, Prishtine, 10000, Kosovo
Email: flaka.pasha@uni-pr.edu; +383 44584005

Bisphenol A is used to manufacture polycarbonate plastics and epoxy resins.[4] Out of the total production of BPA, 65% is dedicated to polycarbonate synthesis, 25% for epoxy resins and the rest 10% for our daily use products such as food storage containers, food antioxidants, metal food cans, baby bottles, thermal papers, dental seals, medical devices, personal care products, safety helmets, sunglasses, lenses, cosmetics, infant incubators, CD/DVDs, hair dryers, fridges, computers and smartphones.[5]

Bisphenol A is synthetized by the condensation of phenol with acetone in the presence of a catalyst, a strongly acidic ion-exchange resin. BPA consists of a central tetrahedral carbon atom with two methyl and two phenol groups. BPA is relatively water-soluble (120-

300 mg/L),[6] dissociates in alkaline environment, has a moderate bioaccumulation rate, low vapor pressure, high melting point, and low half-life in air (0.2 days).[7,8]

BPA leaches into environment and impacts human health during its production, processing or waste disposal.[9] BPA leaching also occurs when polycarbonate and epoxy resin containing products are exposed to heat, are re-used or their pH changes.[10] BPA products in contact with heat, acidic or basic conditions accelerate the hydrolysis of the ester bonds between BPA molecules, thus exposing humans to its harmful metabolites. This happens when people heat cans to sterilize food, place acidic or basic food in cans or polycarbonate plastic, and keep heating or washing these products.[11,12] Even though ingestion of contaminated food is the most common way how human get exposed to BPA, inhalation and skin absorption are considered to be of great importance too.[13,14]

Also, moderate levels of active unconjugated BPA have been detected in human serum, adipose tissue, breast milk, placenta, maternal and fetal plasma, indicating that BPA can accumulate in human body.[15,16,17]

The United States Environmental Protection Agency (EPA) reported that more than 400,000 kilograms of BPA leach into environment every year [18], alarming us on the great burden of exposure, BPA's cumulative effects and life-long disadvantageous health impact.

Bisphenol A mechanisms of action and its disrupting potential

BPA is qualified as a xeno-estrogen that disturbs synthesis, transport, activity and metabolism of endogenous estrogens, consequently affecting the development, growth and reproduction of organisms.[19,20]

BPA can mimic or antagonize endogenous hormones, subsequently perturbing endocrine function, by binding weakly to several steroid receptors including the estrogen receptors (ER α and β) and thyroid hormone receptor.[21,22,23] As well BPA strongly binds to transmembrane endoplasmic reticulum, G protein-coupled receptor 30 (GPR30) and estrogen-related receptor gamma (ERRγ).[24,25] BPA can also activate peroxisome X receptor (PXR) and the aryl hydrocarbon receptor (AhR), often involved in cross-talk with steroid receptors.[26,27]

Many of these receptors play an important role in gene regulation, suggesting that BPA may influence normal differentiation and maturation processes especially during embryonic and fetal development.

The United States Environmental Protection Agency established a reference dose (RfD) for humans of 50 µg BPA/kg body weight (BW) day^{-1}, based on a thousand fold reduction of the lowest observed adverse effect level (LOAEL) of 50 mg kg^{-1}BW day^{-1}.[28,29] Studies indicate that daily human intake of BPA is less than 1 µg kg^{-1} BW day^{-1}, rendering the reference dose to be considered safe to humans.[30]

However, other studies have shown that administration of low-dose BPA as 0.2 µg kg^{-1} BW day^{-1} can reduce fertility and sperm production in male animals.[31,32] At doses of 0.23–23 ng kg^{-1} BPA, the number of ERK-positive cerebellar cells increases and calcium ion signaling in pancreatic cells can be suppressed leading to diabetes mellitus.[33,34,35]

To add, BPA is thought to elicit aneugenic effects by interfering with microtubule assembly, spindle apparatus function, chromosome segregation during mitosis [36,37], and disturbing DNA damage signaling pathways [38], thus affecting DNA stability, leading to potential carcinogenesis.

The content of Bisphenol A in amniotic fluid of pregnant women

Human pharmacokinetic data support rapid metabolism of free BPA to its BPA glucuronide (BPAG) and BPA sulfate (BPAS) metabolites, through UDP-glucuronyltransferase (*UGT2B15*) and sulfotransferase (*SULT1A1*) enzymes, resulting in faster urinary excretion of BPA in adults.[39,40]

In comparison to adults, human fetuses and neonates have reduced capacity for chemical detoxification.[41,42] Studies report that mammalian placenta presents with β-glucuronidase (*GUSB*) and steroid sulfatase (*STS*), breaking down inactive BPA metabolites to free BPA.[43,44]

Performing liquid chromatography coupled with mass spectrometry (LC/MS) to compare levels of

conjugated and free BPA, in second and third trimester amniotic fluids, detected free BPA levels to comprise of 83% and 91% of total BPA, highlighting the role placental β-glucuronidase has on deconjugating BPA, thus exposing fetuses to even higher amount of free BPA and potentiating its adverse effects.[45]

A considerate number of studies measured BPA in fetal cord blood [46,47], fetal liver [48,49,50], and amniotic fluids [51,52], on concentrations varying from 0.14 to 9.2, 1.3 to 50.5, and 0.36 to 5.62 ng/g, respectively.

Potential correlations between maternal and fetal blood in pregnant women, and between peripheral blood and peritoneal fluid in non-pregnant women, unveiled BPA levels ranging from non-detectable to 4.46ng/ml for maternal serum (MS) and from non- detectable to 4.60ng/ml in fetal serum (FS) of pregnant women. In the other hand, BPA levels in non-pregnant woman ranged from 1.30 to 8.17ng/ml in peripheral blood and from 0.19 to 13.45ng/ml in peritoneal fluid. Thus, positive correlation between maternal and fetal serum was found, highlighting a continuous distribution of BPA between the mother and fetus. Further, differing BPA concentration levels between pregnant and non-pregnant women reveal the role pregnancy has in underestimating the actual levels of BPA in blood.[53]

A more complex study, using novel enzyme-linked immunosorbent assay (ELISA), compared BPA concentration on blood samples obtained from healthy premenopausal women, women with early and full-term pregnancy, ovarian follicular fluid, amniotic fluid and umbilical cord blood at full-term delivery.

Surprisingly, results reviled there was 5-fold higher concentration of BPA in amniotic fluid in comparison to other fluids, ranging between 8.3 +/- 8.7 ng/ml at 15-18 weeks of gestation. Findings suggest significant exposure during the prenatal period and accumulation of BPA in fetuses, which must be cautiously considered in evaluating the potential human exposure to endocrine-disrupting chemicals.[54]

Differently, measuring BPA concentration levels in pregnant Korean women resulted in slightly higher BPA concentrations, ranging from non-detectable to 66.48 microg/L in mother serum, and from non-detectable to 8.86 microg/L in umbilical cords.[55] These higher BPA rates in Korean pregnant women may be attributed to different geographical exposure rates to BPA, having in mind that BPA market in Asia raised 13% annually from 2000 to 2006.[56] So, different geographical exposure rates, should be considered when interpreting BPA concentration levels.

Moreover, a nested cross-sectional study revealed significant racial disparities in maternal and fetal BPA concentrations. African-Americans had 10-fold higher maternal serum BPA concentrations than Caucasians (30.13 vs 3.14 ng ml(-1); P=0.038), Hispanics had intermediate concentrations with a trend towards higher concentrations compared with Caucasians (24.46 vs 3.14 ng ml(-1); P=0.051) and Hispanics had higher fetal BPA concentrations than non-Hispanics (2.05 vs 0.35 ng ml(-1);P=0.025). These findings potentiate the immediate need to determine if such differences come from different levels of BPA exposure, fetal-placental transfer and its metabolism, or racial genetic variations.[57]

It is crucial to know that measuring BPA as the end analyte might lead to inaccurate estimates, considering potential interferences from background sources during sample collection and analysis. Aglycone BPA and its primary conjugates as BPAG, BPAS, represent better candidates for biomarkers of BPA exposure, since they are not prone to external contamination and require in vivo metabolism.[58] To 2016 only ten studies reported analytical methods to measure BPA metabolites instead of just BPA. Research was limited by either lack of commercial or custom-synthesized BPA conjugates, or lack of labeled internal standards.[59,60,61,62,63,64,65,66]

In order to achieve even more accurate and comprehensive representation of human exposure to endocrine disrupting chemicals, such as BPA, it is crucial for the future studies to consider cumulative effect of EDCs, knowing that humans are not exposed separately to just one EDC at a point of time.[67,68,69]

BPA adverse health effects in fetuses and disease progression later in life

Exposure of rodent fetuses to Bisphenol A, at doses similar to environmental exposure, is found to cause postnatal estrogenic effects, as alteration of mammary gland morphology, detrimental long term effects in vagina and faster growth and puberty in females. As

well, reduced sperm production in males, increased prostate weight, and disruption of sexual differentiation in the brain was noticed.[70,71,72,73,74,75,76]

Short time exposure to so considered "safe levels" of BPA, proved to have direct adverse effect on remodeling uterine spiral arteries, thus limiting blood supply to fetus [77], resulting to implantation failure, spontaneous abortion, recurrent miscarriages, or even leading to an increased risk of pre-eclampsia.[78,79,80,81]

Studies support that women with detectable bisphenol A (BPA) concentrations have significantly higher risk of being infertile. La Rocca et al. [82] found that the mean concentration of BPA was twice as high in infertile than fertile women (10.6 vs. 4.8 ng ml1). Among infertile women, estrogen receptor alpha (ERα) and beta (Erβ), androgen receptor (AR) and pregnane X receptor (PXR) were significantly expressed higher than in fertile patients, highlighting the distorting effect BPA has on these receptors.[83]

Increased BPA concentrations are also reported to raise the occurrence of polycystic ovary syndrome (PCOS) [84], and are related to abnormalities in uterus morphology and endometriosis [85]. Some other studies prove that BPA may cause atopic hyperplasia, uterine polyps or even cervical sarcoma and nipple adenoma.[86,87,88]

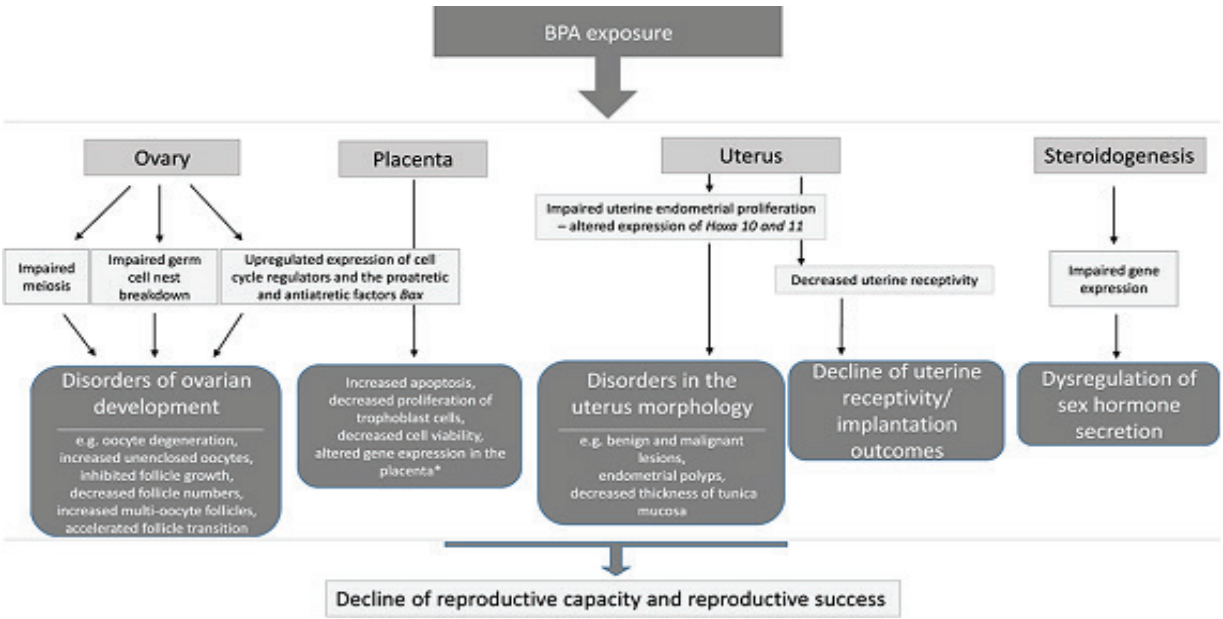

Figure 1: Effect of BPA on women reproductive processes. BPA, bisphenol A [89]

In addition, BPA-treated testes contain mostly spermatogonia and spermatocytes with markedly less round spermatids, indicating signs of meiotic arrest. Neonatal BPA exposure disrupts meiosis during the first phase of spermatogenesis, due to inhibition of *BOULE* (conserved key regulator for spermatogenesis expression and up-regulation of ERα/β expression in BPA-exposed developing testis) [90]. This situation leads to increased presence of apoptotic cells in seminiferous tubules, sperm cells DNA damage and decreased sperm counts[91].

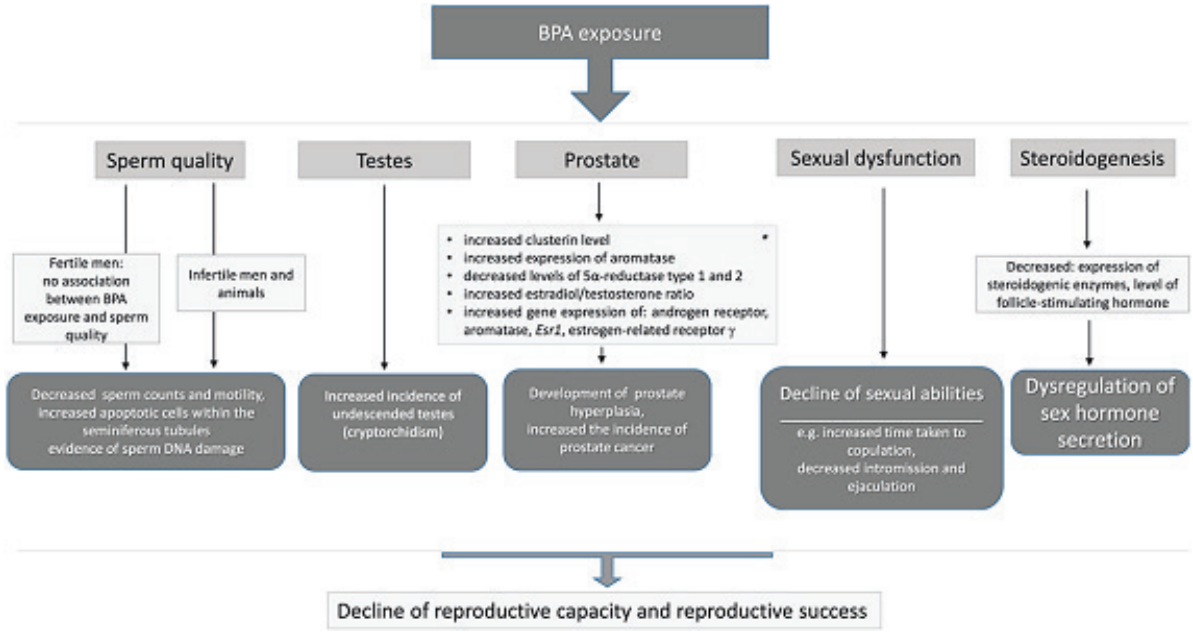

Figure 2: Effect of BPA on male reproductive processes. BPA, bisphenol A [89]

Rather than just having disruptive effects in reproductive tract, high BPA concentrations correlate with increased incidence of obesity and earlier puberty in females, altered physical and mental development in children, modified childhood behavior, cardiovascular disease and immune system dysfunction.[92,93,94,95]

A ten year study, comparing BPA levels in amniotic fluid between pregnant mothers with normal and abnormal karyotype fetuses, highlighted that mothers with abnormal karyotype fetuses had higher levels of BPA concentrations in amniotic fluid, in comparison to pregnant women with normal karyotype fetuses. Therefore, these findings highlight the distorting potential BPA has in DNA stability and carcinogenesis induction.[96]

Studies aiming to evaluate the role of BPA in carcinogenesis[97,98] have indicated that exposure to BPA may increase the incidence of multiple cancers, as breast cancer [99,100,101], ovarian cancer [102,103], uterine cancer [104], prostate cancer [105,106], testicular cancer [107], and liver cancer. [108]

Conclusions and Perspectives

Governmental restriction on BPA and general public concern regarding bisphenols adverse health effects, increased manufacturers interests on developing BPA substitutes such as Bisphenol S (BPS) and Bisphenol F (BPF). [109] Due to their stability in sunlight and high temperature, they were initially thought to be safer alternatives.[110] In contrast, in vitro studies found that BPS and BPF can elicit even greater estrogenic activities than BPA [111], can decrease cell viability, increase DNA damage and induce reproductive and neural toxicity. [112,113,114,115,116]

In addition, having in mind BPA's accumulation potential, its distribution to fetal-placental unit, interspecies placental differences [117], high BPA exposure in early weeks of gestations, racial disparities, varying geographical exposure rates, and BPA's cumulative effects with other EDCs, no endocrine disruptor dose should be assumed to be safe in pregnancy. [118,119]

Therefore, increasing population's awareness around BPA adverse health effects through health education, and avoiding exposure to products containing BPA, remains the fastest and easiest way to limit BPA long life term adverse health outcomes.

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