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Killing two birds with one stone: Pregnancy is a sensitive window for endocrine effects on both the mother and the fetus

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ABSTRACT

Pregnancy is a complex process requiring tremendous physiological changes in the mother in order to fulfill the needs of the growing fetus, and to give birth, expel the placenta and nurse the newborn. These physiological modifications are accompanied with psychological changes, as well as with variations in habits and behaviors. As a result, this period of life is considered as a sensitive window as impaired functional and physiological changes in the mother can have short- and long-term impacts on her health. In addition, dysregulation of the placenta and of mechanisms governing placentation have been linked to chronic diseases later-on in life for the fetus, in a concept known as the Developmental Origin of Health and Diseases (DOHaD). This concept stipulates that any change in the environment during the pre-conception and perinatal (*in utero life* and neonatal) period to puberty, can be "imprinted" in the organism, thereby impacting the health and risk of chronic diseases later in life. Pregnancy is a succession of events that is regulated, in large part, by hormones and growth factors. Therefore, small changes in hormonal balance can have important effects on both the mother and the developing fetus. An increasing number of studies demonstrate that exposure to endocrine disrupting compounds (EDCs) affect both the mother and the fetus giving rise to growing concerns surrounding these exposures. This review will give an overview of changes that happen during pregnancy with respect to the mother, the placenta, and the fetus, and of the current literature regarding the effects of EDCs during this specific sensitive window of exposure.

1. Introduction

Endocrine disrupting compounds (EDCs) are defined by the World Health Organization (WHO) as exogenous substances, or mixtures of substances, that alter the function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its

Abbreviations: **AHR**, aryl hydrocarbon receptor; **As**, arsenic; **BFR**, brominated flame retardants; **BPA**, bisphenol A; **Cd**, cadmium; **Co**, cobalt; **Cr**, chromium; **CRP**, C-reactive protein; **DDE**, dichlorodiphenyldichloroethylene; **DDT**, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane; **DEHP**, di(2-ethylhexyl)phthalate; **DES**, diethylstilbestrol; **DINP**, diisononyl-phthalate; **DMBA**, dimethyl-Benz(a)anthracene; **DNMT1**, DNA (cytosine-5)-methyltransferase 1; **DOHaD**, Developmental Origin of Health and Diseases; **EDCs**, endocrine disrupting compounds; **EGF**, epidermal growth factor; **EGFR**, epidermal growth factor receptor; **ER**, estrogen receptor; **ERK**, extracellular signal-regulated kinases; **FSH**, follicle-stimulating hormone; **GBH**, glyphosate-based herbicides; **GDM**, gestational diabetes mellitus; **GPx**, glutathione peroxidase; **HBCDD**, hexabromocyclododecane; **hCG**, human chorionic gonadotropin; **Hg**, mercury; **IGF2**, insulin growth factor-2; **IFNγ**, interferon-γ; **IUGR**, intrauterine growth restriction; **IVF**, vitro fertilization; **LH**, luteinizing hormone; **MBP**, monobutyl phthalate; **MBzP**, monobenzyl phthalate; **MCNP**, monocarboxyisononly phthalate; **MCOP**, monocarboxyoctyl phthalate; **MCP-1**, monocyte chemoattractant protein-1; **MEHP**, mono-2-ethylhexyl phthalate; **MEP**, monoethyl phthalate; **Mn**, manganese; **MXC**, methoxychlor; **Ni**, nickel; **NMU**, N-Nitroso-N-methylurea; **OP**, organophosphate; **OPFRs**, organophosphate flame retardants; **PABC**, pregnancy-associated breast cancer; **PAHs**, aromatic hydrocarbons; **Pb**, lead; **PBBs**, polybrominated biphenyls; **PBDEs**, polybrominated diphenyl ethers; **PCBs**, polychlorinated biphenyls; **PCDFs**, polychlorinated dibenzofurans; **PCOS**, polycystic ovarian syndrome; **PFCs**, perfluorinated compounds; **PFOA**, perfluorooctanoic acid; PFHxS, perfluorohexane sulfonate; **PFOSA**, perfluorooctanesulfonamide; **PL**, placental lactogens; **PPARγ**, peroxisome proliferator-activated receptor γ; **PR**, progesterone receptor; **PrlR**, prolactin receptor; **RXR**, retinoid X receptor; **Sb**, antimony; **Se**, selenium; **Sn**, tin; **sncRNA**, small non-coding RNA; **SOD**, superoxide dismutase; **TBBPA**, tetrabromobisphenol A; **TBT**, organotin tributyltin; **TCDD**, 2,3,7,8-tetrachlorodibenzo-p-dioxin; **TDCIPP**, tris(1,3-dichloroisopropyl)phosphate; **TNFα**, tumor necrosis factor-α; **TR**, thyroids receptors; **V**, vanadium.

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progeny, or (sub)populations (IPCS, 2002). The endocrine system has a crucial role in growth, development, reproduction, energy balance, metabolism, and body weight regulation through the secretion of hormones that interact with their specific receptors located in various tissues. Any dysregulation of the endocrine system, including by EDCs, can thus have an important impact on health and lead to diseases. The Endocrine Disruption Exchange database (https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list) listed 1482 chemicals with endocrine-disrupting potential in 2020, highlighting the importance of research on this issue. Importantly, many of these EDCs have been detected in pregnant women, as reported by the Maternal-Infant Research on Environment Chemicals (MIREC, Canada) study and the National Health and Nutrition Examination Survey (NHANES, US) (Lee et al., 2017; Woodruff et al., 2011).

Given the complexity of pregnancy, it is no surprise that most of the organs of the mother are impacted by pregnancy. Physiologically, in addition to changes that occur in the reproductive system and mammary gland development, changes can also be observed in metabolism, the endocrine system, and the immune system. Psychologically, alterations in the mother are triggered to promote maternal nursing behavior. For the growing fetus, development, organogenesis, and tissue differentiation are regulated by tightly orchestrated cellular, biochemical, and molecular events. Embryogenesis also involves early programming within tissues that will determine functions and behavior throughout life. These changes are progressive, being modulated by the needs of both the mother and the growing fetus. An important number of hormones, neuropeptides and growth factors are involved during the pregnancy period and detailed actions of each of these have been previously reviewed (Fig. 1) (Tal et al., 2000). Failure to adapt or dysregulation of these factors can lead to significant consequences for the mother that can reverberate on the fetus. Importantly, the high number of critical cellular messengers are all potential targets for EDCs, as EDCs can affect the endocrine system by a multitude of mechanisms (Table 1) (La Merrill et al., 2020), rendering pregnancy a particular vulnerable window of susceptibility for both the mother and the baby-to-come. Understanding the roles of these messengers in the mother's physiology is crucial to understand how EDCs can impact pregnancy.

Table 1
Proposed mechanisms of action of common endocrine disruptors.

EDC	Proposed mechanism of action	Reference
BPA, BPFA and BPS	Estrogenic activity; Anti-androgenic activity and modulation of glucocorticoid, peroxisome proliferator- activated receptor and thyroid systems	Laws et al., 2000; Lee et al., 2003, Roelofs et al., 2015; Rubin, 2011; Acevedo et al. (2013)
DES	Estrogen receptor agonist and anti-androgenic action	Korach et al., 1978; Herbst et al., 1999; Veurink et al., 2005; Titus-Ernstoff et al. (2001); Boylan (1978)
Phthalates	Estrogenic, anti-estrogenic, anti-androgenic and metabolic actions	Harris and Sumpter, 2001; Chen et al., 2014, Desvergne et al., 2009
Lindane	Interference with aryl hydrocarbon receptor action	Bandiera et al., 1997
Atrazine	Increases aromatase expression	Sanderson et al. (2001); Enoch et al. (2007)
TCDD	Aryl hydrocarbon receptor binding	Al-Saleh et al., 2013; Drwal et al., 2019; Brown et al. (1998)
PFOA	Estrogenic activity	Buck et al., 2011
Unconventional oil and gas mixture	Aryl hydrocarbon receptor binding; inhibit estrogen receptor action	Lee et al. (2017); Sapouckey et al. (2018)

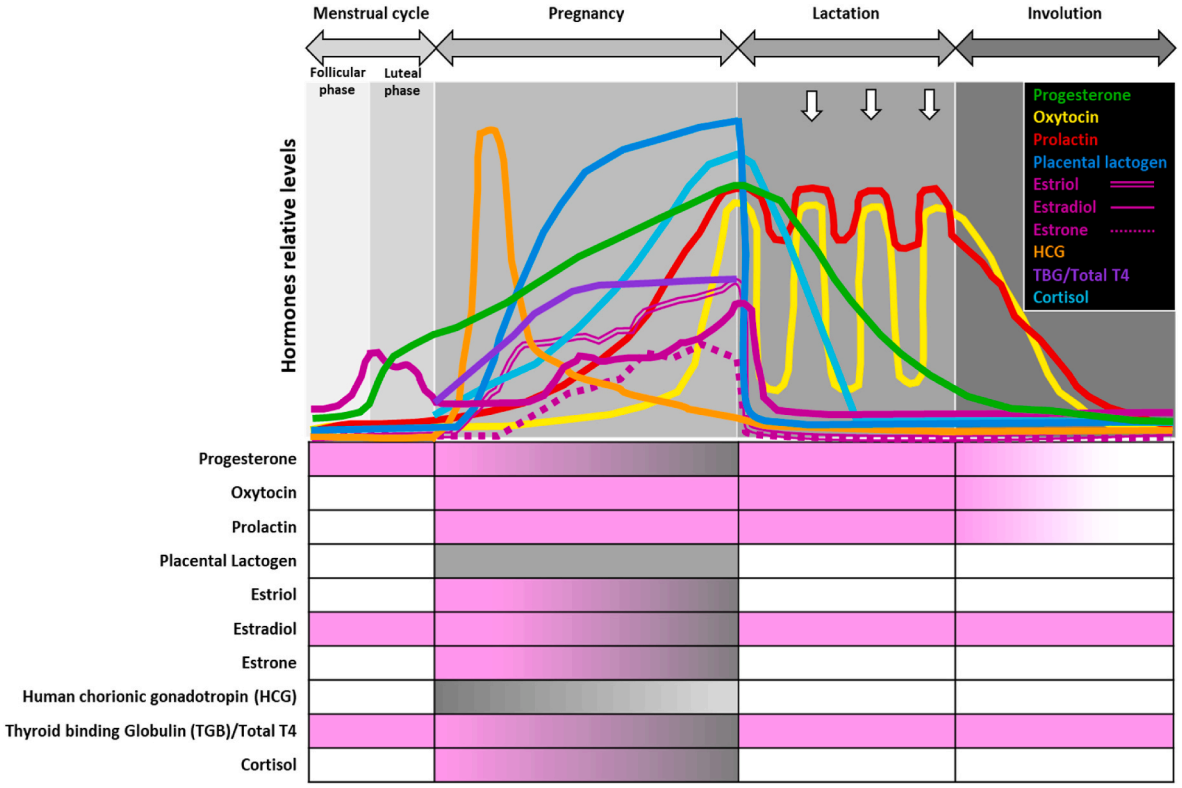

Fig. 1. Relative levels of hormones in women. In the table, pink represents hormones that are mainly produced by the mother, while gray represents hormones that are produced by the fetus/placenta axis. White arrows represent suckling of the offspring. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

1.1. Maternal programing: from a woman a to a mother-to-be

1.1.1. Increased exposure during pregnancy through food and cosmetics

Humans are continuously exposed to EDCs, whether at work or in their living environment (Lohmann et al., 2007). EDCs can be found in many everyday products, including plastic bottles and food containers, detergents, furniture, toys, and cosmetics, to name a few. However, exposure via food and drinking water is considered to be the main route of exposure for many EDCs (Monneret, 2017). For instance, while humans can be exposed to bisphenol A (BPA), a well-known and studied EDC, through wastewater, air, dust, and soil (Valentino et al., 2016), ingestion of BPA from food or water accounts for 90–99% of exposure in adults and children (Geens et al., 2012; Huang et al., 2017; Russo et al., 2019). Importantly, physiologic changes that occur in the mother and the growing fetus during pregnancy accentuate the demand for energy, resulting in increased food and water intake. Thus, as a result, one can assume that exposure to EDCs will be increased during pregnancy. The estimated overall daily intake of BPA in adults is 30.76 ng/kg bw/day, while a significantly higher daily intake, corresponding to 42.03 ng/kg bw/day, has been observed in pregnant women, supporting a higher exposure to BPA through increased food and water consumption (Huang et al., 2017). It is also known that detectable levels of organophosphate (OP) pesticides, some of which are other known EDCs, are found in 50% of fruits, vegetables, and cereals (European Comission, 2008). An analysis of surveillance and food epidemiology data has shown that foods of animal origin are major sources of phthalates, another subgroup of compounds that are often used as plasticizers or softeners in industrial production, in part because they are slightly lipophilic and can bioaccumulate in foods containing fat (Pacyga et al., 2019; Serrano et al., 2014). Similarly, the main routes of exposure to polycyclic aromatic hydrocarbons (PAHs), which are other known EDCs, for the general population are from eating grilled food, breathing air from an open fireplace, or from smoking (Guo et al., 2021). Therefore, both the type and the quantity of food consumed by pregnant women can influence their exposure.

The main source of exposure of the general population to perfluorinated compounds (PFCs) is also food (Tittlemier et al., 2007), while water is an important source in contaminated areas, for example in communities close to production facilities (Bjorklund et al., 2009; Hoffman et al., 2011; Shoeib et al., 2004, 2011). These products have the property of repelling water, fats, and dust; they are thus useful in the kitchen, including non-stick coatings on utensils and cookware, kitchenware and food packaging (e.g.: bags of microwave popcorn), which are directly in contact with the food. These compounds are resistant to degradation and therefore remain in the environment for a very long time. They also persist in the human body due to renal tubular reabsorption and their binding to proteins (Genuis et al., 2010). Recent national biomonitoring surveys in the United States (Centers for Disease Control and Prevention, 2009) and Canada (Health Canada, 2010, 2013) showed that almost all participants had low levels of PFCs in their blood (Velez et al., 2015b). They have also been detected in umbilical cord blood and breast milk (Arbuckle et al., 2013; Fromme et al., 2010), confirming the exposure of pregnant women. Finally, cadmium (Cd), like other metals including mercury (Hg) and lead (Pb), has estrogenic effects at extremely low doses. A study on the exposure of pregnant women and fetuses to metals in Canada (MIREC) found that over 90% of women had detectable blood levels of Pb, Cd, manganese (Mn) and Hg during pregnancy; in the cord blood, although Cd was rarely detected, Pb, Mn and Hg were present in most of the samples (Arbuckle et al., 2016b). Together, these data suggest that increased water and food consumption during pregnancy will likely enhance a woman's exposure to EDCs, and that avoiding certain food types could reduce that exposure.

Another important source of exposure to EDCs in women is cosmetics. Accordingly, exposure to parabens is more common in women than in men likely due to their presence in many cosmetic products, which generally have a higher use in women (Cabaleiro et al., 2014; Guo et al., 2014). Parabens are found in 80% of personal care products as they are commonly used to prevent the growth of bacteria and mold in cosmetics, perfumes, and other products. Applied to the skin, parabens are easily absorbed and thus enter the body, making dermal absorption the main route of exposure. During pregnancy, parabens were present in 100% of maternal urine samples examined (Pycke et al., 2015). In a study conducted in France, most pregnant women used cosmetics such as foundation, mascara, eye pencil and shadow, make-up remover and nail polish during their pregnancy (Marie et al., 2016).

Phthalates, in addition to their use as plasticizers or softeners, are also used as perfume stabilizers in many cosmetics and other scented products such as perfumes, styling and personal care products. They can also easily penetrate the skin, thus resulting in potential significant exposure (Lyche et al., 2009). Metabolites of phthalates (Table 2) have been measured in the urine of 50% of women at various times during pregnancy, supporting exposure to phthalates in this population (Arbuckle et al., 2016a). Similarly, triclosan, a synthetic product that has been used for over 40 years as an anti-bacterial, antifungal, antiviral, anti-tartar, and preservative, is commonly found in cosmetic and personal care products, such as soap, toothpaste, mouthwash, moisturizing lotion, shaving cream, deodorant and make-up removing cleaning sponges and towels. Triclosan can therefore be absorbed through the skin, mouth and intestine or by inhalation. In humans, triclosan is found in blood, urine and even breast milk. Triclosan breaks down into toxic, carcinogenic, bioaccumulative and persistent compounds (Weatherly and Gosse, 2017). In one study, triclosan and triclocarban (metabolite) were measured in maternal third trimester urine samples, and detected in all study participants (Pycke et al., 2014).

In conclusion, given that many EDCs are present in food and personal care products, and that pregnancy is a highly active anabolic state, one can assume that exposure would be greater in pregnant women than in non-pregnant women (Biesterbos et al., 2013) and indirectly lead to exposure in the growing embryo and fetus. Special care should therefore be taken to limit exposure to the various EDCs described above in women of childbearing age and pregnant women.

1.1.2. Changes in habits during pregnancy and women's awareness

Several organizations around the world have mobilized to develop information documents or propose recommendations to warn pregnant women of the risks associated with exposure to EDCs, including the French medical profession (Rouillon et al., 2017) and various American and Canadian medical associations (Barrett et al., 2014). For example, recommendations have been made not to use hair dye and to use fewer cosmetics and lotions during pregnancy. Other examples include the recommendation of avoiding the use of certain types of plastics, reducing the consumption of canned products or other more likely contaminated food. Thus, the focus is on encouraging pregnant women

Table 2
Phthalates and their monoester metabolites.

Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)
Di-n-butyl phthalate (DBP)	Mono-n-butyl phthalate (MBP)
	Mono (3-carboxypropyl) phthalate (MCPP)
Di-isobutyl phthalate (DiBP)	Mono-isobutyl phthalate (MiBP)
Benzylbutyl phthalate (BzBP)	Monobenzyl phthalate (MBzP)
Di-2-ethylhexyl phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP)
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)
Di-n-octyl phthalate (DOP)	Mono-(3-carboxypropyl) phthalate (MCPP)
Di-isononyl phthalate (DiNP)	Mono-isononyl phthalate (MNP)
	Mono-(carboxyoctyl) phthalate (MCOP)
Di-isodecyl phthalate (DiDP)	Mono-(carboxy-isononyl) phthalate (MCNP)

Source: https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/phthte_g_met.pdf

to make healthy choices regarding their exposure to EDCs, as they would more naturally do for their physical activities and their diet.

Interestingly, answers to current questions regarding women's knowledge about EDCs and whether they change their eating habits and overall behaviors when they become pregnant to decrease exposure to EDCs remain sometimes surprising. For example, in a study on the knowledge of EDCs by pregnant women, more than half of the women participants had never heard of EDCs (Rouillon et al., 2017). For women who had heard of EDCs, they associated them primarily with pesticides, BPA, and parabens. Despite this, the number of EDCs they could name ranged from 0 to 4. In the same study, 40.3% of women were already or intended to reduce their utilization of industrial and chemical products during pregnancy. They were inclined to reduce the consumption of industrial products, to use glass containers, to reduce the use of plastic containers, not to heat food in plastic containers in a microwave oven and to reduce consumption of canned food. In a French study including women of childbearing age, women who cited plastic as a source of exposure to EDCs used plastic containers as much as women who did not (Jacquey, 2016), suggesting that even though women are aware of the risk, they do not always take the necessary steps to avoid it. The same behavior is noted with respect to the use of cosmetics and personal care products, with only 13.0% of the women questioned planning on reducing the use of cosmetics, even though 91.3% of the women admitted that cosmetics were sources of exposure to EDCs (Marie et al., 2016). The same observation was made in a study (Barrett et al., 2014), while conflicting results were found in which the use of cosmetics decreased with the advancement of pregnancy and after childbirth (Lang et al., 2016). With respect to potential barriers to behavioral change towards organic food or cosmetics, women cited the price (48.9%), mistrust of the label (11.3%), the low variety (10.0%), habits (7.0%) and accessibility (5.6%) (Rouillon et al., 2017). Importantly, changes in women's habits during pregnancy are dependent on their place of birth, culture, socio-economic status, and level of education (Barrett et al., 2014; Jacquey, 2016; Lang et al., 2016; Marie et al., 2016; Rouillon et al., 2017).

1.1.3. Changes in the reproductive organs and in the mammary gland

Tightly orchestrated events happen within the different organs of the mother's reproductive system to initiate and establish a healthy pregnancy, and then for successful delivery and nursing of the newborn. First the establishment of a receptive endometrium, implantation, and maintenance of the early pregnancy, which involves both the uterus and the ovaries, and the preparation of the mammary gland for lactation are required. These systems both respond to and signal through hormones, growth factors and neuropeptides that result in physiologic alterations (Fig. 1). Any dysregulation in this cascade can lead to abnormal pregnancy, impact the growing fetus, result in abortion and reverberate on the offspring's health later on.

One of the major roles of the ovaries is to produce mature oocytes through folliculogenesis that can be fertilized. Folliculogenesis requires precise variations in estrogens, progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which can all be affected by EDCs and lead to fertility issues. For a more complete description of the effects of EDCs on folliculogenesis, the reader is referred to Delbes et al. in this special issue (Delbes et al., 2021). Following ovulation, the cells from the theca surrounding the oocyte develop into the corpus luteum. This large endocrine gland produces progesterone, as well as estrogens in lower quantity, to prime the endometrium of the uterus for implantation. In the absence of pregnancy, this structure will undergo degradation through luteolysis and form the corpus albicans. However, human chorionic gonadotropin (hCG), produced early in pregnancy by the syncytiotrophoblast, will maintain the structure, and thus sustain progesterone secretion. In early pregnancy, progesterone is considered to be the most important hormone as it can maintain pregnancy alone (Csapo et al., 1973; Kumar and Magon, 2012; Tal et al., 2000). Decreased levels of progesterone induced by removal of the corpus luteum increases the risk of abortion (Csapo et al., 1973; Kumar and Magon, 2012; Tal et al., 2000). The placenta will take over the production of progesterone and estrogens after about 8 weeks of pregnancy in humans, leading to degeneration of the corpus luteum (Fig. 1).

In parallel, the uterus endometrium is constantly remodeled at each menstrual cycle mainly by the ovarian hormones. Estrogens and progesterone induce both physiological and functional changes in the endometrium to prepare for a potential pregnancy, going from a proliferative to a glandular secretory endometrium (Cunha et al., 2018a; Habiba et al., 2021; Kelleher et al., 2019) (Fig. 1). When implantation occurs, further physiological, functional, and molecular modifications happen to support the growing embryo. Progesterone is crucial to prevent premature contractions of the uterus by relaxing smooth muscle. Meanwhile estrogens initiate the uterine growth process in early pregnancy and the increase of blood flow in the uterus by having a vasodilatation effect (Cunha et al., 2018a, 2018b; Habiba et al., 2021; Kelleher et al., 2019).

The mammary gland is also influenced by the variations of ovarian and other circulating hormones. Mammary gland development begins during embryogenesis, but, unlike most organs, mainly occurs postnatally and is tightly regulated by hormones, growth factors and peptides. Pregnancy is an important stage of development for the mammary gland as it is during that period that the mammary gland undergoes alveologenesis and becomes functional, getting ready to nurse the offspring. During alveologenesis, the epithelium undergoes extensive cellular proliferation and differentiation that lead to the formation of the milk-producing functional units of the gland, the alveoli (or acini) (Brisken and Rajaram, 2006). Ovarian hormones estrogen and progesterone, pituitary prolactin, placental lactogens (PL) as well as thyroid hormones, among others, have been demonstrated to play crucial roles in this process. Progesterone signaling has been demonstrated to be crucial for both side branching and alveolar formation as in mice lacking the progesterone receptor (PR) alveologenesis does not occur (Aupperlee et al., 2009; Berryhill et al., 2016; Brisken and Ataca, 2015; Hewitt and Korach, 2000; Hilton et al., 2015; Hinck and Silberstein, 2005; Humphreys et al., 1997a, 1997b; Lydon et al., 1995, 1999; Macias and Hinck, 2012; Sternlicht, 2006). A similar phenotype was observed in mice lacking the prolactin receptor (PrlR), demonstrating that prolactin is required for alveoli proliferation and differentiation (Brisken, 2002; Gallego et al., 2001; Horseman, 1999; Miyoshi et al., 2001; Ormandy et al., 1997). Although the direct role of estrogens seems to be minimal at this stage (Bocchinfuso et al., 2000; Feng et al., 2007; Hewitt et al., 2002; Hewitt and Korach, 2000; Mehta et al., 2014; Mueller et al., 2002), it stimulates prolactin secretion by the anterior pituitary gland, and induces the expression of the PR and PrlR, thus contributing indirectly to alveologenesis. The role of thyroid hormones and receptors (TR) is not as clear, but it has been demonstrated that they potentiate milk production by acting on prolactin (Bhattacharjee and Vonderhaar, 1984; Campo Verde Arbocco et al., 2017; Capuco et al., 2008).

The pregnancy-related function, development and differentiation of the ovaries, the uterine endometrium and the mammary gland are thus interconnected, influencing each other mainly through hormonal signaling. In accordance, chemical or genetic dysregulation of signaling pathways controlled by these hormones and receptors can lead to infertility, miscarriage and lactation defects. While a considerable number of studies have evaluated the effects of various EDCs on the female reproductive system both in humans and animal models, fewer data are available regarding the effects of EDCs on the mother specifically during pregnancy.

1.1.3.1. Bisphenol a and diethylstilbestrol. Several studies have focused on the association between pregnancy-related outcomes and the well-known estrogenic compounds BPA and diethylstilbestrol (DES) (Table 1). As BPA's effects on ovarian morphology, steroidogenesis, folliculogenesis and overall pregnancy outcomes are well-documented,

and have been discussed in many reviews for both humans and animals (Kawa et al., 2021; Machtinger and Orvieto, 2014; Pivonello et al., 2020; Rattan and Flaws, 2019; Rattan et al., 2017; Richter et al., 2007; Ziv-Gal and Flaws, 2016), they will just briefly be described here, focusing on exposure during pregnancy and the consequences for the mother. In women, higher levels of BPA have been associated with lower fertility and preterm birth, and negatively associated with ovarian response, including peak estradiol levels, the number of oocytes retrieved and implantation failure, in women undergoing *in vitro* fertilization (IVF) treatment (Bloom et al., 2011; Caserta et al., 2013; Ehrlich et al., 2012a, 2012b; Fujimoto et al., 2011; Hanna et al., 2012; Kamalakaran et al., 2011; La Rocca et al., 2014; Mok-Lin et al., 2010; Wang et al., 2018; Zhang et al., 2021). Absence of effects were also reported in a number of studies (Buck Louis et al., 2014; Huang et al., 2019; Jukic et al., 2016; Minguez-Alarcon et al., 2015; Mínguez-Alarcón et al., 2019; Philips et al., 2018; Shen et al., 2020; Velez et al., 2015a; Yeum et al., 2019). Differences between those results could be linked with many factors, including concomitant exposure to other EDCs, age of the women and father-related factors. It has also been suggested that exposure to BPA could be linked with a reduction of the ovarian reserve or primary ovarian insufficiency (Czubacka et al., 2021; Özel et al., 2019; Park et al., 2021; Souter et al., 2013; Zhou et al., 2016). One study reported that BPA is associated with miscarriages (Sugiura-Ogasawara et al., 2005).

Similarly, in animal models, some studies, including some using high doses that are not representative of the human exposure, demonstrated that the number of litters, pups per litter, implantation sites and overall fertility were reduced upon exposure to BPA during gestation (Berger et al., 2007, 2008, 2010; Cabaton et al., 2011; Li et al., 2016; Moore-Ambriz et al., 2015; Pan et al., 2015; Tachibana et al., 2007; Xiao et al., 2011), while others did not find any effects (Avtandilyan et al., 2019; Kobayashi et al., 2010, 2012; Santamaria et al., 2016; Vigezzi et al., 2015; Xi et al., 2011). Here again, different parameters might explain the difference between the studies, including the age of the animals, the strain used, the dose and the mode and duration of exposure.

Although many studies have focused on defects in the offspring, exposure of millions of pregnant women around the world to DES has also resulted in pregnancy-related effects on the mothers. These women had enhanced premature labor, and increased risk of spontaneous abortion, preterm birth, and neonatal death (reviewed in Al Jishi and Sergi, 2017; Reed and Fenton, 2013; Bibbo et al., 1978; Colton et al., 1993; Dieckmann et al., 1953; Greenberg et al., 1984; Hadjimichael et al., 1984; Hilakivi-Clarke, 2014; Titus-Ernstoff et al., 2001). An increased risk for breast, endometrial and ovarian cancers was also found at follow up many years later (Beral, 1980; Beral and Colwell, 1980; Bibbo et al., 1978; Hadjimichael et al., 1984; Hoover et al., 1977; Vessey et al., 1983).

Like BPA, most of the studies of DES using animal models exposed during pregnancy focused on the effects on the offspring and only a few reported the effects on the dams. One study reported fewer litters, smaller litter size, smaller birth weight of the pups and impaired lactation in rats exposed to 0.1–100 ppm of DES through food during the entire pregnancy period or from day 13 of pregnancy; the effects were more prominent when dams were treated for the entire pregnancy and with higher doses (Kawaguchi et al., 2009). Delayed onset of labor, weight loss for the dams, smaller litter size and weight loss for the pups were also reported in other studies using prolonged or higher DES dose exposure (Boylan, 1978; Clevenger et al., 1991; Zimmerman et al., 1991). Generally, no effects on litter number and size or pups' weight were reported when lower doses and/or exposure duration were used (Boylan et al., 1983a, 1983b).

1.1.3.2. Phthalates. In women, exposure to phthalates has been associated with various reproductive and pregnancy-related defects that have been the subject of a few reviews (reviewed in Zarean et al., 2016; Jurewicz and Hanke, 2011; Marie et al., 2015). In brief, exposure to phthalates during pregnancy was associated with increased risk of pregnancy loss, preterm birth and/or shorter pregnancy duration (Adibi et al., 2009; Ferguson et al., 2014; Hoyer, 2001; Huang et al., 2014; Latini et al., 2003; Meeker et al., 2009; Weinberger et al., 2014; Whyatt et al., 2009; Wolff et al., 2008; Zhang et al., 2009). On the other hand, exposure to phthalates was suggestive of a shorter time to pregnancy (Velez et al., 2015a), or no effect on, or increased, gestational age (Huang et al., 2009; Suzuki et al., 2010; Wolff et al., 2008). There were some inconsistencies in other parameters, such as birth or placenta size (Mustieles et al., 2019; Philippat et al., 2012, 2019; Snijder et al., 2012; Wolff et al., 2008). Some of these discrepancies between results may come from the analyses of phthalates in human samples, including the type of phthalates or metabolites measured and the type of samples (cord blood, serum, urine …).

Accordingly, in animal models, the degree of effects observed varied between phthalate congeners. In a continuous breeding protocol using CD-1 mice, exposure to di-n-octyl phthalate did not cause any apparent defect in reproductive function, while exposure to di-n-propyl phthalate or di-n-pentyl phthalate reduced fertility (number of litters, of pups per litter, of live pups) (Heindel et al., 1989). DEHP, the most used, studied and potentially toxic phthalate, is associated with decreased fertility, fetal resorptions, decreased fetal weight and fetal malformation; the effects were more evident when high doses were administered during pregnancy in animal models, and were dependent on the time of administration (Agarwal et al., 1989; Li et al., 2012; Nikonorow et al., 1973; Schmidt et al., 2012; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Singh et al., 1972; Tomita et al., 1986). Some of these effects could be linked with ovarian dysfunctions (reviewed in Patel et al., 2015; Lovekamp-Swan and Davis, 2003; Brehm et al., 2018; Davis et al., 1994). No effects on number of litters or litter size were reported in other studies, in particular those focusing on the effects on offspring (Grande et al., 2006; Maranghi et al., 2010; Schmidt et al., 2012).

1.1.3.3. Pesticides and persistent organochlorines. Pesticides are a wide family of compounds, some having proven or suspected endocrine disruptive properties. An important number of studies have evaluated fertility of men working in agriculture, but fewer studies focused on women. Nevertheless, an increased risk of infertility and abortion in women has been associated with agricultural occupations and/or lifestyle factors (Arbuckle et al., 1999; Curtis et al., 1999; Fuortes et al., 1997; Greenlee et al., 2003; Smith et al., 1997). More specifically, DDT and its metabolites have been shown bind to the estrogen receptor (ER) and affect the estrogenic signaling by various ways (reviewed in Roy et al., 2009). These compounds can induce premature delivery in rabbits and sea lions, and are linked with preterm birth, spontaneous abortion, and decreased fertilization rate in human (Cioroiu et al., 2010; DeLong et al., 1973; Hart et al., 1971, 1972; Longnecker et al., 2001; Younglai et al., 2002). Exposure to methoxychlor (MXC), an estrogenic insecticide developed to replace DDT, during pregnancy dysregulates embryo transport rate and increases embryonic implantation loss in rats and mice (Cummings and Perreault, 1990; Hall et al., 1997). Degeneration of two-cell embryos was observed in female mice exposed to the pesticide lindane prior to or just after mating (Scascitelli and Pacchierotti, 2003). Another study showed that exposure to lindane in early pregnancy causes an absence of any implantation site, total resorption of fetuses when administered in mid-pregnancy, and perinatal death of the pups when administered in late pregnancy (Sircar and Lahiri, 1989).

Dioxins comprise many persistent pollutants, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), chlorinated dibenzodioxins, polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs). Members of this huge family of compounds are widely dispersed in the environment, and most of them have been demonstrated to have endocrine disruptive activity and to cause reproductive defects, including during pregnancy, and to have transgenerational effects

(reviewed in Viluksela and Pohjanvirta, 2019, and in Robaire et al., 2021). In humans, serum PCBs levels were associated with reduced fertility and lower weight at birth (Buck Louis et al., 2013; Chevrier et al., 2013; Law et al., 2005; Tsukimori et al., 2012; Yang et al., 2008). TCDD has well-known anti-estrogenic properties, induced in large part through its binding to the aryl hydrocarbon receptor (AHR), that can influence progesterone and prolactin signaling (reviewed in Safe et al., 2013; Safe, 1995). The accidental release of TCDD in Seveso in 1976, as well as some epidemiological studies in other populations, allowed for the observation of the effects of TCDD in women, for which an increased time to pregnancy and reduced fertility were observed (Eskenazi et al., 2010). Similar results were obtained in animal models; TCDD has been shown to affect steroidogenesis, ovulation, early embryo development, reduced body weight at birth, but also impaired lactation, due to both nursing behavior effects, and impaired mammary gland differentiation (Guo et al., 1999; Li et al., 1995a, 1995b; Moran et al., 2001; Takeda et al., 2020; Vorderstrasse et al., 2004).

More recently, concerns are being raised regarding the effects of glyphosate-based herbicides (GBH) on health. In rats exposed to paraquat, glyphosate-Roundup (RU) or both, it has been demonstrated that exposure to these pesticides during the first seven days of pregnancy decreases the weight of the ovaries, number of implanted sites and corpora lutea, and increases pre-implantation loss (Almeida et al., 2017). These defects were associated with increased oxidative stress and altered uterine histology. In mice exposed to 0.5% pure glyphosate or RU from day 1 to day 19 of pregnancy, a decrease in the female to male ratio was observed, as well as a decrease in ovarian weight (Ren et al., 2018). In humans, only a few studies evaluated the relationship between glyphosate levels in women and adverse pregnancy outcomes (Arbuckle et al., 2001; Curtis et al., 1999; Sanin et al., 2009; Sathyanarayana et al., 2010), and most of them found significant effects on the parameters measured. A negative correlation was found between glyphosate urine levels and shorter gestational length in 2018 (Parvez et al., 2018). An exposure to glyphosate was associated with higher risk for late spontaneous abortions (Arbuckle et al., 2001). Moreover, a recent study has demonstrated that GBH and RU alter the placental permeability and the fetal venous flow rate in a human placental ex vivo model (Simasotchi et al., 2021). Importantly, this study shows clearly that the RU formulants, which are declared inert by the company, alter the fetal-placental circulation and placental integrity according to time of exposure. Interestingly, the formulants, include polyoxyethanolamines, PAHs, and heavy metals, and could explain the toxicity of GBH and RU, as well as other pesticides that contain these compounds.

1.1.3.4. EDCs effects linked with hydraulic fracturing. The negative environmental consequences of hydraulic fracturing for the extraction of oil and natural gas are giving rise to increased attention to this process over the last few years, which has resulted in questions regarding impacts on wildlife and human health. Many chemicals used during the extraction process are EDCs (Bolden et al., 2018; Elliott et al., 2017; Tachachartvanich et al., 2020). Nagel's group has provided many data regarding the endocrine disruptive effects on surface water associated with oil and gas industry wastewater disposal sites, that were also discussed in several reviews (Balise et al., 2016, 2019a, 2019b; Kassotis et al., 2014, 2015a, 2015b, 2016a, 2016b, 2016c, 2018, 2020; Nagel et al., 2020; Sapouckey et al., 2018; Webb et al., 2014). As is the case for other EDCs, the adverse effects of chemicals used in oil and natural gas extraction during pregnancy and for pregnancy outcomes in humans are poorly known. From the few studies looking at pregnancy-related outcomes, associations were found between exposure to oil and gas industry activities and preterm birth, miscarriage or stillbirth, lower birth weight, birth defects and sex ratio in some studies, although no associations were found in some studies regarding the same outcomes, in both workers from the industry and the populations living near oil and natural gas operation sites (Axelsson and Molin, 1988; Axelsson and Rylander, 1989; Bamber et al., 2019; Caron-Beaudoin et al., 2021; Casey et al., 2016; Chevrier et al., 2006; Currie et al., 2017; Deziel et al., 2020; Hill, 2018; Janitz et al., 2019; Lin et al., 2001a, 2001b; McKenzie et al., 2014, 2019; Oliveira et al., 2002; San Sebastian et al., 2002; Stacy et al., 2015; Tang et al., 2020; Tsai et al., 2003; Walker Whitworth et al., 2018; Xu et al., 1998; Yang et al., 2000a, 2000b, 2002a, 2002b, 2004). Thus, while some discrepancies can be identified when comparing the conclusions of these studies, adverse outcomes found by many of them demonstrate the need for further investigation and raise concerns for pregnant women.

1.1.3.5. Flames retardants. Flame retardants are molecules added to combustible materials such as foam, plastics, textiles, and wood products, among others, to reduce fire hazards and meet safety standards (Alaee et al., 2003). Brominated flame retardants (BFR), which include tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCDD), and the polybrominated diphenyl ethers (PBDEs), represent a diverse group of flame retardants that have a bromine in their structure (Alaee et al., 2003). Importantly, many of them have been identified as EDCs. Many studies have demonstrated that PBDEs, as well as HBCDD although less studied, dysregulate thyroid hormone homeostasis in human and animals, including a few studies during pregnancy (Abdelouahab et al., 2013; Chevrier et al., 2010; Dianati et al., 2017; Ema et al., 2008; Hagmar et al., 2001; Kim et al., 2013; Stapleton et al., 2011; Tung et al., 2016; Zota et al., 2011). Although the associations were not significant in all studies, BFRs or organophosphate flame retardants (OPFRs) were correlated with longer time to pregnancy and decreased fertility/fecundability (Buck Louis et al., 2013; Chevrier et al., 2013; Gao et al., 2016; Harley et al., 2010). Whether or not this is due to thyroid-related effects remains to be determined.

1.1.3.6. Others less-known EDCs. Other compounds have also been demonstrated to have endocrine disruptive effects during pregnancy. For instance, exposure to solvents, such as xylenes or ethelyne oxide, dysregulates the estrous cycle, prevents ovulation and increases gestation time in rodents, and increase the risk of infertility, potentially linked with ovarian dysfunction, and abortion in humans (Lawson et al., 2012; Rowland et al., 1996; Smith et al., 1997; Ungvary et al., 1980). As indicated earlier, a growing number of studies suggest that some metals can act as endocrine disruptors (Bodwell et al., 2004, 2006; Davey et al., 2007; Kaltreider et al., 2001; Rivera-Nunez et al., 2021). Furthermore, a few studies have demonstrated an association between higher levels of various metals, such as As, Cd, Hg, Pb, Sb, tin (Sn), Co, Mn, and selenium (Se), and spontaneous abortion (Baser et al., 2020; Harris et al., 2020; Nyanza et al., 2020; Saric, 1984; Wang et al., 2020a, 2020b).

2. The placenta: a transient organ that has long-term impact on health

The placenta, after being neglected for many years, is now at the centre of understanding physiopathological disorders occurring during pregnancy (Aplin et al., 2020; Weinberg, 2021). This transient multifunctional endocrine organ has many physiological functions crucial for maternal physiology adaptation to pregnancy and fetal development, including the exchange of respiratory gases, metabolites, nutrients, and waste products, as well as the production of hormones and the metabolism of xenobiotics (Fig. 1). Any disequilibrium of placenta homeostasis, (formation, function, structure, and physiology) could impact both maternal and fetal health.

The placenta by its location and roles at the interface between mother and fetus, is also the programming agent of adult noncommunicable diseases (Barker and Thornburg, 2013; Godfrey, 2002; Jansson and Powell, 2007). Many researchers have suggested that the placenta acts on behalf of the fetus as both a sensory and effector organ to communicate the environmental information for its integration into

the fetal developmental process. The placenta is thus important for monitoring fetal health (and, to some extent, maternal health) and qualifies as a target to assess the expression of specific biomarkers (Gupta and Sastry, 2000). Multiple factors, including nutrition, stress, environmental toxicants, and maternal diseases, can alter placental function and development, inducing long-lasting harmful effects to the fetus, such as cardiovascular and metabolic diseases (Burton et al., 2016; Ganguly et al., 2020; Marciniak et al., 2017).

EDCs are detectable in the maternal-placental-fetal unit throughout gestation (reviewed in (Padmanabhan et al., 2021). Through their action, EDCs can disrupt the normal placental endocrine functions, as well as structure and transport, and thus disturb the maternal and fetal endocrine systems and health. Hormones produced by the placenta (Fig. 1) are major factors that influence the developmental trajectory of the offspring in a dose-, time-, and organ-specific manner (reviewed in Gingrich et al., 2020). Thus, because of the rapid changes during pregnancy and high level of activity in the placenta, hormonal changes during pregnancy and placental function can provide insight into the effects of EDCs and lay the basis for our understanding of how EDCs can affect children's future development. Of note, EDCs affect pregnancy not only by acting directly on the endocrine systems, but also indirectly by disrupting maternal, placental, and fetal homeostasis (e.g. increases inflammatory and oxidative state, altering metabolomics and microbiome profiles etc.) (recently extensively reviewed in Padmanabhan et al., 2021).

2.1. Effect of EDCs on placenta development

Placental development involves two pathways of differentiation that lead to the formation of two distinct phenotypes: villous trophoblast and extra-villous trophoblast (Aplin et al., 2020). In the villous phenotype, the trophoblast differentiates from the fusion of mononuclear cytotrophoblasts with the underlying multinucleated syncytiotrophoblast or syncytium (Vaillancourt et al., 2009). Throughout pregnancy, the syncytiotrophoblast layer is the main site of hormone production and placental function and transport of oxygen and nutrients required for maintenance of pregnancy and fetal growth and development and acts as a direct link between maternal and fetal blood. Alterations in syncytium formation are associated with obstetric complications and adverse effects on fetal growth and development (Aplin et al., 2020; Burton et al., 2016). Placental histological changes have been noted after exposure to EDCs (reviewed in Gingrich et al., 2020; Padmanabhan et al., 2021). For example, active and passive maternal smoking, sources of PAHs and Cd, has a damaging effect on the placenta in all trimesters of human pregnancy (Ganer Herman et al., 2016). Changes in placental vasculature and modification of the normal pattern of fibrin deposition might explain the increased risk of adverse outcomes during pregnancy in smokers (Bush et al., 2000b). In accord with this observation, the same group has shown that high concentrations of placental Cd were linked to smaller volumes and surface-to-volume ratio of fetal capillaries, increased maternal blood space relative to placental volume, and a thicker villous trophoblast membrane (Bush et al., 2000a). DES (10–15 μg/kg) has been reported to induce morphological changes in mouse (Kagawa et al., 2014; Nagao et al., 2013) and human placenta acting on trophoblast stem cell differentiation (Tremblay et al., 2001). Phthalates have been shown to inhibit trophoblast invasion, a critical mechanism for early pregnancy loss (Gao et al., 2017). In a mouse model, BPA (0, 0.4, 4, 40, or 400 μM in drinking water) exposure altered placental spiral artery remodeling and trophoblast invasion, which induced preeclampsia-like features (Ye et al., 2019).

Maternal exposure to PBDE was associated with reduced placental length, breadth, and surface area (Zhao et al., 2018). Increased maternal concentrations of urinary phthalates throughout pregnancy was associated with alteration in placental size and shape in the Ma'anshan Birth Cohort (Zhu et al., 2018). The authors showed that exposure to phthalates was linked with thicker and more circular placenta, and these associations seemed stronger among male than female placentas. Total urinary metabolites of DEHP (∑DEHP) also showed an inverse association with placental weight at term, suggesting placental insufficiency (Mustieles et al., 2019; Philippat et al., 2019). Triclosan, benzophenone-3, phthalates (monocarboxy-isononly phthalate (MCNP) and monocarboxyoctyl phthalate (MCOP)) have been linked with decreased birth weight/placental weight ratio (Philippat et al., 2019). The birth weight to placental weight ratio serves as an index of placental efficiency, and alterations of this ratio (increase or decrease) suggests an inability of the placenta to function appropriately and consequently results in altered fetal growth and development. In accord with this, higher ∑DEHP urinary concentrations in pregnant women were associated with intrauterine growth restriction (IUGR) (Zhao et al., 2015) and lower gene expression of trophoblast differentiation (Adibi et al., 2010). These findings suggest that EDCs could affect placental formation and consequently placental transport and endocrine functions. The potential mechanisms involved in these actions of EDCs on placenta have recently been reviewed (Gingrich et al., 2020). However, to date, too few studies have looked at the effect of EDCs on placental index. Future studies are needed to incorporate the birth weight to placental weight ratio, an easily obtainable measure that could help to better understand the impact of EDCs on fetal short, mid-, and long-term health outcomes.

2.2. Effect of EDCs on placental functions

Since the placenta is an endocrine organ, EDCs could affect placental hormonal production (reviewed in Gingrich et al., 2020; Padmanabhan et al., 2021). Exposure of human placental explants to BPA interferes with hCG secretion (Mørck et al., 2010). Furthermore, a low dose of BPA decreased the expression of CYP11A1 and CYP19, and placental aromatase activity causing a decrease in estradiol and progesterone production via the activation of the extracellular signal-regulated kinases (ERK) signaling pathway (Chu et al., 2018). Decreased placental progesterone production was also associated with the presence of Cd in the placenta (Piasek et al., 2001). The organotin tributyltin (TBT), a known obesogenic EDC (Veiga-Lopez et al., 2018), has been shown to affect progesterone production and 3β-HSD activity in human placental choriocarcinoma cell lines (Cao et al., 2017; Hiromori et al., 2016). TBT, through the activation of PPARγ or retinoid X receptor (RXR), also increases the production of hCG in human placental choriocarcinoma, JAR and JEG-3, cells (Chu et al., 2018; Hiromori et al., 2016; Nakanishi et al., 2006). Interestingly, TBT has been shown to increase di- and tri-acyl glycerol in JEG-3 cells (Gorrochategui et al., 2014). An increase in placental leptin has also been observed with third-trimester maternal urinary concentrations of As (Ahmed et al., 2011).

Alterations in placental function may also be mediated through changes in the inflammatory cascade, oxidative stress, and hormonal support, with many of these changes involving epigenetic alterations. A number of placental functions have been shown to be affected by EDCs, such as growth factor expression and signaling (Guyda, 1991; Zhang et al., 1995; Zhang and Shiverick, 1997), aryl hydroxylase (CYP1A1) activity and induction (Pereg et al., 2002), steroidogenesis (Augustowska et al., 2003), aromatase (CYP19) activity (Caron-Beaudoin et al., 2017; Nativelle-Serpentini et al., 2003; Sanderson et al., 2001; Thibeault et al., 2018) transporters and efflux pumps, lipid peroxidation, and oxygen tension (reviewed in Gingrich et al., 2020). For example, even low-level exposures to EDCs affect calcium transport (Hamel et al., 2003; Lafond et al., 2004), serotonin transporter and receptors, and dopamine receptors in human placenta (Desrosiers et al., 2007; Viau et al., 2007) and these alterations were related to low birth weight. The effects on placental function are linked with the stage of development, type of insult and fetal sex, leading to sex-dependent placental responses (Dearden et al., 2018; Rousseau-Ralliard et al., 2019; Sundrani et al., 2017; Tarrade et al., 2015). For example, phthalates have been shown to be peroxisome proliferator-activated receptor γ (PPARγ) agonists in female and antagonists in male placentas using primary isolated villous

trophoblasts (Adibi et al., 2017). Sex-dependent placental responses are observed due to adverse maternal environment (Dearden et al., 2018; Sundrani et al., 2017) associated with different epigenetic signatures (Barouki et al., 2018), either through DNA methylation or small non-coding RNA (sncRNA) expression (Deshpande and Balasinor, 2018). Indeed, an adverse maternal environment can be associated with different epigenetic signatures in the placenta. In a human placental cell line, BPA down-regulated Wnt2 expression by increasing DNA methylation of Wnt2 genes via DNA (cytosine-5)-methyltransferase 1 (DNMT1) (Ye et al., 2019). An association between maternal exposure to BPA, phthalates and synthetic phenols and altered placental expression of miR-146a, miR-142–3p, miR15a-5p and miR-185 has also been reported (De Felice et al., 2015; LaRocca et al., 2016). Alterations in sncRNA expression has also been described in human placentas from mothers exposed to phthalates and synthetic phenols (Zhong et al., 2019). Furthermore, significant alteration of the methylation of 39 genes have been identified in human placenta of women with increased phthalate concentration in their urine (Grindler et al., 2018). Placental ErbB signaling is an important signaling pathway in response to DNA methylation and gene expression induced by phthalate exposure. This pathway works through tyrosine kinases (such as epidermal growth factor (EGF)), and epidermal growth factor receptor (EGFR) that stimulate placental growth and function (Bass et al., 1994; Lemmon and Schlessinger, 2010). Moreover, phthalate and synthetic phenol metabolites affect the methylation of the imprinted genes H19 and insulin growth factor-2 (IGF2), which results in the alteration of the placental transcriptome (Grindler et al., 2018; LaRocca et al., 2016).

Together, these studies demonstrate the importance of a healthy placenta for a successful pregnancy and for the health of the fetus. As a result, exposure to EDCs can have important impacts on pregnancy outcome and on the future health of the fetus.

3. Fetal programming: how changes in the fetal environment influence the future

3.1. Embryogenesis

Embryonic development is a tightly regulated process which depends on appropriate endocrine signaling. Fetal tissue is known to be highly dynamic as the demands of embryonic and fetal growth require constant changes (Feil and Fraga, 2012). The pluripotency of embryonic cells allows fetal tissue to be able to form all the necessary biological systems for adulthood, but this property also makes these cells highly sensitive to environmental exposures such as EDCs. Exposure to exogenous agents during embryogenesis, including EDCs, may result in abnormal development. Traditionally, birth defects associated with exposure to chemicals during development have been thought of as structural and functional malformations that can be described broadly by the term teratogenesis. However, there has been increasing evidence to support the critical role of the developmental environment in the process of metabolic disruption during embryogenesis. As described above, the DOHaD hypothesis states that the developmental environment to which the future child is exposed can be linked to disease later in life (Barker, 2007). Developmental programming refers to permanent changes in physiology, metabolism, or the epigenome. Environmentally induced changes in developmental programming can be manifested as metabolic adjustments in the fetus. This phenomenon is often referred to as metabolic imprinting, which describes adaptations that occur in early life in response to a specific environmental exposure, such as nutritional status. While the most extensively studied influence to a healthy gestation is the fetal response to maternal nutrition, recent evidence suggests that exposure to EDCs during embryogenesis could result in cognitive, behavioral, and metabolic disorders in the offspring (Yang et al., 2019). For example, the flame retardant triphenyl phosphate (TPP), which has recently been characterized as having the potential for endocrine and metabolic disrupting capabilities (USEPA, 2015), accelerated the onset of diabetes in UC Davis type 2 diabetes mellitus male rats. This rat model represents the physiopathology and progression of type 2 diabetes mellitus in humans (Cummings et al., 2008). In an animal model, it has been demonstrated that TPP (5, 25, or 50 mg/kg) perturbed the expression of genes associated with the insulin signaling pathways, including *Igf1r, Igf2r*, *Irs1 and Irs2* (Philbrook et al., 2018).

Depending on dose and duration, exposure to EDCs during fetal development can result in fetal loss, preterm birth, birth abnormalities, long term phenotypic changes and the development of disease later in life. Exposure to EDCs during critical time frames during development is worrying as key endocrine organs, which control weight and metabolism, are developing (reviewed in Heindel et al., 2017). If exposure to an EDC occurs during this time, the endocrine system could be perturbed and may present as metabolic disease later in life. Studies have shown that a variety of pesticides, plastics, metals and flame retardants could be considered obesogens and may have some responsibility for the growing obesity epidemic (Grun et al., 2006). For example, it is well documented that BPA can promote adipocyte differentiation and proliferation in murine cells lines (reviewed in Heindel et al., 2017).

A potential mechanism by which EDCs can interfere with normal endocrine signaling is via epigenetic modifications, which include several molecular modifications such as methylation, acetylation and phosphorylation that regulate genome activity independent of any alteration in DNA sequence. Epigenetic-induced alterations in gene expression are thought to play a critical role in regulating cellular genomic activity which could influence differentiation and the development of an organism. Increased sensitivity can be displayed as changes in epigenetic marks, such as DNA methylation patterns, in fetal tissue. For example, it has been shown that sites of heavy methylation differ from fetal tissue to adult tissue in humans (Huse et al., 2015). DNA methylation plays a normal part of fetal development where targeted genes associated with growth development often become methylated and demethylated, meaning that methylation patterns will change often as organs gain complexity and functionality (Slieker et al., 2015). Furthermore, decreased DNA methylation, or hypomethylation, has been associated with obesity and several components of metabolic disease in humans (Luttmer et al., 2013; Soubry et al., 2016).

Some studies have examined the connection between *in utero* exposure to EDCs and epigenetic modifications. For example, perinatal PBDE exposure is associated with decreased DNA methylation in genes involved in neuronal pathways in rat offspring (Byun et al., 2015). Another study demonstrated that early embryonic exposure to the OPFR tris(1,3-dichloroisopropyl) phosphate (TDCIPP) induced hypomethylation of DNA in zebrafish (Volz et al., 2016). Global hypomethylation of DNA has also been observed following OPFR exposure in previous studies. For example, it has been demonstrated that TDCIPP and other OPFR mixtures induced global DNA hypomethylation in zebrafish following embryonic exposure (Volz et al., 2016). Additionally, a study which examined epigenetic effects following exposure to PBDE, found that *in utero* and perinatal PBDE exposure in rats was associated with global DNA hypomethylation in offspring (Byun et al., 2015). In mice, *in utero* exposure to an OPFR mixture resulted in sex-dependent effects on pups (Adams et al., 2020). It was found that female pups appeared to be more sensitive to the effects of OPFRs compared to males (Adams et al., 2020). Specifically, *in utero* exposure to OPFRs resulted in increased hepatic gene expression of hormones and metabolic enzymes in females and decreased hepatic gene expression of the same genes in males (Adams et al., 2020). However, these results were in contrast to another study examining TPP specifically and whether the compound would induce sex-dependent metabolic disruptions (Wang et al., 2018). Here, the researchers found that low doses of TPP increased body weight and altered the metabolic profile in males, but not in females. Interestingly, a study in mice described a potential role for DNA methylation in DEHP induced cardiac effects and highlight the importance of sex as a variable in EDC exposure studies (Svoboda et al., 2020). Arterial blood pressures were reduced at postnatal day 200

in response to *in utero* DEHP exposure (300 mg/kg/day) in male rats only (Martinez-Arguelles et al., 2013). The impacts of EDCs specifically on cardiometabolic outcomes, the fetal reproductive system and mammary gland development following *in utero* exposures are discussed further in the sections below.

3.2. Role of endocrine disruption in cardiometabolic outcomes

The identification of adipose tissue as an endocrine organ and therefore, a target highly susceptible to disturbance by EDCs, results largely from the discovery of adipokines like leptin, as well as the nuclear receptor PPAR-γ, a critical regulatory component of lipid metabolism and adipogenesis (Janesick and Blumberg, 2016; Nadal et al., 2017). As the fetal/neonatal period is a critical window in the development of adipocytes, chemical exposures during this time can alter an individual's growth trajectory and increase the risk of insulin resistance, obesity, and metabolic disorders later in life (Chevalier and Fenichel, 2016; Darbre, 2017; Hatch et al., 2010; Newbold et al., 2009). Development and maturation of brain circuits involved in the regulation of food intake and metabolism occur during this time as well (Heindel et al., 2017). In addition, adipose tissue is strongly linked to steroid hormones (estrogen, androgens, and glucocorticoids) as an important site for both metabolism and secretion of sex steroids, as well as glucocorticoid metabolism (Kershaw and Flier, 2004). Adipose tissue also maintains a close relationship with the immune system via adipokines (Janesick and Blumberg, 2016; Tilg and Moschen, 2006) and its function is a key determinant of cardiovascular health (Callaghan et al., 2020). All these properties imply that metabolic disruption could

Table 3
Effects of common endocrine disruptors on metabolic programming in animal models.

	Species	Concentration	Exposure Window (Route)	Effects	Reference
Bisphenol A (BPA)	OF-1 mice	10 or 100 μg/kg/day	GD 9–16 (sc injection)	↓ glucose tolerance, ↑ insulin resistance, at 6 months in treated male offspring compare to controls	Alonso-Magdalena et al. (2010)
	C57BL/6 mice	10 μg/kg/day or 10 mg/kg bw/day	2 weeks prior mating - PND21 (diet)	↑ body fat and perturbed glucose homeostasis in F1 and F2 male offspring but not female offspring	Susiarjo et al. (2015)
	Sprague-Dawley rats	0.1 mg/kg bw/day (low dose) or 1.2 mg/kg bw/day (high dose)	GD 6 - PND21 (drinking water)	↑ in body weight in offspring apparent soon after birth and continued into adulthood	Rubin et al. (2001)
	Sprague-Dawley rats	1 mg/L	GD 6 - PND21 (drinking water)	↑ body weight at PND 21 (in females). ↑ parametrial WAT weight, ↑adipocyte hypertrophy	Somm et al. (2009)
	Wistar rats	40 μg/kg/day	GD 1 to the end of lactation (gavage)	Extensive fatty accumulation in liver and ↑ serum ALT at 26 weeks (male offspring)	Jiang et al. (2014)
	C57BL/6J mice	5 mg/kg/day	Post conception day (PCD) 1 – PCD 20 (gavage)	At weaning (PND21): significantly ↓body weight in both male and female offspring from the exposure group compared to control; significant ↓ in serum lipid parameters and an ↑ in serum glucose level in treated males, but not in females	Shu et al. (2019)
Di-(2-ethylhexyl) phthalate (DEHP)	Sprague-Dawley rats	300 mg/kg/day	GD 14 until birth (gavage)	Exposed male offspring showed ↓ activity at PND60; ↓systolic and diastolic systemic arterial pressures and ↓activity at PND200	Martinez-Arguelles et al. (2013)
	Wistar rats	1, 10 or 100 mg/kg/day	GD 9–21 (gavage)	At PND 60 exposed offspring showed ↑ blood glucose, impaired serum insulin, glucose tolerance, glucose-stimulated insulin secretion and ↓pancreatic insulin content	Rajesh & Balasubramanian (2015)
	C3H/N mice	0.05, 5 or 500 mg/kg of body weight per day	8 weeks: 2 weeks prior to mating -PND21 (diet)	Female offspring in the exposure groups showed significant ↑ in body weight at PND 21; significant ↑ body weight and visceral fat tissue at PND 84 Male offspring: ↑ in body weight at PND 21, significant in 5 mg/kg DEHP group; significant ↑ body weight and visceral fat tissue at PND 84 in all treated groups	Schmidt et al. (2012)
	Yellow agouti (A^{vy}) mice	25 mg of DEHP/kg of chow (equivalent to 5 mg/kg/day DEHP maternal dose)	2 weeks prior to mating - PND21 (diet)	Longitudinal analysis across 2 and 8 months showed ↑weight gain in exposed females with ageing, compared to controls; altered body composition in adulthood; ↑body fat percentage and ↓lean mass Exposed male offspring did not exhibit statistically significant differences in the measured longitudinal metabolic outcomes	Neier et al. (2019)
Diisononyl-phthalate (DINP)	Yellow agouti (A^{vy}) mice	75 mg of DINP/kg of chow (equivalent to 15 mg/kg/day DINP maternal dose)	2 weeks prior to mating - PND21 (diet)	Exposed female offspring exhibited altered body composition in adulthood and modestly impaired glucose tolerance longitudinally Exposed male offspring did not exhibit statistically significant differences in the measured longitudinal metabolic outcomes	Neier et al. (2019)
Perfluorooctane sulfonate (PFOS)	CD-1 mice	0.3 or 3 mg/kg/day	GD 0 - PND21 (gavage)	↑ serum fasting glucose and insulin levels in male, but not female offspring at PND 21 and in offspring of both sexes at PND 63 Phenotypes of insulin resistance and glucose intolerance evident in the F1 adults (PND63). The effects were exacerbated under HFD	Wan, H. T. et al., 2014
Triclosan (TCS)	Sprague Dawley (SD) rats	10 or 50 mg/kg/day	GD 0 - PND 21 (gavage)	↑ blood glucose and serum HDL-C observed in F1 old rats (PND 364) exposed to 10 mg/kg/day TCS and in both adult and old F1 rats exposed to 50 mg/kg/day TCS; ↑serum TG and LDL-C at two doses in both adult (PND 147) and old F1 rats and ↑serum leptin at two doses in old F1 rats; ↓hepatic glycogen at 50 mg/kg/day TCS in adult F1 rats and at two doses in old F1 rats	Ma, Y. et al., 2020

contribute to disease development beyond obesity, such as diabetes, cardiovascular disease and even cancer (Callaghan et al., 2020; Janesick and Blumberg, 2016). Furthermore, pancreatic failure and/or peripheral tissue insulin resistance can be both programmed by adverse *in utero* exposures (Fernandez-Twinn et al., 2019). Importantly, ERs are present in human beta cells, where they play essential roles in islet function and survival, making beta cells sensitive for disruption by ER-active EDCs (Sargis and Simmons, 2019). ERα and ERβ are also expressed in pre-adipocytes; during development, estrogens contribute to an increase in adipocyte number and subsequent adipocyte function (Cooke and Naaz, 2004). A recent review on EDCs and obesity suggests the existence of a "vicious spiral" responsible for the appearance, increase and persistence of metabolic diseases through lifespan. The description of this spiral illustrates that EDCs may lead to increases in body fat; as many EDCs are lipophilic, increases in body fat in turn may result in further storage of EDCs. This could cause a positive feedback loop, in which the continuous increase in body fat results in the continued accumulation in the number of EDCs in the body (Darbre, 2017).

Many examples from animal, including some with high doses non representative of human exposure, and epidemiological studies have demonstrated that early life exposure to certain EDCs may have an influence on perinatal and postnatal cardiometabolic programming as well, contributing to higher cardiometabolic risks at adulthood (Table 3) (Philips et al., 2017; Shu et al., 2019). For example, early life BPA exposure has been shown to affect metabolic programming (weight and glucose metabolism) in offspring. Increase in body weight in rat offspring was measured soon after birth, and remained into adulthood, upon a perinatal exposure to low doses of BPA (Rubin et al., 2001). Additionally, female offspring of dams exposed to BPA during gestation and lactation showed adipocyte hypertrophy and overexpression of lipogenic genes and lipogenic enzymes (Somm et al., 2009). Gestational BPA exposure (10 or 100 μg/kg/day) as reported to trigger glucose intolerance, insulin resistance and altered pancreatic β-cell function in male mice offspring at 6 months of age (Alonso-Magdalena et al., 2010). In addition, metabolic disruption due to maternal BPA exposure (10 μg/kg/day or 10 mg/kg bw/day) has been reported across multiple generations in the mouse (Susiarjo et al., 2015). Furthermore, perinatal BPA exposure (40 μg/kg/day) predisposed development of hepatic steatosis in rat offspring, possibly mediated via compromised hepatic mitochondrial function and up-regulated hepatic lipid metabolism (Jiang et al., 2014).

Experimental evidence has shown that fetal phthalate exposure can affect adipogenesis, lipid accumulation and insulin resistance by regulating the activation of PPARγ (Table 3) (Hao et al., 2012). *In utero* and lactational exposure to DEHP (0.05, 5 or 500 mg/kg) in mice has been linked to obesity, as it led to increased weight gain in the offspring, which persisted into adulthood (Schmidt et al., 2012). In another study, female mice exposed *in utero* to DEHP (25 mg/kg in dams' food) showed increased body fat and decreased lean mass, whereas exposure to diisononyl-phthalate (DINP; 75 mg/kg in dams' food) only induced impaired glucose tolerance. In contrast, phthalate-exposed males did not exhibit significant differences in the measured metabolic outcomes (Neier et al., 2019). Gestational exposure to DEHP (1, 10, 100 mg/kg/day) has been shown to cause elevated blood glucose levels by interfering with pancreatic β-cell function and insulin signaling in rat offspring (Rajesh and Balasubramanian, 2014, 2015). In humans (Table 4), many epidemiological studies have reported inconsistent results regarding the association between early life phthalate exposure and the risk for obesity later in life (Buckley et al., 2016; Harley et al., 2017; Maresca et al., 2016; Shoaff et al., 2017; Vafeiadi et al., 2018). However, the existing data suggest that child growth and adiposity may be affected by early life phthalate exposure in a sex-specific manner and depends on the timing of exposure. Prenatal exposure to phthalates has been associated with lower systolic blood pressure at 4 and 7 years of age in girls, but not in boys (Valvi et al., 2015). Furthermore, a negative association between concurrent phthalate metabolite concentrations and systolic/diastolic blood pressure at age 4 in boys and girls was observed (Vafeiadi et al., 2018). No association was found between *in utero* phthalate and BPA exposure and lipid profile at 8–14 years, however higher concurrent urinary levels of certain phthalate metabolites corresponded with lower total cholesterol and low-density lipoprotein (LDL-C) during peripuberty (Perng et al., 2017).

In utero per- and polyfluoroalkyl substances (PFAS) exposure has been related to higher neonatal mortality and growth deficits in mice. Gestational PFOA has been shown to affect the expression of genes involved in lipid and glucose homeostatic control, as early as GD14 in mice offspring (Abbott et al., 2012). Gestational and early postnatal PFOS exposure at environmental equivalent dose (0.3 or 3 mg/kg) has resulted in glucose intolerance and insulin resistance in mice offspring (Wan et al., 2014). In humans, higher maternal serum PFOA concentrations during pregnancy were associated with a more rapid increase in BMI in their children between 2 and 8 years and with greater adiposity at 8 years (Braun et al., 2016). Further, gestational and cord serum PFOA and PFHxS concentrations were shown to be positively associated with cardiometabolic risk scores at age 12 years (Li et al., 2021).

Finally, triclosan has also been shown to affect metabolic programing early in life. In older rats exposed *in utero* to triclosan (10 or 50 mg/kg), decreased hepatic glycogen content and increased serum and hepatic triglycerides content along with up-regulation of genes implicated in pathways of carbohydrate and lipid metabolism in liver were described (Ma et al., 2020). Together, these studies demonstrate that *in utero* exposure to EDCs can be linked with various metabolic pathologies later in life.

3.3. The fetal reproductive system and mammary gland development

Healthy development of the ovaries is crucial for fertility later-on during the reproductive life as the non-renewable pool of oocytes is formed during embryogenesis. Although in rodents and other species folliculogenesis begins after birth, in humans and nonhuman primates' follicular development is initiated at midgestation. All steps involved in this process are critical (Smith et al., 2014); impaired development may contribute to childhood and adult diseases, such as gonadal dysgenesis or ovarian cancer, and lead to infertility (Goswami and Conway, 2005). These early stages of follicle development are completely gonadotropin independent in all mammalian species studied. However, in many species, it has been demonstrated that fetal ovaries can synthetize steroid hormones, and express hormonal receptors (Garverick et al., 2010; Juengel et al., 2002; Lun et al., 1998; Pepe et al., 2002), and that exposure to steroid hormones at that time can be linked with diseases. For example, prenatal exposure to androgens can lead to polycystic ovarian syndrome (PCOS) in various species (reviewed in Franks et al., 2011). Inhibition of aromatase in female baboons in late pregnancy resulted in decreased estradiol levels in maternal and umbilical vein serum, and in a reduction in the number of primordial follicles and high levels of malformed follicles in fetal ovaries (Pepe et al., 2002; Zachos et al., 2002, 2004). Interestingly, these effects could be restored by the administration of estradiol, confirming a crucial role of estrogens in fetal ovarian development (Zachos et al., 2002). Other studies have suggested that progesterone and estradiol inhibit the primordial to primary follicle transition, and that their decrease in late pregnancy or birth, depending on the species, allows for the initiation of primordial follicle assembly and development (Kezele and Skinner, 2003). Thus, there is strong evidence that dysregulation of steroid hormones during development can impact ovarian health and function later in life.

The development of the uterus begins during embryogenesis, while full maturation of the uterus does not occur until the end of puberty (for a comprehensive review the reader is referred to (Habiba et al., 2021). Fetal development of the endometrium is independent of steroid hormones, as ER and PR knockout mice show unaltered fetal development (Lubahn et al., 1993; Lydon et al., 1995). However, the fetal endometrium is thought to be responsive to hormonal action as ER and PR are

Table 4
Endocrine disruptive compounds and cardiometabolic programming: epidemiological evidence.

Study (N)	Compound	Exposure assessment	Outcome assessment	Effect size [β, OR, RR (CI95%)]	Reference
Longitudinal birth cohort study Mother-child pairs (Columbia Center for Children's Environmental Health (CCCEH)) (*N* = 424) 5 years: 178 ♀/148 ♂ 7 years: 173 ♀/157♂	Phthalate: DEHP DiBP DnBP BBzP DEP DOP	Measurement of phthalate metabolites in urine (SG adjusted) in 3rd trimester urine samples and in children at age of 3 and 5 years	BMI *z*-scores (age- and sex-adjusted BMI) at 5 and 7 years of age, fat mass, waist circumferences at 7 years of age	Higher maternal non-DEHP scores were associated with a ↓ in the z score of BMI (β = −0.30, 95% CI: 0.50, −0.10, n = 156), lower fat percentage (β = −1.62; 2.91, −0.34, n = 142) and a smaller waist circumference (β = −2.02; 95% CI: 3.71, −0, 32, n = 124) in boys. No association in girls (for BMI z score, β = 0.07, 95% CI: 0.18, 0.31, n = 181). Interactions between sex and the non-DEHP association with outcomes were statistically significant (p < 0.01)	Maresca et al. (2016)
Longitudinal cohort study Mother-child pairs (Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)) (*N* = 345)	Phthalate: DEP DBP DiBP BzBP DEHP DOP DiNP DiDP	Measurement of phthalate metabolites in urine (SG adjusted) twice during pregnancy (mean ± SD: 14.0 ± 4.8 and 26.9 ± 2.5 weeks gestation)	BMI *z*-scores, fat mass and waist circumferences at multiple ages between 5 and 12 years of age	Metabolites of DEP, DBP, BBzP, DEHP were positively associated with BMI *z*-score, waist circumference *z*-score, and percent body fat at multiple ages. At age 12, ↑odds of being overweight/obese with each doubling of prenatal concentrations of DEP (odds ratio = 1.3; 95% confidence intervals: 1.1, 1.5) and DEHP (1.3; 1.0, 1.6) metabolites in both sexes and for DBP metabolite (1.4; 1.1, 1.8) in boys.	Harley et al. (2017)
Prospective cohort study Mother-child pairs (The Mount Sinai Children's Environmental Health Study) N = 180 82♀/98♂	Phthalate: DEP DBP DiBP BzBP DEHP	Measurement of phthalate metabolites in urine (adjusted for creatinine levels) in 3rd trimester urine samples	Body composition (Tanita scale), % fat mass ((fat mass/weight) × 100) and BMI z scores at multiple follow-up visits between ages 4 and 9 years	Children in the highest tertile of ΣDEHP metabolites had about 3.06% (95% CI: 5.99, −0.09%) lower fat mass at 4–9 years of age than children in the lowest ΣDEHP tertile.	Buckley et al. (2016)
Prospective pregnancy and birth cohort study Mother–child pairs (Health Outcomes and Measures of the Environment (HOME) Study) N = 219	Phthalate: DEP DBP DiBP BzBP DEHP	Measurement of phthalate metabolites in urine (adjusted for creatinine levels) maternal samples at 16- and 26-wk gestation and child urine samples annually from 1 to 5 years of age and at 8 years of age.	BMI *z*-scores, waist circumference, and % total body fat at 8 years of age	No association for prenatal phthalate metabolite concentrations and excess child adiposity. BzBP metabolite concentrations in maternal and child urine samples were inversely associated with child adiposity, the strongest associations observed with prenatal exposure; a 10-fold increase in prenatal urinary BzBP metabolite concentrations was associated with a 1.7% reduction in body fat at age 8 (95% CI: −3:6, −0:2) 10-fold increase in ΣDEHP metabolites concentrations at 1 years of age was associated with a 2.7% decrease [95% confidence interval (CI): −4:8, −0:5] in body fat at age 8, while a 10-fold increase at 5 years was associated with a 2.9% increase (95% CI: 0.3, 5.5) Association between DEP metabolite concentrations and child body fat % became positive in direction with child age (from null during pregnancy (b = −0:3, 95% CI: −1:9, 1.2) and 1–4 y of age, to positive at 8 y of age (b = 1:8, 95% CI: 0.0, 3.6)	Shoaff et al. (2017)
Longitudinal cohort study Mother-child pairs (The Rhea pregnancy cohort, Crete, Greece) N = 500	Phthalate: DEP DBP DiBP BzBP DEHP	Measurement of phthalate metabolites in urine (adjusted for creatinine levels) in 1st trimester maternal urine samples and their children at 4 years of age	BMI *z*-scores, waist circumference, waist-to-height ratio, skinfold thickness, systolic and diastolic BP z-scores (age, sex, and height specific) and serum lipids at 4 and 6 years of age; Leptin, adiponectin, and CRP levels at 4 years of age	No consistent association between prenatal phthalate exposure and child adiposity and cardiometabolic measures. Early life child phthalate exposure associated with lower BMI z-scores in boys and higher BMI z-scores in girls. Each 10-fold increase in	Vafeiadi et al. (2018)

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Table 4 (*continued*)

Study (N)	Compound	Exposure assessment	Outcome assessment	Effect size [β, OR, RR (CI95%)]	Reference
				ΣDEHP metabolites was associated with a change in waist circumference of −2.6 cm (95% CI: −4.72, −0.48) in boys vs. 2.14 cm (95% CI: −0.14, 4.43) in girls (p-sex interaction = 0.003) and a change in waist-to-height ratio of −0.01 (95% CI: −0.03, 0.01) in boys vs. 0.02 (95% CI: 0.01, 0.04) in girls (p-sex interaction = 0.006). DEP urine metabolite concentration was associated with lower systolic BP z-scores (adj. β = −0.22; 95% CI: −0.36, −0.08) at 4 years. DnBP and BBzP metabolites were associated with lower diastolic BP z-scores (adj. β = −0.13; 95%CI: −0.23, −0.04, and adj. β = −0.11; 95% CI: −0.21, −0.01, respectively). A 10-fold increase in DiBP metabolite concentration was associated with 4.4% higher total cholesterol levels (95% CI: 0.2, 8.7).	
Prospective cohort study Mother–child pairs (Spanish population -based birth cohort study INMA) N = 391 205 ♀/186 ♂	Phthalate: DEP DBP DiBP BzBP DEHP	Measurement of phthalate metabolites in urine (adjusted for creatinine levels) in 1st and 3rd trimester maternal urine samples	Age- and sex-specific z-scores for weight between birth and 6 months of age BMI *z*-scores at 1, 4 and 7 years Waist to height ratio at 4 and 7 years Age- and height-specific z-scores for systolic and diastolic BP at 4 and 7 years	The ΣHMWPm was associated with lower weight z-score difference between birth and 6 months (β per doubling of exposure = −0.41; 95% CI: 0.75, −0.06) and BMI z-scores at later ages in boys (β = −0.28; 95% CI: 0.60, 0.03) and with higher weight z-score difference (β = 0.24; 95% CI: 0.16, 0.65) and BMI z-scores in girls (β = 0.30; 95% CI: 0.04, 0.64) (p for sex interaction = 0.01 and 0.05, respectively) The ΣHMWPm was associated with significantly lower systolic BP *z*-scores in girls for all ages combined (adjusted β = −0.39; 95% CI: 0.65, −0.12 for the 2nd tertile and −0.28; −0.55, −0.01 for the 3rd tertile of exposure), but not in boys (*p*-sex interaction = 0.11 and 0.10 for the 2nd and 3rd tertiles of exposure, respectively). The ΣLMWPm was associated with lower systolic BP *z*-scores in girls (adjusted β = −0.23; 95% CI: 0.50, −0.04 in 2nd tertile and −0.40; −0.66, −0.12 in 3rd tertile of exposure) but not in boys (*p*-sex interaction = 0.17 for the 2nd and <0.01 in the 3rd tertile of exposure)	Valvi et al. (2015)
Longitudinal cohort study Mother–child pairs (Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) Project) N = 248	BPA Phthalates: DEP DBP DiBP BzBP DEHP	Measurement of BPA and phthalate metabolites (SG - adjusted) in maternal urine at three time points across pregnancy (1st, 2nd, and 3rd trimesters) and child's urine at 8–14 years of age	Anthropometry (weight and height), serum lipid profile (total cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) (Total cholesterol – HDL-C – (Triglycerides/5)) at 8–14 years of age	*In utero* BPA and phthalate exposure was not associated with lipid profile at 8–14 years of age; In boys, urinary levels of MCPP, MEP and ΣDBP at 8–14 years were each inversely corelated with total cholesterol and LDL-C, estimates for MCPP, MEP and ΣDBP were respectively −7.4% [−12.8, −2.0], −5.7% [−10.4, −1.0] and −6.7% [−11.8, −1.6] for total cholesterol and −12.7% [−21.6, −3.8], −10.8% [−18.5, −3.1] and −9.9% [−18.4, −1.5] for LDL-C In girls, higher urinary ΣDEHP correlated with lower LDL-C (−7.9% [−15.4%, −0.4%]).	Perng et al., 2017
Longitudinal cohort study Mother–child pairs (Health Outcomes and	Per- and polyfluoroalkyl substances:	Per- and polyfluoroalkyl substances in maternal serum samples (at 16- and 26-	Serum glucose, insulin, triglycerides, HDL, leptin and adiponectin concentrations, waist	Gestational and cord serum PFOA concentrations were positively associated with cardiometabolic	Li, N. et al., 2021

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Table 4 (*continued*)

Study (N)	Compound	Exposure assessment	Outcome assessment	Effect size [β, OR, RR (CI95%)]	Reference
Measures of the Environment (HOME) Study) N = 221	PFOA PFOS PFNA PFHxS	gestational week and at delivery), umbilical cord, and child serum samples at ages 3, 8, and 12 years	circumference, calculated HOMA-IR, triglyceride/HDL ratio, adiponectin/leptin ratio, cardiometabolic risk scores and BP z-scores at 12 years of age.	risk scores (βs and 95% confidence intervals [95% CIs]: gestational 0.8 [0.0, 1.6]; cord 0.9 [-0.1, 1.9] per interquartile range increase). Gestational and cord PFHxS associated with higher cardiometabolic risk scores (βs: gestational 0.9 [0.2, 1.6]; cord 0.9 [0.1, 1.7]).	
Longitudinal cohort study Mother–child pairs (Health Outcomes and Measures of the Environment (HOME) Study) N = 285 (between 2 and 8 years of age) N = 204 (at 8 years of age)	Per- and polyfluoroalkyl substances: PFOA PFOS PFNA PFHxS	Per- and polyfluoroalkyl substances in prenatal serum samples (at 16- and 26-gestational week and at delivery)	BMI z-scores between 2 and 8 years of age, waist circumference, and body fat at 8 years of age	Children born to women in the 2nd and 3rd terciles of PFOA concentrations had an 84% (RR: 1.84; 95% CI: 0.97, 3.50) and 54% (RR: 1.54; 95% CI: 0.77, 3.07) ↑ risk of being overweight or obese at 8 years of age compared to children in the 1st tercile, respectively. ↑ body fat in children born to women in the 2nd tercile (3.6%; 95% CI: 1.8, 5.5), but less elevated in the 3rd tercile (1.5%; 95% CI: −0.4, 3.4) compared to children in the 1st tercile. ↑ waist circumference among children in the 2nd (4.3; 95% CI:1.7, 6.9) and 3rd tercile (2.2; 95% CI:−0.5, 4.9) compared to children in the 1st PFOA tercile. Between 2 and 8 years of age, BMI z-scores increased at a greater rate among children in the 2nd (0.44; 95% CI: 0.23, 0.64; 2nd PFOA tercile × age p-value = 0.033) and 3rd (0.37; 95% CI: 0.14, 0.60; 3rd PFOA tercile × age p-value = 0.110) PFOA tercile compared to children in the 1st tercile (0.12; 95% CI: −0.08, 0.32). PFOS, PFNA and PFHxS were not associated with child adiposity at 8 years of age or changes in BMI z-scores between 2 and 8 years of age.	Braun, J. M. et al., 2016.

expressed, at least in human and mice (Brandenberger et al., 1997; Cunha et al., 2017, 2018a, 2018b; Glatstein and Yeh, 1995; Inoue et al., 2001; Jefferson et al., 2000), rendering the uterus vulnerable to EDCs.

Mammary gland development during embryogenesis is also minimal (reviewed in Cyr et al., 2016; Robinson, 2007), as most of the development occurs around puberty and during pregnancy, mostly under the influence of ovarian and pregnancy-related hormones (Paine and Lewis, 2017; Sternlicht, 2006), as described above. During fetal life, a rudimentary ductal epithelium is formed, surrounded by a specialized stroma, named the fat pad. Similar to the uterus, steroid hormones are not required for embryonic mammary gland development. Indeed, although ductal elongation and alveologenesis do not occur in mice lacking ERα, and secondary branching and alveologenesis are deficient in mice lacking PR and PrlR (Bocchinfuso et al., 2000; Korach et al., 1996; Lydon et al., 1995; Mueller et al., 2002; Ormandy et al., 1997), they all present with the rudimentary tree at birth. Interestingly, like the fetal endometrium, studies have shown the expression of hormonal receptors in the mammary gland of embryos in various species, including human and rodents (Heuberger et al., 1982; Hovey et al., 2002; Keeling et al., 2000; Naccarato et al., 2000), suggesting that they can respond to hormones.

Therefore, even though fetuses are exposed to high levels of maternal hormones during pregnancy, fetal development of the ovaries, the uterus and the mammary gland appear to be mostly independent of hormones. However, it is believed that during this period, hormones have organizational effects on these tissues, inducing permanent changes that influence responses to hormonal cues, health of the tissues and behavior later in life (Berenbaum and Beltz, 2011; Wallen, 2009). Accordingly, an increasing number of studies demonstrate in females, that inappropriate exposure to hormones or dysregulation of hormone signaling, such as those induced by EDCs, during this sensitive window of exposure can have important effects on the female reproductive system and thus impact their own capacities to become mothers. Indeed, a considerable number of studies have evaluated the effects of exposure to EDCs during the pre-conception and perinatal (*in utero* life and neonate) period on fetal ovaries, uterus and mammary gland development and diseases. However, a considerably lower number of studies concentrate on exposure during the *in-utero* life only.

3.3.1. *Bisphenol A and diethylstilboestrol*

Similar to pregnant women, some of the first evidence of the effects of fetal exposure to EDCs on the main reproductive organs of the female fetus, i.e. ovary, uterus and mammary gland, comes from BPA and DES, and have been reviewed elsewhere (Al Jishi and Sergi, 2017; Caserta et al., 2013; Kawa et al., 2021; Marie et al., 2015; Matuszczak et al., 2019; Pivonello et al., 2020; Rattan and Flaws, 2019; Richter et al., 2007; Ziv-Gal and Flaws, 2016). In animal studies, it has been demonstrated that prenatal exposure to BPA modifies the structure and gene expression signatures in the post-natal mammary gland (Table 5), in both the epithelium and the stroma, increases hyperplasia and sensitivity to N-Nitroso-N-methylurea (NMU)- or dimethyl-Benz(a) anthracene (DMBA)-induced mammary tumors, induces precocious

Table 5
Effect of an *in vitro* exposure to common endocrine disruptors on the mammary gland in animal models.

	Species	Concentration	Exposure Window	Effects on development	Chemically-induced Breast cancer (when assessed)	Reference
BPA	Sprague-Dawley rats	0.25, 2.5, 25, or 250 μg/kg BW/day	GD9-birth GD9-PND21	Increased preneoblastic and neoblastic lesions		Acevedo et al. (2013)
	Sprague-Dawley rats	25, or 250 μg/kg BW/day	GD10-21	Increased cell proliferation	Increased DMBA-induced breast cancer when DMBA is given at PND100, but not PND50	Betancourt et al. (2010)
	Sprague-Dawley rats	25, or 250 μg/kg BW/day	GD10-birth	Increased number of undifferentiated structures and change in gene expression		Moral et al. (2008)
	Wistar rats	25 μg/kg BW/day	GD8-23	Hyperplasia at PND110 and PND180	Increased NMU-induced breast cancer given at PND50	Durando et al. (2007)
	Wistar rats	25 or 250 μg/kg BW/day	GD8-23	Hyperplasia at PND 110, increased angiogenesis, dysregulation of signaling		Durando et al. (2011)
	Wistar-Furth rats	2.5, 25, 250 or 1000 μg/kg BW/day	GD9-PND1	Ductal hyperplasia at PND50 and PND45, carcinoma in situ at PND50 and PND95		Murray et al. (2007)
	CD-1 mice	25 Ug/kg BW/day	GD8-12 GD8-16 GD15-18 GD8-18	In animal treated after GD 12: Early decreased epithelial elongation; later increased epithelial volume and altered duct morphology		Hindman et al. (2017)
	CD-1 mice	25 or 250 μg/kg BW/day	GD9-birth	Increased (25 μg/kg) or decreased (250 mg/kg) mammary gland development at 1 month old; increased development at 6 months old		Markey et al. (2001)
	CD-1 mice	25 or 250 μg/kg BW/day	GD9-birth	Increased % of TEBs. Alveolar buds and lobuloalveoli at 4 months old		Markey et al. (2003)
	CD-1 mice	25 or 250 ng/kg BW/day	GD9-PND4	Decreased ductal elongation, increased number of TEBs relative to ductal area around puberty; increased lateral branching at 4 months		Munoz-de-Toro et al. (2005)
	CD-1 mice	0.5, 5 or 50 mg/kg BW/day	GD10-17	Increased development at PND20 (5 mg/kg)		Tucker et al. (2018)
	CD-1 mice	250 ng/kg BW/day	GD8-GD18	increased ductal area, ductal extension and area subtended by ductal tree delayed lumen formation, increased cell size; altered stroma at GD18		Vandenberg et al. (2007)
	CD-1 mice	25 μg/kg BW/day	GD9-18	Dysregulation of collagen in the stroma; increased mammary gland stiffness at 12 weeks old		Wormsbaecher et al. (2020)
	FVB/N mice	25 or 250 μg/kg BW/day	GD9-birth	no effect on ductal elongation at 3 and 5 weeks old	Earlier DMBA-induced tumor onset	Weber Lozada and Keri (2011)
BPFA	CD-1 mice	0.5, 5 or 50 mg/kg BW/day	GD10-17	Increased development at PND20 (all doses), PND28 (0.5 mg/kg) and PND35 (0.05, 5 mg/kg)	Preneoblastic lesions in older animal	Tucker et al. (2018)
BPS	CD-1 mice	0.5, 5 or 50 mg/kg BW/day	GD10-17	Increased development at PND20 (5 mg/kg), PND35 (all doses) and PND56 (0.5 mg/kg)	Preneoblastic lesions in older animal, more frequent than BPA	Tucker et al. (2018)
	CD-1 mice	25 Ug/kg BW/day	GD9-18	No effect observed on mammary gland stiffness (no other parameters analyzed)		Wormsbaecher et al. (2020)
DES	Sprague-Dawley rats	1.2 to 12,000 μg	GD10 + GD13 GD15 + GD17 + GD19 GD15 + GD18	High doses resulted in alteration of the nipple in neonates		Boylan (1978)
	Sprague-Dawley rats	1.2 μg	Gestation week 2 Gestation week 3		Increased number of tumor induced by DMBA; earlier onset when DES is given in the second week of gestation	Boylan and Calhoon (1979)
	Sprague-Dawley rats	1.2 μg	GD15 + GD18		Increased number and early onset of tumor induced by DMBA	Boylan et al., 1983
	CD-1 Mice	100 μg	GD9-18	increased mammary gland stiffness at 12 weeks old		Wormsbaecher et al. (2020)
Phthalates	Sprague-Dawley rats	N-butyl benzyl phthalate (BBP)	GD10-21	Change in morphology, alteration of gene expression		Moral et al. (2011)

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Table 5 (*continued*)

	Species	Concentration	Exposure Window	Effects on development	Chemically-induced Breast cancer (when assessed)	Reference
		120 or 500 mg/BW/day				
Lindane	CD-1 mice	15 mg/kg BW/day	GD9-GD16	No effects		Maranghi et al. (2007)
Atrazine	Long-Evans rats	0.09, 0.87, 8.73 or 100 mg/kg BW/day (metabolites)	GD15-19	Delayed mammary gland development		Enoch et al. (2007)
	Long-Evans rats	100 mg/kg BW/day	GD15-19	Delayed mammary gland development, elevated estrogen and progesterone receptors levels		Moon et al. (2007)
	Long-Evans rats	100 mg/kg BW/day	GD12-19	Delayed mammary gland development		Rayner et al. (2004)
	Long-Evans rats	100 mg/kg BW/day	GD13-15 GD15-17 GD17-19 GD13-19	Delayed mammary gland development, more important in GD17-19 and GD13-19 groups		Rayner et al. (2005)
TCDD	Sprague–Dawley rats	1 μg/kg BW/day	GD15	Increased number of TEBs and lobules II at PND50	Increased DMBA-induced breast cancer when DMBA is given PND50	Brown et al. (1998)
	Long-Evans rats	1 μg/kg BW/day	GD15 GD20	Delayed mammary gland development; effects were significant only with the group exposed at GD15		Fenton et al. (2002)
PFOA	CD-1 mice	0.3, 1.0, or 3.0 mg/kg BW/day	GD1-17 GD10-17	Dose-dependent developmental delays		Macon et al. (2011)
	CD-1 mice	0.01, 0.1, 0.3 or 1.0 mg/kg BW/day	GD1-17	Dose-dependent developmental delays		Tucker et al. (2015)
	CD-1 mice	5 mg/kg BW/day	GD1-17 GD8-17 GD12-17	Reduced mammary gland development at PND 10 and PND20 for all treatments		White et al. (2007)
	CD-1 mice	3 or 5 mg/kg BW/day	GD1-17 GD8-17 GD7-17 GD10-17 GD13-17 GD15-17	Delayed mammary gland development for all group		White et al. (2009)
	C57Bl/6 mice	0.01, 0.1, 0.3 or 1.0 mg/kg BW/day	GD1-17	Delays that were significant for the 0.3 and 1.0 doses		Tucker et al. (2015)
Unconventional oil and gas mixture	C57Bl/6 mice	3, 30, 300, or 3000 μg/kg BW/day	GD10-birth	No effect before puberty; Increased epithelial density and intraductal hyperplasia at adulthood		Sapouckey et al. (2018)

puberty, as demonstrated by vaginal opening, increases length of the estrous cycle, promotes vaginal cornification and decreases the number of corpora lutea (Betancourt et al., 2010; Durando et al., 2007, 2011; Markey et al., 2001; Moral et al., 2008; Murray et al., 2007; Nikaido et al., 2004; Paulose et al., 2015; Vandenberg et al., 2007; Wadia et al., 2013; Wormsbaecher et al., 2020). Similarly, the consequences of *in utero* exposure to DES have been well-documented and are described in many good reviews (reviewed in Al Jishi and Sergi, 2017; reviewed in Hilakivi-Clarke, 2014; reviewed in Sharara et al., 1998); reviewed in Newbold, 2004). In humans, daughters exposed *in utero* to DES showed various malformations of the reproductive tract, increased infertility, increased preterm birth and spontaneous abortion and higher risk for births that were small for gestational age (Hatch et al., 2011; Hoover et al., 2011; Kaufman, 1982; Kaufman et al., 2000; Senekjian et al., 1988). An increased risk for clear cell adenocarcinoma of the vagina and cervix was also found; for breast cancer, the results from the different cohorts tend to be significant only in aged women (Bibbo et al., 1978; Hatch et al., 1998; Herbst, 1979; Herbst et al., 1977, 1979a, 1979b; Palmer et al., 2002, 2006; Robboy et al., 1977, 1984; Scully et al., 1974; Tournaire et al., 2015; Troisi et al., 2019; Verloop et al., 2010). Many of these effects were reproduced in animal studies, including higher risk for breast cancer (Boylan, 1978; Boylan and Calhoon, 1979, 1981; Boylan et al., 1977, 1983a, 1983b; Honma et al., 2002; McLachlan et al., 1980, 1982; Newbold, 2004; Newbold et al., 2006; Wormsbaecher et al., 2020) (Table 5).

3.3.2. Phthalates

While many studies have evaluated the effects of an *in-utero* exposure to phthalates in male, fewer have evaluated the effects for females. Prenatal exposure to butyl benzyl phthalate (120 or 500 mg/kg) results in a delayed vaginal opening and changes in mammary gland structure, proliferation, and gene signatures after birth in rats (Moral et al., 2011). *In utero* exposure to MBzP and monoethyl phthalate (MEP) is associated with higher levels of testosterone in girls (8–13 years old) (Watkins et al., 2014). Interestingly, the effects of phthalates may differ depending on the time of exposure, as mean mono-2-ethylhexyl phthalate (MEHP) levels across pregnancy were associated with decreased odds of having a Tanner Stage>1 for breast development, while they were associated with increased odds of having a Tanner Stage>1 for pubic hair development when exposure occurred in the third trimester (Watkins et al., 2014, 2017).

3.3.3. Pesticides and persistent organochlorines

A few studies have investigated the effects of a prenatal exposure to DDT or DDE in offspring. In humans, a retrospective study of women exposed to DDE during pregnancy, age at menarche for female offspring was reduced by 1 year for each increase of 15 μg/l of DDE in maternal serum (Vasiliu et al., 2004). *In utero* exposure has also been linked with increased breast cancer risk (Cohn et al., 2015; Krigbaum et al., 2020; McDonald et al., 2020). For example, in a series of studies conducted by Cohn and collaborators, high levels of o,p′-DDT, an isomer of DDT, in maternal serum sampled during pregnancy or immediately after delivery predicted a nearly four-fold increase in the daughter's risk of developing breast cancer.

The effects of a prenatal exposure to the pesticide atrazine have also been documented, but mainly for the mammary gland. In a series of

experiments, the Fenton group showed that exposure to atrazine (between 0.09 and 100 mg/kg) at different times of gestation in rats led to delayed vaginal opening and mammary development in the offspring (Enoch et al., 2007; Moon et al., 2007; Rayner et al., 2004, 2005). Interestingly, when these females exposed to atrazine *in utero* were bred, the weight gain of the pups was decreased, suggesting impaired lactation (Rayner et al., 2005).

In contrast, the effects of *in utero* exposure to TCDD in rodents have been well-studied across the entire female reproductive system. Reported effects include the presence of vaginal threads, increased frequency of cleft clitoris, delayed vaginal opening, altered vaginal estrous cyclicity, reduced fertility, delayed mammary gland development and increased susceptibility to DMBA-induced breast cancer, decreased ovarian weight and cystic endometrial hyperplasia (Brown et al., 1998; Fenton et al., 2002; Flaws et al., 1997; Gray and Ostby, 1995; Gray et al., 1997; Jenkins et al., 2007). Women exposed *in utero* to TCDD during the Seveso incident also showed decreased fertility and potentially altered thyroid homeostasis (Eskenazi et al., 2021; Warner et al., 2020).

Other common pesticides or persistent organochlorines have also been associated with reproductive defects in females exposed *in utero*. For example, exposure to lindane (15 mg/kg) in mice from gestational day 9–16 induced increased uterus weight, earlier vaginal patency and reduced diameters of primary oocytes on post-natal day 22 (Maranghi et al., 2007). In humans, prenatal exposure to polybrominated biphenyls (PBBs), as measured by levels in maternal serum, is associated with a lower age at menarche in their daughters (Blanck et al., 2000).

3.3.4. *Perfluorooctanoic acid (PFOA)*

A few studies have evaluated the effects *in utero* PFOA exposure. It has been demonstrated that *in utero* exposure to PFOA in mice results in decreased body weight and persistent delayed mammary gland development (White et al., 2007, 2009, 2011). In mice exposed to PFOA from gestation day 1–17, puberty was slightly delayed in females, but accelerated in males (Lau et al., 2006). More studies are certainly needed to further study the effects of PFOA, as well as other perfluoroalkyl acid (PFAA), on the development of the reproductive system.

3.3.5. *Other less-studied EDCs*

Exposure to a mixture of compounds used in hydraulic fracturing *in utero* resulted in decreased levels of prolactin, FSH and LH and impaired folliculogenesis, in female mice (Kassotis et al., 2016a). It also resulted in increased epithelial density and cellular proliferation in female mammary glands at adulthood, which also presented Terminal-end buds (TEB)-like structures that are highly proliferative and express ERα (Sapouckey et al., 2018).

4. Concluding remarks

Pregnancy is a complex process involving many tightly orchestrated events that occur in both the developing fetus and the mother. It is becoming more and more apparent that EDCs can affect the overall health of pregnant women, and in some cases, the health of their offspring. Given that in addition to the large number of chemicals that already exist and have not yet been tested, or fully tested, for reproductive effects, new chemicals are developed each day in the pharmaceutical, agricultural, industrial and materials science sectors, many of them with the capacity to influence endocrine systems, exposure to EDCs during pregnancy is a concern. It is imperative that further studies address critical questions concerning mechanisms of toxicity, lifelong consequences for offspring of maternal exposure to these compounds and potential for intervention strategies, including workplace safety and social interventions, to prevent or minimize these exposures.

Author contributions

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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