Plastics derived endocrine-disrupting compounds and their effects on early development

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Abstract
Despite the fact that the estrogenic effects of bisphenols were first described 80 years ago, recent data about its potential negative impact on birth outcome parameters raises a strong rationale to investigate further. The adverse health effects of plastics recommend to measure the impacts of endocrine-disrupting compounds (EDCs) such as bisphenols (BPA, BPS, BPF), bis(2-ethylhexyl) phthalate, and dibutyl phthalate (DBP) in human health. Exposure to these compounds in utero may program the diseases of the testis, prostate, kidney and abnormalities in the immune system, and cause tumors, uterine hemorrhage during pregnancy and polycystic ovary. These compounds also control the processes of epigenetic transgenerational inheritance of adult-onset diseases by modulating DNA methylation and epimutations in reproductive cells. The early developmental stage is the most susceptible window for developmental and genomic programming. The critical stages of the events for a normal human birth lie between the many transitions occurring between spermatogenesis, egg fertilization and the fully formed fetus. As the cells begin to grow and differentiate, there are critical balances of hormones, and protein synthesis. Data are emerging on how these plastic-derived compounds affect embryogenesis, placentation and feto-placental development since pregnant women and unborn fetuses are often exposed to these factors during preconception and throughout gestation. Impaired early development that ultimately influences fetal outcomes is at the center of many developmental disorders and contributes an independent risk factor for adult chronic diseases. This review will summarize the current status on the impact of exposure to plastic derived

Abbreviations: 11β-HSD 2, 11β-hydroxysteroid dehydrogenase type 2; ARs, androgen receptor; BPA, bisphenol A; BPA, bisphenol F; BPS, bisphenol S; C/EBPa, CCAAT/enhancer-binding protein alpha; CD-1, cluster of differentiation-1; CPT1A, carnitine palmitoyltransferase 1A; DBP, dibutyl phthalate; DEHP, [diethylhexyl phthalate or bis(2-ethylhexyl) phthalate]; EDC, endocrine disrupting chemicals; ERR-γ, estrogen-related receptor γ; ERs, estrogen receptors; EZH2, enhancer of zeste homolog 2; gD, gestational day; Hoxa10, homeobox A10; IGF-1, insulin like growth factor 1; IGF-2, insulin like growth factor 2; LINE-1, long interspersed nuclear element-1; MEHHPP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEP, monoethyl phthalate; MEST, mesoderm specific transcript; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; miRNA, micro-RNA; p, p'-DDE, p, p'-dichlorodiphenyl dichloroethylene; PBDE, polybrominated diphenyl ethers; PCOS, polycystic ovary syndrome; PE, preeclampsia; PFAS, perfluoroalkyl substances; POPs, persistent organic pollutants; PPARγ, peroxisome proliferator-activated receptor protein gamma; SCD-1, stearoyl-CoA desaturase-1; SOX, sry-related high mobility group box; SREBP-1c, sterol regulatory element-binding protein 1; TBBPA, tetrabromobisphenol A; THRs, thyroid hormone receptors.

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EDCs on the growth, gene expression, epigenetic and angiogenic activities of the early fetal development process and their possible effects on birth outcomes.

KEYWORDS
11β-HSDs, ARs, birth outcome, bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), DNA methylation, EDC, endocrine disruptor, environmental estrogens, epigenetics, ERs, exposure, fetal programming, genome program, IGFs, miRNA, obesity, phthalate, placenta, plastics, polycystic ovary syndrome, preeclampsia, THRs

1 | INTRODUCTION

Almost all aspects of daily life involve plastics. Plastics are used in transport, telecommunications, clothing, footwear, and also as packaging materials that facilitate the transport of a wide range of food, drink, and other goods. Extensive studies have reported different aspects of plastics, especially its effects in the environment and threats to natural surroundings, wildlife, and most importantly human health. Components used in plastics, such as phthalates, bisphenols (BPA, BPS, BPF), polybrominated diphenyl ethers (PBDE), and tetrabromobisphenol A (TBBPA), are detected in human tissues. These compounds are released from plastic products and are also known as endocrine-disrupting compounds (EDCs) owing to their ability to modulate the endocrine system. Plastics compounds are detected in the human population, and studies using laboratory animals as model organisms indicate potential adverse health effects of these chemicals (Talsness, Andrade, Kuriyama, Taylor, & vom Saal, 2009). EDCs are therefore of concern due to their potential to interfere with the physiology of living organisms. Plastic derived compounds in particular bisphenols and phthalates are ubiquitously present and we are being exposed to them constantly in our daily lives. It is therefore almost impossible to compare the health of people exposed to bisphenols and phthalates as compared to those who are not. EDCs can be exposed through a dermal route, food container surfaces, food wrappers, exposure through consuming marine fishes, handling electronic gadgets, and packaging items. Although, an adult human can clear these EDCs efficiently, the unborn fetus and placenta do not have enzymatic machinery to protect them from these exposures.

In general, EDCs may disrupt the endocrine system by competing with endogenous steroid hormone and binding to receptors and hormone transport proteins or by altering the metabolism or synthesis of endogenous hormones. Eventually they can alter gene expression (Wetherill et al., 2007). Body burdens of chemicals that are used in plastic manufacturing are correlated with adverse effects in the human population, including reproductive abnormalities (Thompson, Moore, vom Saal, & Swan, 2009).

This is of particular concern for the early developmental period as this period is sensitive to changes in the hormonal milieu, which can result in organizational changes of a permanent nature (Guillette Jr., Crain, Rooney, & Pickford, 1995). Epigenetic changes following early developmental exposure to EDCs are also observed in animals (Skinner & Anway, 2007). Human exposures to EDCs during the vulnerable developmental time period are documented in several studies affecting fetal liver (Schecter et al., 2007) amniotic fluid (Ikezuki, Tsutsumi, Takai, Kamei, & Taketani, 2002) and cord blood (Guvenius, Aronsson, Ekman-Ordeberg, Bergman, & Noren, 2003; Schonfelder et al., 2002). Data from animal and human studies suggest that EDCs may also play a role in the decline in human sperm counts in particularly in the US and Europe (Levine et al., 2017; Mocarelli et al., 2008), transient increases in the frequency of developmental abnormalities of the male reproductive tract (Guo, Wang, Liu, & Olive, 2008) and the trend toward precocious puberty in human females (Schoeters, Den Hond, Dhooge, van Larebeke, & Leijjs, 2008). Ample evidence indicates that exposure of EDCs during early life causes a variety of later-occurring diseases, from cancer to cognitive impairments (Carter & Blizard, 2016; Kitraki, Nalvarte, Alavian-Ghavanini, & Ruegg, 2015; Sanchez de Badajoz, Lape-Sanchez, & Sanchez-Gallegos, 2017). There is growing evidence for the role of EDCs in the development of metabolic diseases, primarily when exposure occurs during critical periods of development such as in early life or during the pregnancy or postnatal period (Gore et al., 2015; Martinez-Ibarra et al., 2019).

Among the best-studied environmental chemicals that may negatively affect the early developmental stages is BPA. Exposure of BPA and its substitutes during pregnancy is being investigated extensively recently using models. Recent data about their effects on developmental parameters are summarized in Table 1. In humans, BPA is detected in amniotic fluid, neonatal blood, placenta, and adult tissues at levels that would affect biological systems (Vandenberg et al., 2010). BPA is a xenoestrogen, exhibiting estrogen-mimicking, hormone-like properties.
The abundance of hormone receptors makes the placenta highly sensitive to BPA. BPA has been found to bind to both of the nuclear estrogen receptors (ERs), ERα and ERβ. It is 1,000-fold to 2,000-fold less potent than estradiol. BPA can mimic the action of both estrogen and antagonize estrogen, explaining its roles as a selective estrogen receptor modulator and also a partial agonist of the ER. At high concentrations, BPA also binds to and acts as an antagonist of the androgen receptor (AR). In addition to receptor binding, BPA affects steroidogenesis in Leydig cell, by altering 17α-hydroxylase/17,20 lyase and aromatase expression and interfering with LH

| Compound | Models | Concentration, duration, route | Key findings | References |
|----------|--------|--------------------------------|--------------|------------|
| BPA, BPS | C57BL6J mice | 200 μg/kgbw/d, 2 wks before mating till gD 12.5, feeding | Identical effects of BPA and BPS on placenta; imbalances in neurotransmitter-positive giant cells and decrease in DHA | Mao et al. (2020) |
| BPA | Sheep | 0.5 mg/kgbw/d, gD 30–90 (~147 term), subcutaneous | Sex-specific programming of neonatal growth | Vyas et al. (2019) |
| BPA | CD-1 mice | 0.4–400 μM, gD 7–17, drinking water | Alters placentation and causes preeclampsia-like features in pregnant mice | Ye, Tang, Xiong, Feng, and Li (2018) |
| BPA, BPS, BPF | CD-1 mice | 0.05–5 mg/kgbw/d, gD 10–17, oral gavage | Precocious development of the mammary glands | Tucker, Hayes Bouknight, Brar, Kissling, and Fenton (2018) |
| BPA, BPS, BPF | SD-rat | 5–50 μg/L, gD 1–20, drinking water | Prominent histological changes in testis and epididymis | Ijaz, Ullah, Shaheen, and Jahan (2019) |
| BPA | Kunming mice | 0.5–40 mg/kgbw/d, gD 0.5–17.5, administered | Interferes ovaries development of F1 female mice | Wei et al. (2020) |
| BPA | SD-rats | 0.1%, PND 21–51, drinking water | Morphological changes in the mammary gland development | Varuzza et al. (2019) |
| BPA | C57BL/6J mice | 5–50 μg/ml, complete gDs, drinking water | Decreases in the testosterone concentration and impaired testis functions | Yang et al. (2019) |
| BPS | CD-1 mice | 2–200 μg/kgbw/d, gD 9 through lactation day 20, oral gavage | Alters the development of the male mouse mammary gland | Kolla, McSweeney, Pokharel, and Vandenberg (2019) |
| BPA | CD-1 mice | 10 μg/kgbw/d, gD 11 to PND 7, oral gavage | Alter in the neurobehavioral development of the pups | Palanza, Gioiosa, vom Saal, and Parmigiani (2008) |
| BPA | C57BL/6 mice | 25 mg/kgbw/d, gD 7.5–18.5, diet | Delayed maturation of pancreatic islets, alteration in αβ cell ratio | Whitehead, Guan, Arany, Cernea, and Yang (2016) |
| BPA | SD-rat | 40 μg/kgbw/d, gestation and lactation in F0 mice, Orally | Glucose intolerance in F2 mice, alteration in DNA methylation of glucokinase promoter | Li et al. (2014) |
| BPA | Wistar rats | 50 μg/kgbw/d gestation and lactation, Orally | Abnormal hepatic tissue DNA methylation and development of insulin resistance in pups | Ma et al. (2013) |

Abbreviations: d, day; gD, Gestational day; kgbw, per kilogram body weight; PND, post-natal days; wk., week.
receptor-ligand binding. The adverse effects of low-dose BPA exposure in laboratory animals were first proposed in 1997. The interaction between BPA’s and estrogen-related receptor \( \gamma \) (ERR-\( \gamma \)) was reported later. This orphan receptor (endogenous ligand unknown) behaves as a constitutive activator of transcription. BPA binds strongly to ERR-\( \gamma \), but only weakly to the ER. Binding of BPA to ERR-\( \gamma \) is required for basal level activity and for protection from deactivation by the SERM 4-hydroxytamoxifen (Matsushima et al., 2007). Differential expression of ERR-\( \gamma \) in tissues may account for variations in BPA activities.

Some phthalates and bisphenols contribute to the development of obesity and glucose metabolism disorders (Martinez-Ibarra et al., 2019). Other studies have found correlations between high urinary levels of BPA and phthalates and adverse effects for both mothers and their offspring, including preterm delivery, metabolic dysfunction and altered newborn somatometric parameters. Such evidence supports the adverse effects of BPA, particularly on susceptible groups such as pregnant women. This review highlights the impacts of the exposure of the plastic derived EDCs on early developmental stages such as embryogenesis, fetoplacental growth and development, and their effects on relevant gene expression, epigenetic and angiogenic activities and overall pregnancy outcomes.

1.1 Plastic compounds: Cellular and biochemical effects

Plastics release persistent organic pollutants (POPs) into water, soil, and air that pose significant problems for the environment and human health. Their poor biodegradability explains why they are termed persistent organic pollutants. Plastics and their major components including acrylonitrile, polychlorinated biphenyls, dioxins, phthalates, and bisphenols are accumulated in living organisms due to their ubiquitous presence as industrial materials and everyday products (Żwierello et al., 2020). Exposure to these POPs can lead to metabolic diseases, insulin resistance, inflammation, neurodegenerative disorders, allergies, carcinogenesis. POPs are resistant to metabolic degradation and bioaccumulate in fatty tissues. Their low cost and durability have made plastics an essential ingredient in packaging, healthcare, and construction and transportation industry. Exposure of these plastics and their additives can lead to endocrine activity by targeting different levels of the hypothalamic–pituitary-gonad/thyroid axis. POPs disrupt normal endocrine functions. Even low levels of POPs exposure during the critical developmental period of fetuses, can have a lasting effect throughout their lifespan.

The health and economic benefit of removing BPA from all food related usage was estimated to reduce of childhood obesity and adult coronary heart disease with potential annual economic benefits of $1.74 billion (sensitivity analysis: $889 million–$13.8 billion per year). Thus, avoiding exposure to this environmental estrogen BPA in reproductively active women has a long-term benefit for disease susceptibility of the unborn children (Trasande, 2014). Exposure of plastics derived compounds has been increasingly considered as a contributor to affecting human health throughout the world, in particular to the pathophysiology of developmental programming of endocrine-related metabolic diseases. These compounds are ubiquitous environmentally and in foods and at levels that can play a role in the development of metabolic diseases like obesity and diabetes (Chevalier & Fenichel, 2015).

BPA is one of the highest-volume chemicals (HPV-chemical) produced worldwide. Most people are exposed to this chemical daily by consuming food and beverages into which BPA has leached from polycarbonate containers, including reusable bottles and baby bottles. After BPA was banned in baby bottles in Canada (2008), France (2010), and EU (2011), substitutes such as BPS and BPF were developed as a base material for the production of polycarbonate plastic and epoxy resin (Moon, 2019). These BPA substitute products created an impression of safer “BPA free” products. However, due to structural similarities with BPA, these alternatives are showing similar endocrine-related adverse effects on human health. Bisphenol S (BPS), the predominant replacement chemical for BPA did not show any different effects compared to BPA (Ahmed & Atlas, 2016; Rochester & Bolden, 2015). Exposure to BPA during early human development is also reported to trigger many non-communicable diseases such as hypertension, coronary heart disease, obesity, and diabetes mellitus, that emerge later in life (Akash, Sabir, & Rehman, 2020; Alonso-Magdalena, Rivera, & Guerrero-Bosagna, 2016).

Initially thought to be a weak environmental estrogen, more recent studies have demonstrated that BPA may be similar in potency to 17\( \beta \)-estradiol in stimulating cellular responses, especially at low but environmentally relevant doses (nM). Pharmacokinetics data of bisphenol A in humans after a single oral administration are consistent with data from animal and other human studies (Thayer et al., 2015). Orally administered BPA is rapidly absorbed and transformed to BPA-glucuronide during the first-pass metabolism in the gut wall and liver of humans and other primates. A small amount of BPA converts to a sulfate conjugate. More than 80% of orally administered BPA clears from the body in 5 hr. Although the conjugated forms of BPA are devoid of endocrine activity, these are shown to induce adipogenesis in vitro. The BPA concentration detected in human fetal tissue is closely similar to the levels in maternal blood demonstrating that BPA readily traverses across the placenta.
BPA also moves into maternal milk, resulting in levels of about 1–3 μg/L, which are comparable to, or slightly higher than, those reported for maternal blood. BPA levels were detected in 93% of healthy infants aged 3–15 months who were without known environmental exposure to BPA (Mendonca, Hauser, Calafat, Arbuckle, & Duty, 2014). Unlike an adult, embryonic/neonatal humans and animals cannot conjugate BPA. Thus, the fetus and neonate become a more sensitive and highly exposed subpopulation deserving special attention. After maternal intake through the diet, the highest concentration of BPA (1–104 ng/g of tissue) has been recorded in the placenta and fetus (Jalal, Surendranath, Pathak, Yu, & Chung, 2018).

BPS is widely used in the production of daily consumer products such as plastics, thermal papers, and inner linings of food containers, baby bottles and toys as the attention has been shifted to produce “BPA free” plastics. Use of BPS has been increased considerably over the past few years after banning of BPA for its harmful effects. BPS, which is thought to be a safer substitute to BPA, shows similar results to BPA with human exposure (Rochester & Bolden, 2015; Song, Xie, & Cai, 2017; Thoene, Dzika, Gonkowski, & Wojtkiewicz, 2020). Being relatively inert, BPS leaches slowly from food packaging into the food and water and enters the human body. BPS is metabolized by the liver into BPS-glucuronide and BPS-sulfate and finally excreted in urine and feces (Liao et al., 2012; Song, Xie, & Cai, 2017). Just like BPA, BPS has also proven to show estrogen or anti-androgenic like properties and can bind to estrogen or androgenic receptors and brings about adverse changes in the human body. BPS, when compared with BPA, is more resistant to heat, light and is less biodegradable, which indicates that it may remain in the environment for a more prolonged period compared to other bisphenols like BPA and BPF. Dermal contact, inhalation and ingestion are routes of BPS contamination in humans, although oral intake remains the primary source of entry into humans. Recent studies have found considerable amounts of BPS in human urine, indicating substantial exposure to BPS in humans (Wu et al., 2018). Residues of BPF, another BPA substitute, were detected in the uterus, placenta, amniotic fluid, and fetuses, and the levels of BPF in the intrauterine compartment and maternal blood were comparable (Cabaton, Chagnon, Lhuguenot, Cravedi, & Zalko, 2006). BPF can be converted to conjugated metabolites (BPF-glucuronide, BPF-sulfate and BPF-glucuronide/sulfate) in the maternal liver of a tissue perfusion model and eliminated from the body. BPF sulfate can easily passed to the embryo through the placenta (Iwano, Hozumi, Inoue, & Yokota, 2016).

Phthalate is a synthetic compound used in plastics, personal care products, and building materials. People are exposed to phthalate in everyday life. This plasticizer is excreted in urine 12–18 hr after exposure (Hauser & Calafat, 2005; Stojanoska, Milosevic, Milic, & Abenavoli, 2017; Swan, 2008). Nonetheless, the EU panel estimates 40–69% probability of phthalate exposure causing 53,900 cases of obesity in older women which is associated with a total cost of 15.6 billion Euros (Legler et al., 2015). Among phthalates, high molecular weight DEHP (diethylhexyl phthalate) and low molecular weight dibutyl phthalate (DBP) were detected highest levels in the serum and sweat (Genuis, Beesoon, Lobo, & Birkholz, 2012). Phthalate metabolites such as MEP (monoethyl phthalate) and DEHP (diethyl phthalate) have also been detected in the urine of about 98–100% of pregnant women (Cantonwine et al., 2016; Woodruff, Zota, & Schwartz, 2011). In a sample of 378 pregnant women, at least 93% exhibited detectable concentrations of eight phthalate metabolites in urine between 18 and 22 weeks of gestation (Wenzel et al., 2018). A positive association between phthalate concentrations and maternal BMI in pregnancy has been reported in several studies (American Diabetes Association, 2019; Buser, Murray, & Scinicariello, 2014; Peck et al., 2010; Stahlhut, van Wijngaarden, Dye, Cook, & Swan, 2007; Valvi et al., 2015; Yaghjyan, Sites, Ruan, & Chang, 2015), and higher phthalate levels in urine were observed in African American pregnant women compared to Caucasian (Huang, Saxena, Isganaitis, & James-Todd, 2014; Kobrosly, Parlett, Stahlhut, Barrett, & Swan, 2012; Wenzel et al., 2018). In pregnant women, MEP is the predominant phthalate metabolite in urine. Interestingly, maternal education and income were inversely related to phthalates levels, suggesting that sociocultural and lifestyle patterns might significantly influence exposure (Valvi et al., 2015; Wenzel et al., 2018). In humans, mother urinary phthalate excretion in the third trimesters of pregnancy suggested that prenatal phthalate exposure was associated with altered placental size and shape and that exposure to certain phthalates could induce the placenta to become thicker and more circular instead of round or oval shaped placenta with a centrally inserted umbilical cord (Zhu et al., 2018). Moreover, the association appeared stronger in the male child. Disruption of average placental growth was associated with the exposure of PBDEs measured in umbilical blood samples (Gabory, Roseboom, Moore, Moore, & Junien, 2013). The phthalate metabolites when exposed to rats in utero, altered steroidogenesis and produced a phenotype with reduced testosterone synthesis in fetal Leydig cells (Barlow et al., 2003). In spite of such findings in animals, it did not cause similar changes in humans. These findings suggest that phthalate may have a differential effect in disruption of systems across species. Repeated
measures confirmed the association of phthalate metabolites in the third-trimester human urine samples with a group of target genes involved in the pathways of trophoblast differentiation and steroidogenesis. Metabolites of phthalates such as DEHP, DnBP, DiBP, and BBzP were inversely associated with the expression of a gene known to be involved in trophoblast differentiation (PPARγ, AhR, HCG). The peroxisome proliferator-activated receptor protein gamma (PPARγ) is a master regulator of reproductive and developmental pathways, such as steroidogenesis, differentiation, fatty acid uptake and transport, and inflammation related to parturition (Adibi et al., 2010). PPARγ is expressed in the human trophoblast and is essential for placental development and function. The phthalate metabolites possibly act as an agonist for PPARγ to regulate trophoblast differentiation. In vivo prenatal exposure to a metabolite of DEHP resulted in dose-dependent activation of PPARγ in rat placenta and changes in the expression of its downstream targets, including fatty acid transport proteins and cytochrome oxidase-2. These suggest phthalate and its metabolites act as endocrine-disrupting compounds to modulate placental function.

1.2 Early life exposure of bisphenol a leads to the development of obesity and metabolic disorders in later life

Several animal and epidemiological studies suggest that disturbances in the in-utero environment due to exposure to bisphenols may program the fetus for the development of endocrine-related diseases. There is growing evidence for the role of EDCs in the development of metabolic diseases, primarily when exposure occurs during critical periods of development such as in pregnancy or early life (Gore et al., 2015; Martinez-Ibarra et al., 2019). Some phthalates and BPA contribute to the development of obesity and glucose metabolism disorders (Martinez-Ibarra et al., 2019). Other studies have found correlations between high urinary levels of BPA and phthalates and adverse effects for both mothers and their offspring, including preterm delivery, metabolic dysfunction and altered newborn somatometric parameters. Such evidence supports the adverse effects of BPA, particularly on susceptible groups such as pregnant women. BPA can affect placental development and thereby, fetal programming (Tait, Tassinari, Maranghi, & Mantovani, 2015). Longer exposure periods to BPA at doses from 0 to 3,000 μg/kg/day also triggered a dose-dependent increase in body and liver weight in the male offspring, while adult females displayed a decline in body weight (van Esterik et al., 2014). Jiang et al. performed similar experimental procedures in rats, which resulted in fatty acid accumulation in BPA offspring that contributed to the development of hepatic steatosis (Jiang et al., 2014). In addition, maternal oral BPA exposure altered the expression of several genes that are key in the regulation of adipogenesis including PPARc, SREBP-1c, SCD-1, and C/EBPα in the female offspring (Somm et al., 2009). Decreased physical activity and increased carbohydrate metabolism have also been found in female mice developmentally exposed to BPA (John et al., 2015). The diabetogenic effect appears to be consistent among different studies after prenatal exposure of BPA. Alonso-Magdalena et al. demonstrated that the treatment with BPA (10 or 100 μg/kg/day) from day 9–16 of gestation triggered glucose intolerance, insulin resistance and altered pancreatic β-cell function in male offspring at 6 months of age. However, neither male mice at younger ages nor females displayed any effects (Alonso-Magdalena et al., 2010). Oral exposure in pregnant rats also led to the development of insulin resistance in the offspring at 21 weeks of age (Ma et al., 2013). Interestingly, disturbances of glucose metabolism due to maternal BPA exposure have been reported not only in F1 generation but also in F2 (Li et al., 2014; Susiarjo et al., 2015). Upon BPA exposure of gestating females, metabolic disturbances have been found both in the offspring and later in life in the mothers themselves. These effects have been recently described using a model for BPA-induced metabolic changes in which two doses of BPA were used (10 and 100 μg/kg body weight/d). BPA exposed pregnant females developed severe glucose intolerance and insulin resistance, similar to gestational diabetes. Even though alterations disappeared after parturition, as seen in many cases of gestational diabetes, the remission was only temporary and metabolic disturbances developed again months later. However, non-pregnant-treated female mice showed no changes, indicating that both pregnancy and BPA exposure is necessary to cause the distinct phenotype (Alonso-Magdalena et al., 2010). In this study, the most observed effects were recorded at 6–7 months after the exposure, showing decreased pancreatic β-cell function and mass, reduced insulin levels in plasma and marked glucose intolerance. Interestingly, these effects were accompanied by increased body weight gain and fat accumulation (Alonso-Magdalena, Garcia-Arevalo, Quesada, & Nadal, 2015). All these studies suggest that prenatal BPA exposure results in insulin resistance, leading to the development of obesity.

1.3 The impact of EDC exposure impact on embryo development

The early developmental stages, particularly, embryonic development are a critical window for growth and
genome programming (Assou et al., 2011). It is believed that environmental disturbances during embryogenesis can make subtle functional changes that alter gene expression, cell numbers, physiology and metabolism. All these changes increase the risk of disease/dysfunction even long after the environmental perturbation during development (Heindel et al., 2017; Nesan, Sewell, & Kurrasch, 2018). The increased sensitivity of the developmental stages may reflect the plasticity of developing organisms. During early embryogenesis, differentiation of pluripotent cells into mature cells and tissues are controlled by hormones and other signaling molecules such as growth factors (Heindel & Vandenberg, 2015). The coordinated process of cell differentiation during the developmental stages can be altered by a variety of environmental chemicals, including EDCs.

It is yet unknown how chemical exposure during early development leads to persistent changes that manifest as diseases much later in life, or even in the next generation. However, cumulative evidence points toward a central role for epigenetic mechanisms in these long-lasting effects of EDCs and other chemicals. Epigenetic mechanisms control permanent transcriptional regulation, and changes in epigenetic information can be defined as any long-term change in gene function that persists even when the initial trigger is long gone and that does not involve a change in gene sequence (Lavebratt, Almgren, & Ekstrom, 2012). In recent years, a wealth of experimental studies and some evidence from epidemiology have demonstrated that EDCs indeed induce epigenetic changes (Marczylo, Jacobs, & Gant, 2016).

For decades, researchers have tried to understand some of the earliest steps of embryogenesis in humans and some of the most crucial ones are still a mystery. The reason is that an embryo in a woman’s womb cannot be studied. As a result, these very early stages of development have been “a complete black box”. Use of laboratory models is the only way to gain insight into understanding the early-stages of development. Some of these findings can be extrapolated to human development. Animal models remain essential to understand the fundamental mechanisms underlying the onset of diseases and to discover improved methods for prevention, diagnosis and treatment. Howdeshell et al. first demonstrated that in utero exposure to low doses of BPA (2.4 μg/kg) in mice increased body weight on postnatal day 22, suggesting that early-life exposure to BPA is particularly sensitive in predisposing individuals to weight gain (Howdeshell, Hotchkiss, Thayer, Vandenbergh, & vom Saal, 1999). Afterwards, many investigations have been performed to study the effects of the exposure to this EDC during early life. In one of most comprehensive studies, Angle et al. showed that pregnant mice exposed to BPA at doses ranging from 5 to 50,000 μg/kg/day for gestation day from 9 to 18, showed increased postnatal body weight, adipocyte number, and volume of abdominal fat, together with alterations in plasma levels of insulin, leptin, and adiponectin. The effects, that were maximal at the lowest doses from 5 to 500 μg/kg/day, confirmed the obesogenic roles of BPA (Angle et al., 2013). The dose range of BPA used in this study was 10-fold below (50 μg/kg/day) and 10-fold higher (500 μg/kg/day) the estimated reference dose (Birnbaum et al., 2012). WHO/FAO estimates that mean exposure of adults, young children and teenagers to free BPA from dietary and non-dietary sources range from <0.01 to 0.40, 0.1 to 0.5, and 0.3 to 1.1 μg/kg body weight per day, respectively (Nations, 2011).

Prenatal exposure to alternative bisphenols has not been explored as meticulously. So far, very few studies have reported the effects of BPS and BPF on laboratory animal models. Mersha et al. first reported that in Caenorhabditis elegans, the exposure of embryos to BPA and BPS altered their behavior that was assayed when they had matured into adults (Mersha, Patel, Patel, Richardson, & Dhillon, 2015). Chen et al. performed a comparative study concerning the effects of BPA and BPS on germline and reproductive functions using the same model system. They stated that BPS also caused severe reproductive defects, including germline apoptosis and embryonic lethality in the same manner BPA did (Chen et al., 2016). The impacts of BPA and BPS on the reproductive neuroendocrine system were evaluated during zebrafish embryonic and larval development, where a similar effect for both bisphenols was observed (Qiu et al., 2016). Therefore, these findings raise a new concern about the safety of BPA alternatives and the risk associated with human exposure to mixtures of EDCs. Prenatal risk of BPF toxicity might be even higher than BPA because of the drug-metabolizing system. Ohtani et al. showed that prenatal BPF exposure in mice resulted in alteration in the behavior of offspring, with an increase in anxiety and depression (Ohtani et al., 2017). Compared with BPA, BPF showed larger behavioral adverse effects, indicating the potential risk of using BPF as a substitute for BPA.

1.4 Can exposure of BPA induce epigenetic alterations?

DNA methylation is sensitive to environmental exposure, and is able to influence the human placental methylome, causing aberrant placental development and function, thus influencing fetal outcomes (Xu et al., 2013). Many environmental factors, including the EDCs can have an impact on these processes. It is hypothesized that the appearance of the disease sometime after the prenatal exposure of chemicals is linked to epigenetic modifications. In accordance with this hypothesis, Doliney et al., was the
first to report that epigenetic alterations could happen due to prenatal BPA exposure. The study demonstrated that prenatal exposure of Agouti mice to BPA resulted in the hypomethylation of nine CpG sites on the promoter region of the Aγv gene (Dolinoy, Huang, & Jirtle, 2007). However, supplementation of the maternal diet with methyl group donors, such as folic acid and the genistein easily reversed this hypomethylation. Anderson et al. investigated the effects of multiple physiologically relevant doses of BPA (50 ng/kg, 50 µg/kg, and 50 mg/kg) on DNA methylation patterns of the Aγv gene (Anderson et al., 2012). Their finding confirmed the work by Dolinoy and coworkers that the 50 mg/kg BPA dose caused a shift in coat color of offspring to yellow by decreasing DNA methylation in the retrotransposon upstream of the Agouti gene. To investigate prenatal BPA-induced epigenetic modifications further, Bromer et al. treated CD-1 mice interperitoneally with BPA in utero. BPA exposure decreased methylation of the Homeobox A10 (Hoxa10) gene (Bromer, Zhou, Taylor, Doherty, & Taylor, 2010). Hoxa10 encodes the homeobox protein, a transcription factor, which plays a pivotal role in the embryogenesis of the uterus and embryo implantation via regulation of downstream genes (Zanatta et al., 2010). Hypomethylation of Hoxa10 caused an alteration in the programming of gene expression during development. It also altered the binding of estrogen receptor to the estrogen response element of Hoxa10, which increased responsiveness of the gene to estrogen. It is of note that adult mice, exposed to the same doses of BPA did not show any alteration in the expression of Hoxa10, suggesting that the BPA-induced epigenomic modifications occurred during prenatal stages (Bromer et al., 2010). A recent study highlighted gene-specific methylation changes in stress response pathways upon in vitro exposure of the early trophoblast cells to BPA (Basak, Srinivas, & Duttaroy, 2018). The percentage of promoter methylation was lowered by BPA exposure as compared to those of control cells. DNA methylation of gene promoters often acts to repress gene transcription of mRNA that encode genes for cellular stress and toxicity pathways and thus stress response genes were de-repressed during BPA exposure.

The relationship between obesogenic effects of BPA exposure and epigenetic alterations was investigated in the rat model (Strakovsky et al., 2015). They found that BPA enhanced the differentiation of preadipocytes in rats in utero, associated with global DNA hypermethylation of the CPT1A gene. CPT1 deficiency is responsible for the accumulation of free fatty acids (Onuzulu, Rotimi, & Rotimi, 2019), and hypermethylation of CPT1A suggests its downregulation and therefore the accumulation of free fatty acids, which may lead to obesity. This finding is in agreement with some others, which have linked CPT1 deficiency to insulin resistance and obesity (Koves et al., 2008; Kuhajda & Ronnett, 2007). Epigenetic modifications were studied in cord blood of infants exposed prenatally to BPA (Junge et al., 2018), that may be linked to obesity progression. According to their epidemiological data, prenatal exposure of BPA altered the MEST promoter methylation, leading to increased risks of childhood obesity until about 6 years of age. These findings were further supported by an animal study, where hypomethylation of the MEST promoter was observed in mice exposed to BPA prenatally. MEST is a gene, coding for an enzyme of the α/β hydrolase family and altered expression of MEST has been associated with obesity (Kamei et al., 2007; Karbiener et al., 2015; Soubry et al., 2015), adipocyte size (Takahashi, Kamei, & Ezaki, 2005) and preadipocyte proliferation in mice and humans (Hossner, Yemm, Vierck, & Dodson, 1997). However, this hypomethylation was reversed upon maternal dietary supplementation with 300 µg/kg/day folate.

Defects in expression levels of IGF-2 have been associated with the malfunctioning of β cells and inadequate insulin production (Calderari et al., 2007; Devedjian et al., 2000; Serradas et al., 2002). Interestingly, these studies suggest that male offspring exposed to prenatal BPA were affected more with impairment in pancreatic function and insulin tolerance than females. This finding suggests that estrogen shows a protective role against insulin resistance and diabetes in females, which indicates that the prenatal effects of BPA may be sex-specific. Apart from being sex-specific, few studies have attempted to measure the tissue-specificity of prenatal exposure to BPA. In one such study, liver BPA was associated with markers of global methylation such as long interspersed nuclear element-1 (LINE-1) (Faulk et al., 2015). A follow-up study found links between BPA and repetitive DNA elements, including LINE-1 (Faulk et al., 2016). These results suggest that repetitive DNA elements, markers of global methylation are associated with prenatal BPA exposure in a dose- and tissue-specific manner. Very few studies have also investigated the effects of prenatal BPA exposure on histone methylation. Mice exposed to BPA prenatally showed increased expression of Enhancer of Zeste Homolog 2 (EZH2), a histone methyltransferase enzyme, which is also an epigenetic modifier for breast cancers (Doherty, Bromer, Zhou, Aldad, & Taylor, 2010). These studies affirm that adversity in epigenetic changes is targeted by the exposure of these EDCs.

1.5 Prenatal BPA exposure and its impact on functional miRNAs targets

In recent years, microRNAs (miRNAs) have been widely recognized as key mediators in the epigenetic control of gene expression, that act post-transcriptionally to suppress
miRNAs are short non-coding RNAs and play a crucial role in many fundamental cellular processes, including embryonic development, proliferation and apoptosis (Lee et al., 2004; Vaucheret, Vazquez, Crete, & Bartel, 2004). The biogenesis of miRNA involves the formation of hairpin precursors from larger transcripts, and these precursors serve as substrates for Drosha and Dicer, members of the RNase III enzyme family, to generate mature 20–22 nucleotide single-stranded miRNAs (Lee et al., 2003). A single miRNA can target hundreds of genes and small changes in specific miRNA levels may have multiple downstream effects on cellular functions (Sabry et al., 2019).

Estrogen signaling is believed to be a strong modulator of miRNA biogenesis (Klinge, 2009). Thus, as an estrogen mimic, BPA is likely to interfere with the expression of multiple miRNAs. However, BPA-mediated effects of miRNAs in early-stage development have not yet been widely studied. Prenatal exposure of BPA has been found to be associated with changes in miRNA expression levels (Cameron, Craig, & Trudeau, 2016; Klinge, 2015). In an informative study, Veiga-Lopez et al. showed that in utero exposure to BPA (0.5 mg/kg/day) in 2–3 year-old ewes resulted in upregulation of several miRNAs. Among the upregulated miRNAs, miR-217 and miR-608 had the highest upregulation. miR-217 has been implicated in premature senescence induction in endothelial cells, and miR-608 has been implicated in cell cycle arrest and cell survival. They also found that miR582-5p, miR-524-5p and miR-605 were the most down-regulated miRNAs. mRNA targets for these downregulated miRNAs are not known yet. However, it is believed that these miRNAs regulate the expression of the Sry-related HMG box (SOX) genes, which are essential for sex determination and development of the embryo. (Veiga-Lopez, Luense, Christenson, & Padmanabhan, 2013).

1.6 Plastic compounds and their effects on early placentation

Placental development depends on the invasive properties of the first-trimester trophoblast, which is ultimately derived from the outer trophectoderm layer of the blastocyst (Moser & Huppertz, 2017). Because of its profound effect on caliber and vessel-wall composition, this invasion is important to ensure adequate maternal blood supply to the placenta. This is exemplified by defects in trophoblast invasion and blood flow in pregnancy complications such as preeclampsia. Invasive trophoblasts of the human placenta are critically involved in successful pregnancy outcomes. These trophoblasts remodel the uterine spiral arteries to increase blood flow and oxygen delivery to the placenta and the developing fetus. This invasive behavior of trophoblasts follows a precise chronology of vascular events during the first trimester of gestation. The development of a placental vascular network is essential for the growth and maintenance of the developing embryo (Basak & Duttaroy, 2013; Chaiworapongs, et al., 2011; Chung et al., 2000). Defective invasion of trophoblasts in the uterine spiral arteries is directly involved in pre-eclampsia, a major and common complication of human pregnancy with serious fetal and maternal consequences. It is temporally restricted to early pregnancy, and it is spatially confined to the endometrium, the first-third of the myometrium, and the associated spiral arterioles. Early stages of spiral artery remodeling mimic angiogenesis and therefore remain critical for the early placentation process. Understanding of EDC exposures on the development and function of the placenta such as steroidogenesis, spiral artery remodeling, implantation and cellular invasion, fusion, and proliferation may reveal the pathogenesis of pregnancy complications and causalities of congenital disabilities (Gingrich, Ticiani, & Veiga-Lopez, 2020).

1.7 Fetal development and maternal health: Effects of early exposure of EDCs

Fetal growth is regulated by a complex interaction of maternal, placental, and fetal factors. Fetal growth is largely influenced by endocrine factors and nutritional excess or deficiency that determines important variations (Sferruzzi-Perri, Vaughan, Forhead, & Fowden, 2013). EDC exposures in pregnancy have been associated with changes in the gestational endocrine milieu, including altered levels of sex steroids (Johns et al., 2015; Sathyanarayana, Barrett, Butts, Wang, & Swan, 2014). There is compelling evidence that EDCs such as BPA modulate the immune system and alter the inflammatory cytokine milieu to favor a pro-inflammatory state (Dietert, 2012; Ferguson, Loch-Caruso, & Meeker, 2011; Song et al., 2017). Importantly, aberrant maternal inflammatory pathways have been linked to adverse pregnancy outcomes, including pregnancy loss, preterm labor, preeclampsia, and fetal growth restriction. Epidemiologic and animal studies indicate that such alterations induced in the maternal environment by EDCs may alter the developmental trajectory of the developing fetus via epigenetic modifications (Walker, 2016).

During pregnancy, fetal levels of thyroid hormones are dependent on maternal placental transport, and their physiological level is crucial for normal fetal neurodevelopment.
Exposure to EDCs during critical periods of development, such as early placentation and fetoplacental growth, may have consequences. Some epidemiological studies have reported the correlation between prenatal exposure to EDCs and infant birth outcomes, but the results of these epidemiological studies are contradictory. Many investigators have explored the relationship between EDC exposure and birth weight (Lenters et al., 2016). Lenters et al. examined 17 chemicals (six phthalates, eight perfluoroalkyl substances (PFAS), two PCBs and one oral contraceptive pill (OCP) using Elastic Net Regression analyses highlighting previously unknown relationships between four of these EDCs and birth weight. Two phthalate metabolites (MEHHP, MOiNP), perfluorooctanoic acid (PFOA), and p,p’-dichlorodiphenyl dichloroethylene (p,p’-DDE) were most consistently predictive of term birth weight. A meta-analysis conducted on European birth cohorts, examining occupational EDC exposures using a job-exposure matrix, found that pregnant women exposed to more than one EDC class were more likely to have a low birth weight infant (Birks et al., 2016). There is also sufficient evidence that increased PFAS, especially Perfluorooctanoic acid (PFOA), exposure is associated with low birth weight, whereas mixed results are reported for other EDCs and birth weight (Birks et al., 2016; Lenters et al., 2016). Similarly, inconsistent associations exist for phthalates and BPA (Philippat et al., 2012; Wolff et al., 2008; Zhang et al., 2009), OCPs (Lenters et al., 2016) and PBDEs (Lignell et al., 2013; Serme-Gbedo, Abdelouahab, Pasquier, Cohen, & Takser, 2016). Several studies predicted that exposure to the main EDCs, such as BPA, Persistent organic pollutants (POPs) and PBDEs during intrauterine growth has an impact on fetal growth.

Different EDCs were found in the placenta, and their concentration could be associated with fetal growth restriction, thyroid dysfunction, and neurological disorders (Yang, Song, & Lim, 2019). Phthalates not only cross the fetoplacental barrier but disrupt placentation growth and development in pregnant mice (Zong et al., 2015). Thyroid hormones are among the key regulators of placentation development, and their actions are mainly mediated by the thyroid hormone receptors (THRs) encoded by the Thrα1 and Thrβ1 genes. In animal models, phthalate exposure downregulates both Thrα1 and Thrβ1 genes and inhibits nuclear translocation in the placenta (Yu et al., 2018). Di-(2-ethylhexyl) phthalate was reported to disrupt homeostasis of thyroid function (Ardeshirylajimi, Golchin, Khojasteh, & Bandehpour, 2018) and thyroid hormones (THRs) in pregnant women and fetuses, and affect placentation TH transport (Du et al., 2020). Furthermore, exposure to PBDEs modifies the placental content of IGF-1 (Xu et al., 2013).

1.8 Effects of plastic derived EDCs on fetal programming of adult disease

The early development stage is the most susceptible window for development and genome programming. The critical steps of the events for human birth lie between the transitions from spermatogenesis, fertilized egg and then the fully formed fetus. These EDCs control the processes of epigenetic inheritance of adult-onset diseases by modulating the epimutations of DNA methylation in reproductive cells (Basak et al., 2018; Li et al., 2014; Ma et al., 2013; Susiarjo, Sasson, Mesaros, & Bartolomei, 2013; Ye et al., 2018). Data are emerging from in vitro and in vivo studies about these plastics containing EDCs and these affect the process of placentation since pregnant women and unborn fetus are often exposed to these contaminants during the preconception to the gestational periods. Impaired placentation, that ultimately influences fetus outcome, is the center of many developmental disorders and contributes as an independent risk factor for adult chronic diseases. The long-term adverse health effects of these substances contained in plastics makes it even more imperative to measure the effects of endocrine-disrupting chemicals such as bisphenols and its substitute. Early exposure of BPA even at a low level in laboratory animals resulted in numerous developmental abnormalities and chronic diseases later in life (Braun, 2017; Caporossi & Papaleo, 2017; Ehrlich et al., 2016). In the United States, exposure to BPA was reported as high as 96% of pregnant women when measured in placental perfused model with BPA (10 ng/ml) (Balakrishnan, Henare, Thorstensen, Ponnampalam, & Mitchell, 2010). Human placentas (assayed at term) convert BPA into its conjugate and thereby protect the fetus from adverse effects of the xenoestrogens. Conjugations of BPA escape estrogenicity in vitro. Data show that only negligible amounts of BPA become conjugated in the placenta indicating that the fetus is exposed to free BPA. The previous study demonstrated the ability of the placenta to conjugate BPA using the placental perfusion model of human term placentas. Placentas strongly express ERR gamma (estrogen-related receptor gamma) (Takeda et al., 2009). With a high level of free BPA in the placenta, BPA may accumulate in the placenta by binding ERR gamma. Alteration in the level of ERR gamma after BPA exposure could be an essential parameter to measure (Pjanić, 2017). BPA can modulate gene expression with direct as well as trans-generational effects by epigenetic modification of DNA methylation, histone modification, and/or production of non-coding RNA (Ma et al., 2013).

Prenatal BPA exposure leads to sex-specific programming of neonatal growth. In a study where fetal organogenesis and fetal/postnatal growth trajectory were measured in sheep after exposing BPA subcutaneously from 30 to
90 days of gestation (term 147 days), BPA accumulation was higher in a male fetus as compared to the female fetus (Vyas et al., 2019). BPA-treated male fetuses were heavier than BPA-treated female fetuses. However, this sex difference was absent in the control group. At the organ level, liver weight was reduced in prenatal BPA-treated female fetuses, while heart and thyroid gland weights were increased in BPA-treated male fetuses relative to their sex-matched control groups. Males grew slower during the early postnatal period and caught up later. Females, in contrast, demonstrated the opposite growth trend. The large-animal model indicates that gestational exposure to BPA at levels detected in humans can program metabolic disruptions that are independent of postnatal obesity, leading to insulin resistance (Vega-Lopez et al., 2016). Pregnant mice.

Maternal thyroid hormone plays a vital role in maintaining pregnancy. Studies on zebrafish models show that parental exposure to BPS disrupted thyroid hormone levels not only in the parental generation but also in the F1 generation (Wei et al., 2018). More studies on BPS are required to understand the mechanism of its effect on this system after human exposure.

Fetal growth restriction, reflecting an adverse intrauterine environment, is associated with a substantially increased risk of metabolic, cardiovascular, and behavioral disorders in adult life, a phenomenon called developmental programming (Barker, 2004; Cottrell, Holmes, Livingstone, Kenyon, & Seckl, 2012). Maternal exposure to EDCs reduces fetal growth and causes persisting abnormalities in adult offspring via different mechanisms such as through glucocorticoids. The effects of EDC exposure on glucocorticoids and placental 11β-HSD2 have been studied (Cottrell et al., 2012). Placental 11β-HSD2 deficiency acts via distinct processes to retard fetal growth (Bertram, Trowern, Copin, Jackson, & Whorwood, 2001). BPA is an inhibitor for both 11β-HSD1 and 11β-HSD2, with selectivity to the type I enzyme (Guo et al., 2012). Glucocorticoids, although critical in fetal development for cellular differentiation and organ maturation, are deleterious in excess, resulting in reduced fetal growth and causing the programming of adult hypertension, glucose intolerance, and psychological disturbances (Cottrell & Seckl, 2009). The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyzes the inactivation of cortisol and corticosterone to inert cortisone and 11-dehydrocorticosterone (11-DHC), respectively, and is highly expressed in the placenta, where it is proposed to protect the developing fetus from the deleterious effects of excess maternal glucocorticoids (Bertram et al., 2001). It has been suggested that a reduction in the expression or activity of placental 11β-HSD2, by leading to increased trans-placental passage of active glucocorticoids, reduces fetal growth. In support of this notion, in human and rodent pregnancy, fetal weight is correlated with 11β-HSD2 activity (Murphy et al., 2002).
CONCLUSIONS

In recent years several studies highlighted a relationship between exposure to EDCs, development of the embryo, feto-placental growth, and fetal outcome and negative consequences to the state of health of offspring. EDC exposure on the early developmental stages and subsequent effects on pregnancy complications and fetal outcomes is postulated in Figure 1. International scientific societies, therefore, have recommended the implementation of all possible preventive measures through specific policies and education of health personnel and of the general population with particular emphasis on pregnant women. Despite this, one cannot ignore the fact that the studies on the relationships between EDCs and the fetal outcome often yielded inconsistent results or did not show any adverse changes in humans. Due to the complexity in designing a study to demonstrate a more precise causal-effect relationship between EDCs and embryo outcomes, further research and new scientific approaches are needed. In order to be able to define in more detail the relationship between exposure to EDCs during embryonic and fetal life and the consequences on the development of the fetus and postnatal health, we still need well designed longitudinal research using “omics” technology. As highlighted in the present review, EDCs can impact several stages of human development. Alterations in these pathways in early life can induce persistent effects on later appearing phenotypes and increase disease risks.

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CONFLICT OF INTEREST

All authors report no conflict of interest.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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