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The effects of polycyclic aromatic compounds (PACs) on mammalian ovarian function

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ABSTRACT

Polycyclic aromatic compounds (PACs) are a broad class of contaminants ubiquitously present in the environment due to natural and anthropogenic activities. With increasing industrialization and reliance on petroleum worldwide, PACs are increasingly being detected in different environmental compartments. Previous studies have shown that PACs possess endocrine disruptive properties as these compounds often interfere with hormone signaling and function. In females, the ovary is largely responsible for regulating reproductive and endocrine function and thus, serves as a primary target for PAC-mediated toxicity. Perturbations in the signaling pathways that mediate ovarian folliculogenesis, steroidogenesis and angiogenesis can lead to adverse reproductive outcomes including polycystic ovary syndrome, premature ovarian insufficiency, and infertility. To date, the impact of PACs on ovarian function has focused predominantly on polycyclic aromatic hydrocarbons like benzo(a)pyrene, 3-methylcholanthrene and 7,12-dimethylbenz[a]anthracene. However, investigation into the impact of substituted PACs including halogenated, heterocyclic, and alkylated PACs on mammalian reproduction has been largely overlooked despite the fact that these compounds are found in higher abundance in free-ranging wildlife. This review aims to discuss current literature on the effects of PACs on the ovary in mammals, with a particular focus on folliculogenesis, steroidogenesis and angiogenesis, which are key processes necessary for proper ovarian functions.

1. Introduction

Endocrine disrupting chemicals (EDCs) are a broad group of exogenous compounds that can interfere with hormone action (Gore et al., 2015; Zoeller et al., 2012). While there are a number of naturally occurring EDCs, a large proportion are derived from man-made products including plastics, textiles, detergents, flame retardants, pesticides, cosmetics and electronics (Bergman et al., 2013). To date, nearly 1000 chemicals have been identified as EDCs, representing only a small fraction of the tens of thousands of manufactured chemicals worldwide that have been tested for safety, or waiting to be tested (Gore et al., 2015). Since EDCs are a complex group of structurally diverse chemicals detected as components of complex environmental mixtures, it is often difficult for researchers to predict and establish whether a specific compound will possess endocrine disruptive properties.

Reproductive organs are major targets of EDCs since these chemicals often mimic sex steroid hormones (Reviewed in: (Graceli et al., 2020; La Merrill et al., 2020; Piazza & Urbanetz, 2019; Plunk & Richards, 2020; Rattan et al., 2017; Sifakis et al., 2017). Indeed, many ovarian disorders are characterized by impaired hormone signaling (Reviewed in: (Rosenfield & Ehrmann, 2016)). As the ovary is a major regulator of female reproductive and endocrine function in mammals, the ovary is a vulnerable target for EDC toxicity. Exposure to environmental chemicals may perturb ovarian structure (e.g. follicle dynamics) and function, which can have long-term consequences that influence fertility, pregnancy success, and offspring development (Rattan et al., 2017, 2018, Yu et al., 2019, 2020).

In contrast to commonly studied endocrine disruptors like bisphenol A, phthalates and pesticides that are manufactured for commercial use, polycyclic aromatic compounds (PACs) are ubiquitous environmental contaminants formed from the incomplete combustion or thermolysis of organic material (Hsieh et al., 2021). PACs are a broad class of chemicals that possess two or more fused aromatic rings and encompass polycyclic aromatic hydrocarbons (PAHs), N-, S- and O-containing PAHs, heterocyclic PAHs, halogenated PAHs and their

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alkylated congeners (Achten & Andersson, 2015; Hsieh et al., 2021). While natural sources (i.e., volcanic activity, forest fires) contribute to PAC release, emissions are largely attributed to anthropogenic activity (i.e., vehicle exhaust, cigarette smoke, industrial activity) (Tevlin et al., 2021). In fact, with global urban expansion and reliance on petroleum products, several studies are reporting increased levels of PACs near urban areas and industrial facilities (Cheng et al., 2018; Peng et al., 2016; Tevlin et al., 2021). In general, PACs are highly lipophilic compounds that can be found as complex mixtures adsorbed to particles within the air, water, soil and sediment and are able to persist in the environment (Wallace et al., 2020). Exposure to PACs can occur via inhalation, ingestion, absorption through the skin and other mucosal barriers, as well as be transferred between mother and offspring (Gao et al., 2018; Karttunen et al., 2010). Studies across a wide range of species have shown that PACs are carcinogenic, immunotoxic, genotoxic, cardiotoxic, and adversely affect reproductive and developmental health (Reviewed in: (Abdel-Shafy & Mansour, 2016; Bolden et al., 2017; Kim et al., 2013; Wallace et al., 2020)). Due to their negative impacts on both human and wildlife health, a subset of PACs are listed as Schedule 1 toxic substances under the Canadian Environmental Protection Act (CEPA) 1999 and as priority contaminants by the United States Environmental Protection Agency (USEPA) (Abdel-Shafy & Mansour, 2016; Government of Canada, 2013; Keith, 2015). However, there is increasing concern that this list of priority contaminants should be expanded beyond the traditional parent compounds to include current, environmentally relevant PACs such as alkylated and heterocyclic derivatives (Marvin et al., 2020).

While previous reviews have summarized the effects of different EDCs on female reproductive health and the ovary (Bolden et al., 2017; Hannon & Flaws, 2015; Lauretta et al., 2019; Patel et al., 2015; Rattan et al., 2017), evidence regarding the effects of PAC exposure on mammalian ovarian function is limited. Toxicological studies investigating the endocrine disruptive effects of PACs focus largely on parent PAH compounds and overlooks other classes that are also present in the environment and may be more toxic than their parent/unsubstituted compounds (Hsieh et al., 2021; Lam et al., 2018; Lee et al., 2017; Marvin et al., 2020; Provencher et al., 2020). As such, there is an urgent need to consider PACs as a priority environmental contaminant, especially as the risk for exposure continues to grow in parallel with urban/industrial expansion and the global reliance for petroleum products (Marvin et al., 2020). Indeed, while the exact mechanisms by which PACs induce ovarian toxicity are unknown, the next sections will review available literature discussing how PACs disrupt ovarian function. A literature review was conducted using PubMed and Google Scholar to collect relevant papers published between the years 1979 and December 2021 using the following search terms: “ovary”, “polycyclic aromatic compound”, “polycyclic aromatic hydrocarbon”, “follicle”, “steroid”, “angiogenesis”, “granulosa”, “theca”, “reproduction”, “fertility”. We also reviewed relevant literature from the reference lists of the selected papers and focused on studies using mammalian cell lines and/or experimental models. Studies were excluded if: the article was not written in the English language, if the article did not focus on ovarian structure and/or function and if the article did not specify individual PACs used in mixtures.

2. Overview: Ovarian targets of toxicity

The ovary is responsible for regulating reproduction through the coordinated development and release of a mature oocyte (folliculogenesis) (Fig. 1), and is responsible for regulating menstrual/estrus cyclicity and sexual behaviour/characteristics through the synthesis and secretion of steroid hormones (steroidogenesis) (Gibson & Mahdy, 2021). These processes are under control from the hypothalamic-pituitary-ovarian (HPO) axis, whereby gonadotropin-releasing hormone from the hypothalamus facilitates the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary to aid in follicular growth and ovulation (Abedel-Majed et al., 2019; Richards & Pangas, 2010). In humans, a finite number of primordial follicles are fully developed by 6 to 9 months of gestation (post-natal day 3 for rodents) (Rajah et al., 1992; Williams & Erickson, 2000). On average, females are born with 400,000 primordial follicles, which declines exponentially with age (Kerr et al., 2013; Wallace & Kelsey, 2010); this primordial follicle pool is thought to represent a female’s reproductive potential of available oocytes for subsequent fertilization (Rajah et al., 1992; Williams & Erickson, 2000). Chemical insults which deplete the pool of primordial follicles therefore have the potential to adversely affect life-long fertility (Hoyer & Keating, 2014; Johansson et al., 2016). In contrast, xenobiotic exposures which damage primary, secondary, and antral follicles may lead to temporary infertility and anovulation (Hoyer & Keating, 2014); an effect which is reversible if the remaining primordial pool can recruit new follicles and replenish the supply of developing follicles for subsequent ovulation. Lastly, if all populations of follicles are impacted as a result of EDC exposure, either temporary infertility or premature ovarian insufficiency (early menopause) may result in affected women (Hoyer & Keating, 2014).

Steroids produced within the ovary are critical to cyclically modulate gonadotropin responses along the HPO axis and facilitate oocyte maturation, follicle growth, and ovulation (Jamnongjit & Hammes, 2006). Normal ovarian steroid production is hypothesized to follow the “Two Cell/Two Gonadotropin Model” in which theca cells and granulosa cells synthesize sex steroid hormones in response to LH and FSH stimulation from the anterior pituitary (Jamnongjit & Hammes, 2006). The steroidogenic cascade begins with LH and FSH binding to their respective receptors which then facilitates the transcription of several steroidogenic enzymes including steroidogenic acute regulatory protein (STAR), cytochrome P450 cholesterol side-chain cleavage (CYP11A1), 3β-hydroxysteroid dehydrogenase (HSD3B), 17α-hydroxylase (CYP17A1), 17 β-hydroxysteroid dehydrogenase (HSD17B) and aromatase (CYP19A1) (Jamnongjit & Hammes, 2006). Following LH and FSH stimulation from the anterior pituitary, both theca and granulosa cells produce progesterone (P4), while androgens (A4) like testosterone (T) are primarily synthesized within theca cells and estrogens like estradiol (E2) are primarily synthesized within granulosa cells (Jamnongjit & Hammes, 2006). The newly synthesized E2 can feedback to the HPO axis to inhibit gonadotropin hormone secretion or it can be metabolized into its inactive form by CYP1A1, CYP1A2, CYP3A4 or CYP1B1 (Hayes et al., 1996; Jamnongjit & Hammes, 2006; Mlynarcikova et al., 2014).

3. Effect of polycyclic aromatic compounds (PACs) on ovarian development and folliculogenesis in mammals

There is considerable evidence that PACs can function as EDCs and negatively affect reproductive function (Bolden et al., 2017; Khan et al., 2021; Lee et al., 2017; Raez-Villanueva et al., 2021; Zhang et al., 2016). However, reports on the impacts of PACs on the ovary in mammals are limited. Studies have focused largely on PACs such as benzo(a)pyrene (BaP), 7,12-dimethylbenz[a]anthracene (DMBA) and 3-methylcholanthrene (3MC), which are commonly found in high concentrations in tobacco smoke, air pollution, petroleum compounds, furnace gas and food (i.e., charred meat) (Borman et al., 2000; Health Canada, 2015). Indeed, biomonitoring reports show detectable levels of PACs and their metabolites in the blood, urine, placenta, maternal and umbilical cord blood, milk and fat tissue (Guo et al., 2012; Madhavan & Naidu, 1995; Neal et al., 2008; Strickland et al., 1996; Wang et al., 2012). Similarly, detection of PACs in the follicular fluid of females commonly exposed to cigarette smoke and undergoing *in vitro* fertilization (IVF) (Neal et al., 2007, 2008) provide evidence

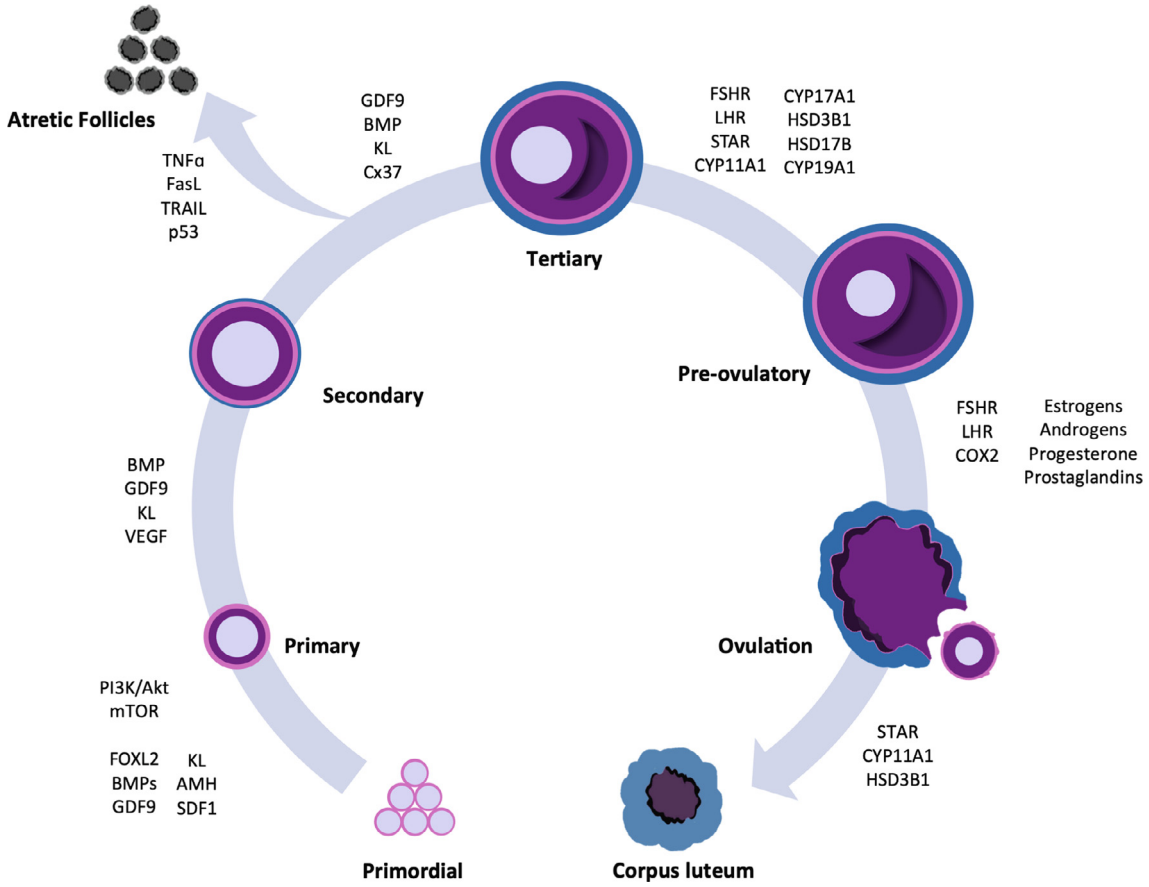


Fig. 1. Summary of ovarian folliculogenesis and signaling factors that regulate transition between each stage of follicle development. PI3k/AKT, phosphoinositide 3-kinase serine/threonine protein kinase; mTOR, mammalian target of rapamycin; FOXL2, forkhead box L2; BMP, bone morphogenic proteins; GDF9, growth differentiation factor-9; bFGF, basic fibroblast growth factor; KL, kit ligand; AMH, anti-Müllerian hormone; SDF1, stromal-derived factor-1; VEGF, vascular endothelial growth factor; TNFa, tumor necrosis factor alpha; Fas ligand, FASL; TRAIL, TNF-related apoptosis-inducing ligand; p53, tumor suppressor p53; Cx37, connexin 37; FSHR, follicle stimulating hormone receptor; LHR, luteinizing hormone receptor; STAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 cholesterol side-chain cleavage; CYP17A1, 17α-hydroxylase; HSD3B1, 3b-hydroxysteroid dehydrogenase; HSD17B, 17b-hydroxysteroid dehydrogenase; COX2, cyclooxygenase-2.

that exposure to various PACs have the potential to disrupt ovarian function.

3.1. Effect of PACs on ovarian germ cells

In vivo and *in vitro* studies have shown that exposure to PACs can damage ovarian germ cells. Mice exposed to BaP *in utero* have significantly reduced ovarian germ cell populations, an effect that diminishes ovarian reserve (Luderer et al., 2019). In postnatal life, 10-week old female mice exposed to 10 mg/kg/day BaP *in utero* had a significant reduction in the number of developing follicles (primordial-antral), possessing only 3% as many healthy follicles compared to control (Luderer et al., 2019). This effect was paralleled with histopathological abnormalities of the surface epithelia (i.e., multiple epithelial layers, invaginations) in exposed animals (Luderer et al., 2019). Interestingly, *in vitro* exposure to BaP also significantly increased germ cell expression of BCL2 associated X protein (BAX), an upstream regulator of caspase-mediated apoptosis (Lim et al., 2016). Pre-treatment with a pan-caspase inhibitor prevented BaP-induced ovarian germ cell death, demonstrating that the ovotoxic effects of BaP on germ cells observed *in vitro* may be caspase-dependent (Lim et al., 2016). More recently, transcriptomic analysis identified changes in genes related to inflammatory processes following fetal exposure to BaP at doses which have been demonstrated to damage ovarian germ cells (Lim et al., 2022), suggesting that inflammation may also play a critical role in the ovotoxic effects of early life exposure to PACs.

3.2. Effect of PACs on oocytes

PAC exposure has also been shown to affect oocyte survival and growth. For example, in 5- to 6-week old mice, exposure to BaP, 3MC and DMBA (80 mg/kg) resulted in increased pyknosis and cytolysis of the oocytes in primordial follicles (Mattison, 1980). BaP exposure has also been shown to impair meiotic progression in both porcine (Miao et al., 2018) and murine (Sui et al., 2020; Sobinoff et al., 2012b; Zhang et al., 2018) oocytes, compromising oocyte maturation and quality through altered spindle assembly, chromosomal alignment, cytoskeleton structures and mitochondrial integrity. In fact, exposure to BaP can cause mitochondrial dysfunction and induce oxidative stress, leading to increased levels of reactive oxygen species (ROS), lipid peroxidation and apoptosis (Lim et al., 2015b; Sobinoff et al., 2012b; Zhang et al., 2018). Similarly, maternal BaP exposure can also significantly alter meiotic progression, cause mitochondrial dysfunction, and induce early apoptosis in offspring, thus compromising oocyte quality and developmental competence (Sui et al., 2020). Together, these effects of BaP may decrease fertilization potential and significantly reduce litter sizes of exposed females (Zhang et al., 2018). Similarly, DMBA has also been shown to directly affect the oocyte whereby porcine cumulus-oocyte complexes cultured with

DMBA *in vitro* exhibited decreased mitochondrial membrane potential, increased cellular ROS, DNA damage and apoptosis, and histone modifications (Song et al., 2017). Single cell RNA-sequencing revealed that the adverse effects of DMBA on oocyte maturation may be attributed, in part, to aberrant signaling pathways related to meiosis (Yang et al., 2020a). In addition, oxidative stress following PAC exposure seems to be central to the observed oocyte damage as antioxidants such as vitamin C, coenzyme Q, or melatonin, reduced ROS levels and apoptosis in exposed oocytes (Yang et al., 2020a).

3.3. Effect of PACs on primordial follicles

The female reproductive life span can be shortened if unexpected alterations occur to the primordial follicle pool, such as aberrant activation and/or follicular atresia (McLaughlin & McIver, 2009). BaP, DMBA and 3MC have all been reported to target primordial follicles, accelerating the depletion of the ovarian reserve (Borman et al., 2000; Matikainen et al., 2001; Mattison, 1980; Mattison & Thorgeirsson, 1979; Rhon-Calderón et al., 2016; Sobinoff et al., 2011, 2012a; Sobinoff et al., 2012b). Moreover, the ovotoxic effects of these PACs may impact offspring born to exposed mothers, as maternal exposure to BaP and DMBA significantly decreased ovarian reserve and the size of the primordial follicle pool in F1 offspring (Jurisicova et al., 2007). Transcriptomic analyses in rodent models revealed that BaP, DMBA and 3MC exposure significantly induced genes and pathways involved in follicle atresia, follicle growth, primordial follicle activation, cell adhesion, cell cycle progression and cell growth and apoptosis (Pru et al., 2009; Rhon-Calderón et al., 2018; Sobinoff et al., 2011, 2012a; Sobinoff et al., 2012b). Studies conducted in knockout mouse models revealed that proapoptotic markers like tumor protein P53 and BAX are required for PAC-induced depletion of primordial follicles and cell death (Jurisicova et al., 2007; Matikainen et al., 2001; Pru et al., 2009). Other studies demonstrated that PI3K/Akt and mTOR signaling pathways are induced by PACs as a compensatory mechanism to activate primordial follicles in an attempt to replenish developing follicles lost to atresia (Sobinoff et al., 2011, 2012a).

3.4. Effect of PACs on pre-antral to antral follicles

There is considerable evidence from *in vitro* and experimental studies demonstrating the adverse effects of PACs on ovarian follicles at multiple stages of follicle development. For example, isolated rat follicles exposed to BaP at doses reported in follicular fluid of IVF patients who smoked (Neal et al., 2008), had significantly decreased follicle growth and cell proliferation (Neal et al., 2010). Similarly, ovaries cultured with DMBA or its metabolite, DMBA-3,4-diol, showed a dose- and time-dependent decrease in both primordial, primary and secondary follicle numbers, with greater sensitivity observed with DMBA-3,4-diol treatment (Igawa et al., 2009; Madden et al., 2014; Zhou et al., 2018). In fact, the rate-limiting enzyme responsible for DMBA-3,4-diol formation, microsomal epoxide hydrolase, was shown to increase in expression just prior to follicle loss, suggesting that bioactivation of DMBA is involved in PAC-mediated ovotoxicity (Igawa et al., 2009; Rajapaksa et al., 2006).

Typically, PACs are metabolized via phase I cytochrome P450 (CYP) enzymes, creating metabolites that may be more toxic than their parent compounds (Lim et al., 2013). In fact, reactive metabolites, BaP-7,8-dihydrodiol-9,10-epoxide (BPDE), BaP-7,8-quinone (BPQ), and phenanthrene-1,2-quinone (PheQ) were detected in BaP or phenanthrene exposed follicles and led to the formation of DNA adducts (Einaudi et al., 2014; Yao et al., 2017). Importantly, sensitivity to DNA damage may depend on the stage of follicle development as immature oocytes of early antral stage and large preantral follicles (exposed 4 and 6 days before ovulation, respectively) were more sensitive to BaP-induced DNA damage than oocytes of antral, primary and primordial follicles (exposed 2, 15 and 22 days before ovulation, respectively) (Einaudi et al., 2014). Of note, while toxic effects of BaP on late antral follicles were not observed, it is plausible that oocytes within antral follicles had already reached maximum maturity at the time of BaP treatment and thus were not sensitive to DNA damage (Einaudi et al., 2014). Typically, DNA damage to oocytes of developing follicles occurs in parallel with follicular atresia and provide evidence of their mutagenic potential and contribution towards the onset of premature ovarian insufficiency in PAC exposed females (Sobinoff et al., 2012b).

PACs can also affect ovarian follicle development via increased oxidative stress. Metabolism of PACs by the endogenous xenobiotic metabolizing enzymes (e.g. CYP1A1 and CYP1B1) may contribute to an increased production of ROS (An et al., 2011; Siddique et al., 2014). In fact, a dose-dependent increase in oxidative stress markers, 8-isoprostane (8-IsoP) and 8-hydroxy-2-deoxy guanosine (8-OH-dG) was observed following BaP treatment of isolated preantral follicles (Siddique et al., 2014). Similarly, 4- to 6-week old mice exposed to BaP for 10 days had significant increases in ROS and oocyte apoptosis; outcomes that interfered with proper oocyte maturation, fertilization rate and reduced fertility in exposed females (Zhang et al., 2018). As such, ovarian responses to mediate oxidative stress are critical for follicle viability. There is evidence that DMBA significantly alters the mRNA expression of genes involved in xenobiotic metabolism, autophagy and oxidative stress response, in association with significant decreases in large primary and secondary follicle numbers (Madden et al., 2014). Similarly, in isolated rat follicles cultured with DMBA for 12, 24 and 48 h, there was a significant increase in ROS production, as well as increased granulosa and theca cell apoptosis at 48 h (Tsai-Turton et al., 2007). Whole rat ovaries cultured with DMBA had significantly higher mRNA expression of the antioxidant enzymes superoxide dismutase enzyme-1 and −2 (Madden et al., 2014); enzymes which are responsible for the detoxification of ROS and demonstrate the pro-oxidant effects of DMBA exposure. Co-treatment of ovaries with DMBA and glutathione (GSH), a phase II antioxidant responsible for the detoxification of ROS generated by PAC metabolites (Lim et al., 2013), alleviated DMBA-induced follicle loss (Tsai-Turton et al., 2007). The observation that GSH may be important for mediating antioxidant responses required for PAC detoxification are further supported by animal studies done in mice genetically deficient in the glutamate-cysteine ligase modifier subunit (GCLM), a critical enzymatic subunit necessary for proper GSH synthesis (Lim et al., 2013, 2015a). Mice that lacked the gene that encoded for GCLM were reported to be more sensitive to the toxic effects of prenatal exposure to BaP on total follicle numbers at all stages of folliculogenesis and fertility (Lim et al., 2013). Taken together, these studies suggest that prototypical PACs such as BaP adversely affect both follicle structure and function, which may contribute to impaired fertility observed in women who smoke (Sadeu & Foster, 2011).

3.5. Other PACs and follicle development

To our knowledge, there is little to no data regarding the impacts of other classes of PACs on ovarian follicle development in mammals. Heterocyclic PACs, as well as N-, O- and S-containing PACs, are polar hydrocarbons commonly found in crude oil, bitumen and petroleum products like diesel and pavement sealants (Idowu et al., 2019). Similar to non-polar PACs, the mutagenic effects of polar PACs require bioactivation and can lead to DNA damage and DNA adduct formation (Idowu et al., 2019). Interestingly, N-containing PAC-mediated DNA adduct formation can occur via nitro reduction or CYP-dependent oxidation pathways (Benigni & Bossa, 2011; Idowu et al., 2019). In human umbilical vein endothelial cells, 1-nitropyrene, which is one of the most abundant N-containing PACs in diesel exhaust, significantly induced DNA damage and ROS production (Andersson et al., 2009). Treatment with dicoumarol, a nitro

reductase inhibitor and aryl hydrocarbon receptor ligand, significantly reduced 1-nitropyrene-induced genotoxicity, suggesting that these effects were mediated by metabolites formed by nitro reduction (Andersson et al., 2009). Similarly, exposure to the S-containing heterocyclic PAC, dibenzothiophene, led to significant concentration-dependent increases in ROS production and mitochondrial-mediated apoptosis in human neuroblastoma cells (Sarma et al., 2017). Together, with changes to pro- and anti-apoptotic gene expression profiles, this suggests that PAC-induced oxidative stress may involve mitochondria-dependent apoptotic pathways (Sarma et al., 2017). Studies conducted in zebrafish (*Danio rerio)* and Japanese medaka (*Oriyzias latipes)* embryos revealed that O-containing PAC toxicity may also be attributed to increased ROS formation and DNA damage (Dasgupta et al., 2014; Elie et al., 2015; Knecht et al., 2013). In fact, pathway analysis of the zebrafish metabolome revealed that O-containing PACs significantly perturb GSH biosynthesis and metabolism (Elie et al., 2015); an effect supported by altered expression of genes important to GSH-mediated detoxification like glutathione S-transferase and glutathione peroxidase (Knecht et al., 2013). Therefore, as oxidative stress and depletion of the antioxidant GSH can induce apoptosis in preovulatory follicles (Tsai-Turton & Luderer, 2006), it is plausible that other substituted PACs like N- or O-containing PACs may impact folliculogenesis in mammals through similar pathways of effect.

4. Effect of PACs on ovarian hormone secretion & angiogenesis

4.1. Effect of PACs on steroidogenesis and ovarian hormone secretion

Though PACs are known endocrine disruptors (Zhang et al., 2016), very few studies have examined the effects of PACs on ovarian steroidogenesis in mammals despite the fact that sex steroid hormones are primarily synthesized by the ovary. Isolated rat follicles exposed to BaP at doses reported in follicular fluid of IVF patients who smoked (Neal et al., 2008), demonstrated a dose-dependent decrease in E2 and anti-Mullerian hormone (AMH) secretion (Neal et al., 2007, 2010). AMH is an important hormone primarily secreted by granulosa cells in early growing follicles that negatively regulates primordial follicle activation and FSH-dependent follicle recruitment (Dewailly et al., 2016). In fact, AMH has been shown to inhibit FSH-dependent induction of aromatase activity and E2 secretion (Andersen & Byskov, 2006; Dewailly et al., 2016).

Interestingly, subacute (14 days) and subchronic (60 days) exposure to BaP extended the length of the estrous cycle, significantly decreased serum E2, LH and P4 levels, and reduced the rate of ovulation and litter size in rats (Archibong et al., 2012; Liu et al., 2020; Xu et al., 2010). Previous studies have attributed the reduction in P4 secretion to a lack of functional corpora lutea in BaP exposed animals (Liu et al., 2020). Indeed, corpora lutea are incredibly important steroidogenic structures that support uterine implantation and maintenance of early pregnancy (Oliver & Pillarisetty, 2021). BaP exposure has also been shown to decrease the mRNA expression of aromatase, the rate-limiting enzyme responsible for E2 synthesis (Xu et al., 2010). In human studies, fetal exposure to cigarette smoke resulted in dysregulation of ovarian estrogen production and estrogen receptor expression (Fowler et al., 2014). These results are consistent with other reports of PACs perturbing estrogen signaling (Lee et al., 2020; Rahmani et al., 2021; Šimečková et al., 2022; Słowikowski et al., 2021). Together, these findings suggest that PACs can act directly at the level of the ovary to disrupt ovarian steroidogenesis. These findings are further supported by epidemiological studies demonstrating an association between PAC exposure, ovarian steroid hormone metabolites and reproductive endpoints (Luderer et al., 2017).

4.2. Effect of PACs on angiogenesis

Given that the ovary is in a continuous state of remodeling, proper establishment of a vascular network is necessary to transport nutrients, oxygen, hormones and waste between the developing follicle, corpus luteum and the circulatory system (Bruno et al., 2009). VEGF is one of the most notable growth factors that facilitates endothelial cell migration and has been shown to significantly alter the total number of healthy and atretic preovulatory follicles, as well as the number of oocytes ovulated in mature rats (Iijima et al., 2005). VEGF expression has been reported to increase in parallel to follicular development and is critical for capillary network formation of the corpus luteum (Ferrara et al., 2004; Greenaway et al., 2005; Yamamoto et al., 1997; Yang & Fortune, 2007). BaP has been shown to interfere with luteal angiogenesis and vascular maturation during pregnancy, impeding the proper formation of corpora lutea (Liu et al., 2020). BaP treated rats possessed significantly fewer corpora lutea and altered vascular branches. In fact, BaP treatment significantly decreased the expression of pro-angiogenic factors, VEGF receptor 2, ANGPT-1, and ANGPT-1 receptor, and decreased expression of anti-angiogenic factor, TSP1 (Liu et al., 2020). The effects of BaP to inhibit angiogenesis may be a direct effect of its action to downregulate VEGF, as has been reported in decidual tissues of mice exposed to BaP (Li et al., 2017), or secondary to perturbations in ovarian steroidogenesis (Hyder et al., 2000).

4.3. Other PACs and steroidogenesis

There are a limited number of studies that have investigated the ovotoxic effects of polychlorinated naphthalenes (PCNs). PCNs are a persistent group of halogenated PAHs previously used in the manufacturing of cable insulation, instrument seals and solvents, and lubricants until commercial production ceased in the 1980s; however, PCNs are also produced as a by-product from chemical and industrial processes involving organochlorides like polychlorinated biphenyls (Fernandes et al., 2017). Porcine antral follicles exposed to a technical mixture of PCN (Halowax 1051) had significant increases in T and decreases in E2 secretion at all doses tested (1–1000 pg/mL) (Gregoraszczuk et al., 2011). Alongside this effect, a low dose of PCN (1 pg/mL) significantly decreased activity of the steroidogenic biosynthetic enzyme HSD17B and increased CYP19A1 activity, while high dose PCN (10–1000 pg/mL) significantly increased HSD17B and decreased CYP19A1 activity (Gregoraszczuk et al., 2011). It was later found that the major chloronaphthalene congeners which constitute 10% of the total technical mixture of PCN (CN73, CN74 and CN75) each possessed androgenic and anti-estrogenic properties in porcine follicles (Barć & Gregoraszczuk, 2014), potentially contributing to the overall observed effect of the Halowax 1051 mixture (Gregoraszczuk et al., 2011). In fact, while each congener increased P4/A4 and T/E2 and decreased A4/T secretion ratios, CN73 was the most potent.

Crude oil is a complex mixture of various PACs. A recent metabolomics study demonstrated that steroid hormone biosynthesis was the one of top metabolic pathways altered across 3 human cell types following exposure to PAC fractions of sediment samples collected from the Alberta oil sands region, the world's third largest heavy crude oil reserve (Sarma et al., 2019). Indeed, it is well known that various individual PACs, as well as environmental PAC mixtures, possess estrogenic or antiestrogenic activity to affect steroid signaling pathways (Reviewed in: (Zhang et al., 2016)). One study reported that 5 major PACs commonly found in crude oil (naphthalene, fluorene, dibenzothiophene, phenanthrene, chrysene) and their alkylated analogues possessed endocrine disruptive properties in human MVLN-*luc* and H295R cells (Lee et al., 2017). Twenty of 30 PACs tested significantly altered steroid production, which may be attributed to the ability of some of these compounds to be potent estrogen receptor agonists. Interestingly, however, the observed effects were influenced by alkyla-

tion (Lee et al., 2017). Similarly, another study conducted in human placental trophoblast cells reported that the alkylated congener of a petroleum-derived S-containing heterocyclic PAC, 2,4,7-trimethyldi benzothiophene, but not its parent compound dibenzothiophene, significantly increased E2 secretion in association with surrogate markers for angiogenesis (Raez-Villanueva et al., 2021).

Numerous studies have demonstrated that PACs affect ovarian function in aquatic species (Reviewed in: (Hodson, 2017; Ruberg et al., 2021; Wallace et al., 2020)). PACs present in petrogenic wastewaters and/or accidental oil spills are subject to chemical, biological and physical weathering processes that increase the relative concentrations of substituted PACs, thus supporting evidence of these substituted PACs contributing to the majority of total PAC burdens in exposed wildlife (Lee et al., 2017; Provencher et al., 2020). While there is limited data in mammals reporting the impact of substituted PACs on ovarian steroidogenesis, studies done in aquatic species support the hypothesis that substituted PACs may have more pronounced effects on steroid synthesis than their parent counterparts. Carp (*Cyprinus caripo)* gonads exposed to hydroxylated analogues of naphthalene, phenanthrene, pyrene and chrysene demonstrated aberrant androgen and estrogen synthesis while the parent compounds had no significant effect (Fernandes & Porte, 2013). In fact, only 9-hydroxyphenathrene had a significant inhibitory effect on ovarian aromatase activity (Fernandes & Porte, 2013). Similarly, Japanese embryo larvae (*Oryzias latipes*) exposed to dibenzothiophene (either parent, alkylated and mixture), a common heterocyclic PAC found in petroleum and petroleum-derived wastewaters, experienced significant reductions in hatching success, with alkylated analogues impacting hatching success to a greater extent (Rhodes et al., 2005). Although there are limited studies regarding the ovarian-specific toxicity of alkylated PACs, the available data points to increased toxicity associated with alkylation status.

5. Mechanisms mediating PAC ovotoxicity

Molecular pathways mediating the effects of PAC-induced toxicity have been well studied (Sobinoff et al., 2012a; Xu et al., 2010; Zhang et al., 2016) and include effects mediated via estrogen receptor (ER), aryl hydrocarbon receptor (AhR) and peroxisome proliferator activated receptor (PPAR) pathways amongst others (Diamanti-Kandarakis et al., 2009). In a recent study conducted by Boonen and colleagues, 9 PACs demonstrated multiple modes of receptor activity involving AhR, ER and PPAR (Boonen et al., 2020). As these receptor pathways are classical targets for EDC toxicity and play an important role in normal ovarian function, their role in mediating PAC toxicity will be discussed below.

5.1. The aryl hydrocarbon receptor (AhR)

The AhR is an important biological sensor that mediates the metabolism, bioactivation and detoxification of endogenous and exogenous compounds (Lauretta et al., 2019). Due to its role in xenobiotic sensing, AhR is activated by a multitude of compounds, including PACs (Horling et al., 2011; Huang et al., 2018; Sadeu & Foster, 2013). AhR expression has been detected in the oocytes, granulosa cells and theca cells of the ovary; with highest expression profiles reported in granulosa cells (Baldridge & Hutz, 2007; Horling et al., 2011). Studies performed in AhR knockout mice reveal that AhR plays an important role in regulating female reproduction and ovarian function (Barnett et al., 2007; Benedict, 2000; Benedict et al., 2003; Hernandez-Ochoa et al., 2010). AhR-deficient mice have shown to have significantly reduced numbers of pre-antral and antral follciles and corpora lutea compared to wildtype mice (Benedict, 2000; Benedict et al., 2003). These effects on ovarian follicle development may be attributed to decreased granulosa cell proliferation and changes in follicular estradiol regulation and responsiveness (Barnett et al., 2007). AhR deletion during different stages of sexual maturity also revealed that a lack of AhR slows follicle growth and decreases estradiol production in prepubertal mice, while ovaries collected from adult mice lacking AhR showed no difference in follicle growth compared to wildtype and significantly increased androgen production (Hernandez-Ochoa et al., 2010). Together this data demonstrates that AhR regulates follicle growth via changes to estradiol biosynthesis and regulators for follicle growth (Hernandez-Ochoa et al., 2010).

Several studies have demonstrated the ability of AhR to mediate the adverse effects of PACs (Billiard et al., 2006; Ohura et al., 2007; Vondráček et al., 2017; Wincent et al., 2015). In fact, BaP exposure has been shown to increase mRNA expression of *Cyp1a1* and *Cyp1b1* in preantral/antral and preovulatory mouse follicles, respectively (Sadeu & Foster, 2013). Interestingly, BaP exposure in isolated follicles (Sadeu & Foster, 2013), as well as in cultured oocytes and granulosa cells (Jurisicova et al., 2007; Matikainen et al., 2001; Pru et al., 2009), increased the expression of apoptotic genes, thus highighting a role for AhR signaling and apoptosis in delayed follicle development, survival and oocyte death. In a study conducted by Neal et al., the authors revealed that co-treatment with the AhR antagonists, resveratrol and 3′,4′-dimethoxyflavone, reversed the inhibition of follicle growth, steroidogenesis and granulosa cell prolifation in isolated rat follicles exposed to BaP (Neal et al., 2010). Similarly, daily 3MC exposure in pubertal rats adversely affected follicle growth and ovulation rates while increasing CYP genes, demonstrating a role for AhR signaling. In fact, 3MC exposure led to epigenomic remodeling and increased AhR binding to promoter regions of genes involved in primordial follicle activation, cell adhesion, stress and tumor progression and apoptosis (Rhon-Calderón et al., 2018); effects that were completely prevented with AhR-specific antagonist, alpha-naphthoflavone (Rhon-Calderón et al., 2016, 2018).

While single prototypical PACs can affect ovarian function via AhR mediated effects, this is not always true when PACs are present in mixtures. For example, Zajda and colleagues exposed human non-luteinized granulosa cells to two types of PAC mixtures (M1, mix of the top 16 priority PACs; and M2, top 5 most detected priority PACs in maternal blood) and reported a significant increase in FSH-stimulated FSH receptor expression, and decreased aromatase expression and E2 output (Zajda et al., 2019). However, the authors observed differential expression profiles of AhR and AhR-related targets (Zajda et al., 2017), thus highlighting the difficulty in determining the exact mechanism of toxicity of these complex mixtures.

5.2. The estrogen receptor (ER)

Estrogens are major sex steroids that play a central role in female fertility and reproduction (Findlay et al., 2010). The effects of estrogen are largely mediated by two estrogen receptors: ER-alpha (ERα) and ER-beta (ERβ). In the mammalian ovary, ERβ is found mainly within granulosa cells, while ERα is found in theca and interstitial cells (Drummond et al., 1999; Enmark et al., 1997; Lenie & Smitz, 2008; Pelletier et al., 2000, 2000; Sar & Welsch, 1999). Evidence from ER knockout (ER-KO) mice models revealed that both ERα and ERβ are critical for normal ovarian function; where ERβ-KO mice showed reduced fertility and ERα-KO and ERαβ-KO mice were completely anovulatory (Reviewed in: (Hewitt & Korach, 2003)).

As established EDCs, various PACs have been reported to have estrogenic and/or anti-estrogenic activity (Zhang et al., 2016). Studies in aquatic species, such as scallops (*Clamys farreri*) have explored the role of ER in mediating the effects of PACs such as BaP. *C. farreri* exposed to BaP at environmentally relevant concentrations had significantly decreased ER expression (3.8 μg/L BaP) during proliferative and growing stages; but an upregulation of ER expression (0.38 μg/L BaP) during mature stages of ovarian development (Yang et al., 2020b). Ovaries of exposed *C. farreri* also demonstrated histopatholog-

ical alterations induced by BaP and significantly reduced E2 secretion during mature stages of development (Yang et al., 2020b). In another study conducted in mature *C. farreri,* exposure to low dose of BaP (0.025 μg/L) significantly induced ER expression, as well as AhR, ARNT and CYP1A1, while high dose BaP (10 μg/L) exposure decreased expression of all markers (Tian et al., 2013). Using human MVLN-*luc* cells to investigate ER binding of major PACs found in crude oil, Lee and colleagues observed seven of the 30 investigated PACs demonstrated ER activity, with greatest ER potency detected in methylchrysene, followed by phenanthrenes and its alkylated derivatives (Lee et al., 2017). The effects of PACs on estrogen synthesis/signaling can be attributed to the crosstalk between ER and AhR and highlight the multiple modes of action for PAC-induced toxicity (Göttel et al., 2014; Matthews & Gustafsson, 2006; Tarnow et al., 2019). Interactions between AhR and ER may lead to increased metabolism of estrogens, impaired transcription, proteasomal degradation, and CYP-driven metabolism (Tarnow et al., 2019). In fact, postnatal exposure to BaP, benz(a)anthracene (BaA) and benzo(k)fluoranthene, which are PACs known to interact with AhR, significantly altered ovarian ERβ expression and resulted in observed changes to ovarian development and function (Kummer et al., 2013). Similarly, in human non-luteinized granulosa cells exposed to different PAC mixtures (M1 and M2) known to activate AhR, genetic silencing of ERα and ERβ revealed that the observed inhibition of E2 secretion may also require regulation by ERα (Zajda et al., 2019; Zajda & Gregoraszczuk, 2020).

5.3. The peroxisome proliferator activated receptor (PPAR)

The peroxisome proliferator activated receptor superfamily is a group of nuclear transcription factors that regulate energy homeostasis and lipid metabolism, inflammation, cell cycle progression, tissue remodelling and steroidogenesis (Komar, 2005). Three PPAR subtypes exist: PPARα, PPARβ/δ, and PPARγ. The expression of PPARα and PPARβ/δ have been detected in the theca and stroma tissues of rats (Komar & Curry, 2002), while high expression of PPARγ has been reported in the granulosa cells in rodents, sheep, and humans (Froment et al., 2006). In particular, PPARγ has been identified in all stages of follicle development and is critical for female fertility (Cui et al., 2002). While genetic deletion of *Ppary* in the ovary did not affect the numbers of follicles at any stage of development nor affect ovulation, female mice were either infertile or exhibited impaired fertility alongside significantly reduced litter sizes (Cui et al., 2002). Similar to AhR, PPARs are also capable of binding to a variety of xenobiotic compounds that can induce the expression of CYPs and modulate enzymes critical for steroid hormone synthesis (Denison & Nagy, 2003; Horling et al., 2011; Huang & Chen, 2017). In 5-week old female mice exposed to BaP for 60 days (subchronic), there was a significant reduction in serum E2 levels and CYP19A1 protein expression, along with decreased primordial follicle populations, increased follicular atresia and granulosa cell apoptosis (Xu et al., 2010). These changes occurred in association with increased ovarian expression of PPARα and PPARγ and suggest that BaP-induced ovotoxicity may be attributed, in part, to PPAR-mediated signaling (Xu et al., 2010).

6. PACs and ovarian disorders in humans

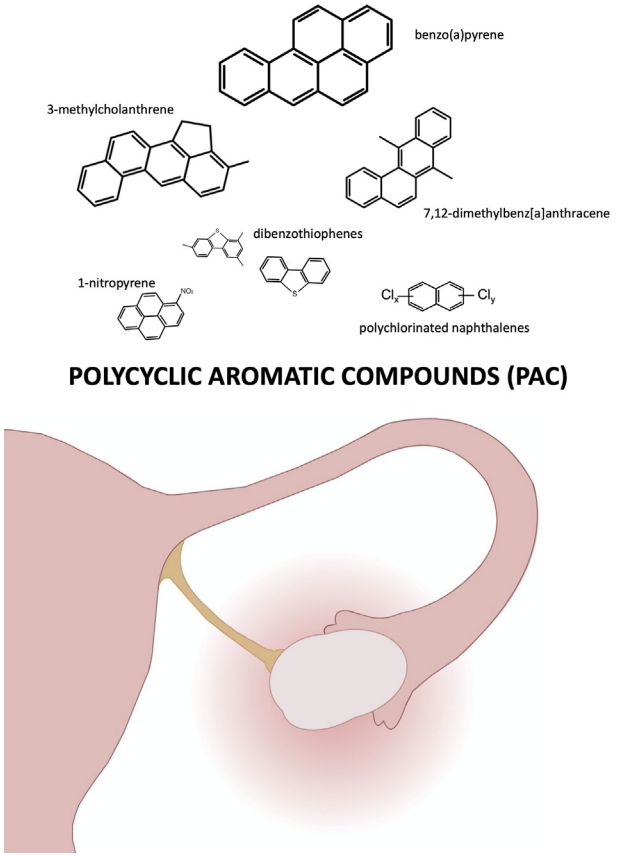
While there is limited evidence on the effects of PAC exposure and reproduction in humans, there is more data reporting adverse effects on male fertility and damage to spermatozoa (Reviewed in: (Madeen & Williams, 2017)) compared to data on female fertility and ovarian function (Netter et al., 2020). Perturbations in the vital processes that support ovarian function can lead to ovarian disorders including polycystic ovary syndrome (PCOS), anovulation, premature ovarian insufficiency (POI), and infertility (Barontini et al., 2001; Mikhael et al., 2019; Molina et al., 2018; Petraglia et al., 2008). While approximately 15% of couples that are of reproductive age are infertile worldwide (Sun et al., 2019), one of the most common causes of female infertility is anovulation, or the failure to ovulate. Moreover, anovulation is predominantly attributed to endocrine abnormalities and altered ovarian function and thus, can occur as a result of PCOS and POI (Balen & Rutherford, 2007).

Polycystic ovary syndrome affects approximately 5–20% of women of reproductive age (Azziz et al., 2016). Women with PCOS have a greater number of follicles that are arrested at the pre-antral and early antral stages (“cysts”), and these follicles fail to mature even when stimulated with exogenous FSH (Erickson et al., 1992). It is also hypothesized that the dysregulation of the HPO axis may contribute to PCOS, whereby the anterior pituitary disproportionately increases LH and FSH production and secretion (Azziz et al., 2016). Together, the disproportionate ratio of LH and FSH and aberrant steroid synthesis may lead to excess androgen biosynthesis and altered development and maturation of ovarian follicles, contributing to anovulation observed in women with PCOS (Reviewed in: (Ashraf et al., 2019). In a case-control study including 80 Chinese women, results showed that serum levels of 6 individual PAHs (naphthalene (Nap), acenaphthylene (Acn), phenanthrene (Phe), fluorene (Flu), acenaphthylene (Ace)), as well as the sum of these PAHs (ΣPAH) were significantly higher in women with PCOS compared to control (ΣPAH odd ratio (OR) 2.39, 95% CI 0.94–6.05) (Yang et al., 2015). Additionally, significant associations between PCOS and levels of Nap and Acn (Nap OR 3.00, 95% CI 1.16–7.73; Acn OR 3.81, 95% 1.45–10.0) were detected (Yang et al., 2015), demonstrating that PACs may contribute to aberrant steroid production and PCOS pathogenesis.

Premature ovarian insufficiency, also known as premature ovarian failure, affects approximately 1% of women before the age of 40 (Webber et al., 2016). This ovarian disorder is characterized by elevated gonadotropins, estrogen deficiency, loss of ovarian follicle reserve, abnormal/absence of menstruation (amenorrhea), and subfertility and/or infertility (Rudnicka et al., 2018). To date, while only 25% of POI cases have a known etiology (Reviewed in: (Rudnicka et al., 2018; Vabre et al., 2017)), POI has been attributed to exhaustion of primordial follicle pool, increased follicular atresia, increased primordial activation, inhibition of ovulation and arrest in preantral stages of folliculogenesis (Vabre et al., 2017). A more recent case-control study also conducted in Chinese women showed that high molecular weight PACs possessed a higher risk of POI compared to low molecular weight PACs (Ye et al., 2020). In particular, 10 out of the 12 individual PAHs tested (naphthalene, acenaphthene, acenaphthylene, phenanthrene, anthracene, fluoranthene, chrysene, benzo(b) fluoranthene, benzo(k)fluoranthene and benzo(a)pyrene), as well as the ΣPAH, were positively correlated with the risk for POI (ΣPAH adjusted OR 1.879, 95% CI 1.423–2.481) (Ye et al., 2020). As POI is also defined by low levels of AMH and high levels of FSH and LH in women before the age of 40, the result showing that PAC levels were also positively associated with serum levels of FSH and LH and negatively associated with AMH levels supports the hypothesis that PAC exposure may increase the risk for POI via aberrant steroid production (Ye et al., 2020).

7. Conclusion and future directions

Polycyclic aromatic compounds are EDCs ubiquitously present in the environment. There are reports across a wide range of species that PACs significantly alter endocrine signaling and reproductive outcomes (Bolden et al., 2017; Brinkmann et al., 2014; Rhodes et al., 2005; Zhang et al., 2016) (Fig. 2). Animal models and *in vitro* work has shown that exposure to PACs like BaP, DMBA and 3MC target different stages of folliculogenesis and deplete ovarian germ cells (Lim et al., 2016; Luderer et al., 2019); exhaust primordial follicles



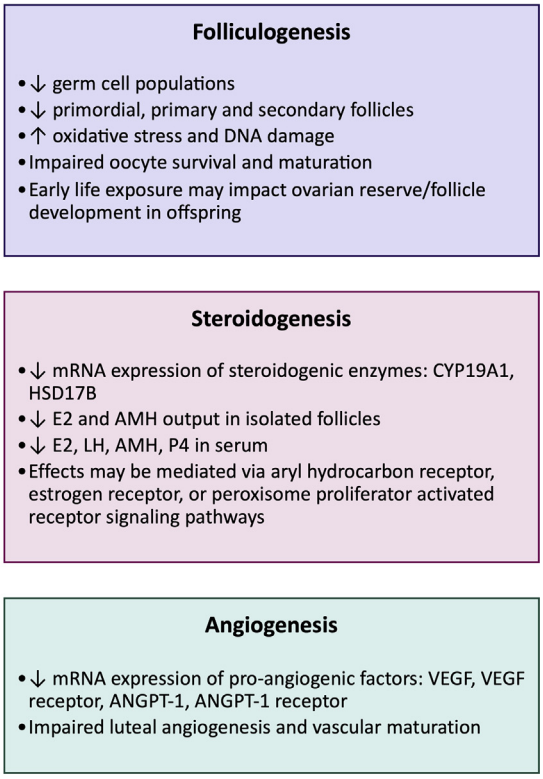


Fig. 2. Summary of the effects of polycyclic aromatic compounds (PAC) on ovarian function in mammals. CYP19A1, aromatase; HSD17B, 17beta-hydroxysteroid dehydrogenase; E2, estradiol; AMH, anti-Müllerian hormone; P4, progesterone; VEGF, vascular endothelial growth factor; ANGPT, angiopoietin factor.

via atresia or accelerated primordial follicle recruitment (Borman et al., 2000; Jurisicova et al., 2007; Matikainen et al., 2001; Mattison, 1980; Mattison & Thorgeirsson, 1979; Pru et al., 2009; Rhon-Calderón et al., 2018; Sobinoff et al., 2011); inhibit pre-antral and antral follicle growth (Einaudi et al., 2014); cause DNA damage and form DNA-adducts (Igawa et al., 2009; Lim et al., 2013; Yao et al., 2017); induce oxidative stress and ROS production (An et al., 2011; Siddique et al., 2014; Tsai-Turton et al., 2007; Zhang et al., 2018); and impede oocyte maturation (Sui et al., 2020). Additionally, evidence has shown that PACs disrupt ovarian steroidogenesis via altered enzymatic expression and activity leading to altered levels in secreted estradiol, androgen and progesterone (Archibong et al., 2012; Dewailly et al., 2016; Liu et al., 2020; Neal et al., 2007; Xu et al., 2010). Limited epidemiological studies have reported effects of PAC exposure on ovarian function in humans (Yang et al., 2015; Ye et al., 2020). Nonetheless, together these studies provide evidence that exposure to PACs can disrupt normal reproductive health and may lead to ovarian disorders like PCOS, POI and infertility.

To date, toxicological research has focused largely on PAHs despite the fact that other classes of PACs are also present in the environment; and sometimes at higher levels than their parent compounds (Provencher et al., 2020; Wallace et al., 2020). There is a growing body of evidence elucidating the biological effects associated with exposure to other classes of PACs, such as heterocyclic PAHs, N- PAHs, halogenated PAHs and alkylated congeners in biota (Reviewed in: (Brinkmann et al., 2014; Khan et al., 2021; Lee et al., 2017; Zhang et al., 2016). In fact, there are reports that degrees of alkylation or substitution can significantly impact total burden in exposed biota (Lee et al., 2017). While some studies have already reported that these other classes of PACs possess endocrine disruptive properties, a large proportion of the available literature has been conducted in aquatic species (Brinkmann et al., 2014; Hellou et al., 1994; Honda & Suzuki, 2020; Jing-jing et al., 2009; Machala et al., 2001; Provencher et al., 2020; Rhodes et al., 2005; Sørensen et al., 2016; Tollefsen et al., 2011; Wallace et al., 2020; Yun et al., 2019), whereas research in mammalian species is currently more limited. This represents a critical knowledge gap as PACs are able to persist in the environment as the widespread risk of exposure is increasing in parallel with global industrialization. While it is generally accepted that PAHs can significantly impair ovarian function and fertility, less is known regarding heterocyclic, substituted, halogenated and alkylated PACs. As such, this warrants further investigations to elucidate the toxic effects of PACs on female reproductive health and ovarian function at biologically relevant levels in mammals. Understanding the health effects associated with exposure to various PACs will help inform environmental policy to ensure that proper mitigation strategies are put in place to reduce any risk posed by PACs on female reproductive health.

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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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