Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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To cite this article: Ilaria Soave, Tommaso Occhiali, Chiara Assorgi, Roberto Marci & Donatella Caserta (2020): Environmental toxins exposure in PCOS women and possible ovarian neoplastic repercussion, Current Medical Research and Opinion, DOI: 10.1080/03007995.2020.1729108

To link to this article: https://doi.org/10.1080/03007995.2020.1729108

Accepted author version posted online: 11 Feb 2020.

Environmental toxins exposure in PCOS women and possible ovarian neoplastic repercussion

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Transparency

Declaration of funding

This manuscript was not funded.

Declaration of financial/other relationships

IS, TO, CA, RM, and DC have disclosed that they have no significant relationships with, or financial interests in, any commercial companies related to this article. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

None reported.

Abstract

Purpose: Over the last two decades, increasing attention has been paid to environmental toxins and their effects on the female reproductive system. Endocrine disrupting chemicals (EDCs) are exogenous substances or mixtures that can mimic the action of steroid hormones and interfere with their metabolism. Advanced glycation end products (AGEs) are proinflammatory molecules that can interact with cell surface receptors and mediate the triggering of proinflammatory pathways and oxidative stress. The purpose of this review is to explore the effects of environmental toxins exposure in the pathogenesis of both polycystic ovary syndrome (PCOS) and OC (ovarian cancer), considered separately, and also to evaluate possible neoplastic ovarian repercussion after exposure in patients diagnosed with PCOS.

Materials and methods: We searched PubMed for articles published in the English language with the use of the following MeSH search terms: “Polycystic Ovary Syndrome” and “Ovarian Cancer” combined with “endocrine disruptors”. Titles and abstracts were examined and full articles that met the selection criteria were retrieved. A manual search of review articles and cross-references completed the search.

Results: Extensive data from different studies collected in recent years concerning the effects of EDCs/AGEs exposure have confirmed their role in the pathophysiology of both PCOS and OC. They favour PCOS/OC development through different mechanisms that finally lead to hormonal and metabolic disruption and epigenetic modifications.

Conclusions: Environmental toxin exposure in PCOS women could favour neoplastic transformation by exacerbating and potentiating some PCOS features. Further research, although difficult, is needed in order to prevent further diffusion of these substances in the environment, or at least to provide adequate information to the population considered at risk.

Keywords: polycystic ovary syndrome; ovarian cancer; endocrine disrupting chemicals; advanced glycation end products

BACKGROUND

Endocrine Disrupting Chemicals and Advanced Glycation End products

Endocrine disrupting chemicals (EDCs) are defined as "exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organisms or its progeny or (sub)population"[1]. Also known as endocrine disruptors, they can mimic the action of steroid hormones and "interfere with the synthesis, secretion, transport, metabolism, binding action or elimination of natural blood-born hormones that are present in the body and are responsible for homeostasis, reproduction and developmental process"[2]. They usually possess a phenol group and express affinity for hormone receptors (e.g. oestrogen, progestin, androgen), although lower than the natural ligand. They may also interfere with the synthesis of carrier proteins, such as sex-hormone binding globulin (SHGB), and alter the transport of steroid hormones to target cells[3,4]. Over the last two decades, increasing attention has been paid to EDCs and their effects on the female reproductive system. More than 800 chemicals have been classified as EDCs, including drugs (diethylstilbestrol (DES)), pesticides (dichlorodiphenyltrichloroethane (DTT), atrazine, vinclozin), polychlorinated biphenyls (PBCs), dioxin and dioxin-like compounds, plasticizers (bisphenol A (BPA), bisphenol F, bisphenol S, phthalates), heavy metals (lead, arsenic, aluminum, cadmium) and the list is growing rapidly[5]. These chemicals are present in common industrial and home products and possess a high potential for bioaccumulation in the food web[6]. Therefore, humans are continually exposed to a mixture of EDCs and the contact with them has become inevitable today[1,7]. In addition, globalisation and consumerism have amplified the phenomenon. Heat-processed food and highly processed products represent an important source of advanced glycation end products (AGEs)[8]. Also called glycotoxins, AGEs are proinflammatory molecules that can interact with cell surface receptors (receptors for AGEs, RAGE) and mediate the triggering of proinflammatory pathways and oxidative stress[9,10]. They are believed to take part in atherosclerosis and diabetes pathogenesis, female fertility disruption and carcinogenesis[8,11-13].

The exact mechanism of action by which EDCs interfere with the female reproductive system is not yet fully understood. However, it is well established that through binding to nuclear hormone receptors, with agonistic or antagonistic effect, they may activate a rapid downstream intracellular signalling, resulting transcription errors (*genomic pathway*)[14]. They primarily alter the oestrogen (E) signalling pathway, probably because it is evolutionarily conserved among animals and regulates many functions of the female reproductive system[15]. They may also act through binding to membrane steroids hormone receptors or G protein-coupled receptor 30 (GPR30), leading to protein kinase activation and recruitment of second messengers, which interfere with synthesis, secretion, transport and metabolism of endogenous hormones (*non-genomic pathway*)[16]. Recently, other mechanisms have been taken into account, including oxidative stress[17] and epigenetic effects[18,19].

Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is a common and complex endocrinopathy that affect women of reproductive age[20]. PCOS affects approximately 5 to 10% of the general female population[21]. Depending on the diagnostic criteria and the geographic location this percentage may rise up to 21%[22]. PCOS was redefined in 2003 in a consensus meeting between the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine (ESHRE/ASRM)[23]. Affected individuals must meet at least two of the following criteria (Rotterdam criteria):

(i) clinical and/or biochemical hyperandrogenism
(ii) oligo-/anovulation
(iii) polycystic ovaries.

The pathophysiology of this endocrine disorder is still unclear, however a genetic basis (multifactorial and polygenic) is suspected[24]. Some authors have suggested a possible autosomal dominant inheritance, based on the higher prevalence of increased androgens (A) levels and insulin-resistance in relatives of PCOS women[25]. In addition a possible role of environmental factors and lifestyle has also been taken into account[24]. Key features of PCOS are hyperandrogenism and insulin resistance, that exhibit in various degree. Hyperandrogenism contributes to clinical phenotypes and fertility dysregulation. The most

common clinical signs include hirsutism, acne, menstrual cycle dysfunction (oligo-/amenorrhea, unpredictable bleeding) and subfertility/infertility[20,26]. Amenorrhea and oligomenorrhea result from anovulation. The lack of endogenous progesterone (P), generally produced by the corpus luteum after ovulation, impedes the triggering of a normal menstrual cycle. In addition, elevated A levels counteract the proliferative effect of E on the endometrium, resulting in a thin endometrial stripe. Insulin resistance (IR) and compensatory hyperinsulinemia are present in the majority of PCOS women[27]. Elevated insulin levels stimulates A production (further promoting anovulation) and may also favour the development of obesity[28]. However, given the fact that obesity itself, in particular central obesity, exacerbates IR, its prevalence increases with the rate of obesity[28]. The metabolic profile of PCOS women is similar to that seen in the metabolic syndrome and includes atherogenic dyslipidemia (increased LDL-cholesterol and triglycerides levels, depressed HDL-cholesterol levels and elevated total cholesterol:HDL-cholesterol ratios) and impaired glucose tolerance. Consequently, patients with PCOS are more likely to develop type 2 diabetes (T2DM)[29] and cardiovascular disease (CVD)[30] when compared to the general population.

Ovarian Cancer

Worldwide, ovarian cancer (OC) is the 7th leading cause of cancer in females[31] and the 1st cause of death from gynaecological malignancies[32] and its incidence is continuously rising both in Western countries and Asian nations[31,33]. Postmenopausal women are more likely to be diagnosed with OC. Although the pathophysiology is poorly understood, several factors including genetic, reproductive, hormonal and behavioural factors, may contribute to the tumorigenic process[34]. Evidence suggests that hormonal imbalance plays a key role in OC development. OC cells express higher levels of oestrogen receptor alpha (ERα) when compared to normal ovarian cells, suggesting that E may provide a favourable hormonal milieu for tumour progression by directly regulating cellular growth and proliferation[35]. Recent advances in molecular techniques have led to consider OC as a complex group of distinct diseases sharing a common anatomical location[36]. In 90% of the cases, OCs arise from the neoplastic transformation of epithelial cells on the ovarian surface[37]. Epithelial ovarian tumours are further divided into type 1 and type 2 subgroups[38]. Type 1 OCs are generally low-grade and well differentiated and include low-grade serous and mucinous carcinoma, endometrioid carcinoma, clear-cell carcinoma and transitional carcinoma. They are usually ovarian derived or may arise from pre-invasive endometriotic lesions. On the other hand, type 2 OCs are high-grade, undifferentiated and metastasized tumours and account for the 75% of all OC diagnoses. This subgroup includes high-grade serous adenocarcinoma, high-grade endometrioid-carcinoma, carcinosarcoma and undifferentiated carcinoma[39,40]. OC is usually considered a sporadic disease, but in 10 to 15% of the cases it shows hereditary etiology[41]. The genetic profiling of OC varies among the two subgroups. Type 1 OCs are usually characterised by genomic stability and frequently exhibit point mutations[42]. Type 2 OCs are usually the result of multiple mutational events that mainly involve p53 genes. The reduced activity of the tumour suppressor protein 53 (TP53) leads to uncontrolled cellular growth and division, favouring the development of cancer[43]. In addition, constitutive mutations in breast cancer antigen (BRCA) 1 and 2 genes are also often associated with type 2 OCs. Indeed, women with a BRCA1 gene mutation have 40% to 60% lifetime risk of developing OC, whereas the risk for women with BRCA 2 gene mutation is 20% to 35%[44].

MATERIAL AND METHODS

We search PubMed for articles published in the English language with the use of the following MeSH search terms: “Polycystic Ovary Syndrome” and “Ovarian Cancer” combined with “endocrine disruptors”. Titles and abstracts were examined by two reviewers (I.S. and T.O.) and full articles that met the selection criteria were retrieved. A manual search of review articles and cross-references completed the search. All selected articles were assessed for study design, patient characteristics, diagnosis of PCOS/OC, type of EDC studied and completeness of information of the data sets.

ENVIRONMENTAL TOXINS EXPOSURE AND PCOS

Increased levels of BPA in biological fluids have been reported in both women and adolescents with PCOS when compared to healthy, non hyperandrogenic and ovulating controls[45-47]. Higher serum levels of other EDCs (PBCs, organochlorine pesticides, perfluorooctanoate, perfluorooctane sulfonate, polycyclic aromatic

hydrocarbons)[48,49] and AGEs have also been observed in PCOS patients[50]. In one study elevated circulating serum levels of AGEs were positively associated with higher serum concentrations of antimüllerian hormone (AMH), testosterone (T) and insulin[51]. The link between environmental toxins exposure and PCOS may lay in the interaction between EDCs/AGEs and sex hormones, but human data are still limited[6]. The molecular similarity of environmental toxins to endogenous steroids hormones may favour the development of PCOS through different mechanisms that could finally lead to hormonal and metabolic disruption (Figure 1).

Hormonal disruption

EDCs may contribute to the destabilisation of hormonal homeostasis both by acting directly at gonadal level (*direct effect*) or via alteration of the hypothalamic-pituitary-ovarian axis (*indirect effect*)[52]. At ovarian level, possible effects on both granulosa and theca cells have been hypothesized. Elevated levels of BPA in follicular fluid may be responsible for decreased expression of aromatase and reduced production of E in granulosa cells, finally disrupting the intrafollicular environment and affecting oocytes growth and maturation[53]. Similar effects have also been shown in case of exposure to other popular plasticizer-phthalates[54]. The impact of BPA on oogenesis may be modulated by the interaction with a variety of receptors, including ERα and β[55], nonclassical membrane ER and GPR30[56]. In theca cells, BPA may stimulate A secretion[53] and may inhibit T clearance and catabolism[57], consequently increasing A circulating levels. In addition, BPA is a powerful SHBG ligand and it is able to displace T from SHBG, increasing free T serum levels[58]. Moreover, the increased levels of A reduce the hepatic clearance of BPA by decreasing the activity of UDP glucuronyl-transferase liver enzyme, consequently increasing free BPA levels and therefore contributing to the perpetuation of BPA/A reciprocal relationship[59]. The result of all these actions is the disruption of A-E balance, thus impairing oocytes maturation. EDCs may also be involved in the pathogenesis of anovulation by suppressing E production through a receptor-mediated signalling pathway (peroxisome proliferator-activated receptors, PPARγ)[60]. AGEs have also been reported to be able to impact oocytes development and maturation through different mechanisms of action: chronic inflammation and oxidative stress are though to play a pivotal role in AGE-mediated disruption of reproductive function in preovulatory follicles in PCOS women[61,62].

Metabolic disruption

As stated before, the metabolic profile of PCOS women is characterized by IR with compensatory hyperinsulinemia and obesity and environmental toxins may be involved in the pathophysiology of both of them. Indeed, BPA may promote the development of IR by reducing adiponectine secretion, resulting in increased oxidative stress, inflammation and disruption of adipogenesis, which favour the onset of both T2DM and CVD[63,64]. In addition, it has also been observed that BPA has a direct effect on pancreatic cells, which contributes to the disruption of glucose homeostasis, leading to hyperinsulinemia, thus further increasing the risk of T2DM[65,66]. In vitro studies have also suggested a possible involvement of AGEs in the pathogenesis of IR. Indeed, glycotoxins may reduce glucose uptake by adipocytes[67] and alter glucose transport in human cells[68]. AGE-induced inflammation may also decrease insulin sensitivity[69]. Moreover, it is well known that obesity itself worsens IR and central and visceral obesity are present in about 30-75% of PCOS women[70]. A positive correlation between glycotoxins serum levels and waist-hip ratio has been reported[68] and in vitro studies support the role of AGEs in stimulating adipogenesis[71]. Moreover, it has also been observed that higher body mass index correlates with lower levels of soluble RAGE, thus reducing AGEs clearance and favouring their deposition in reproductive tissues (e.g. ovaries), possibly affecting steroidogenesis[72,73]. In addition, increased AGEs serum levels potentiate the inflammatory process already present in obese patients and worsen the metabolic aberrations characteristic of PCOS women, thus aggravating the metabolic syndrome components of the disease[74]. Furthermore, EDCs are often classified as “environmental obesogens”. Indeed, they promote fat accumulation, by altering lipid homeostasis and fat storage[75]. The molecular pathways by which these compounds participate in obesity development may include the interaction with both PPARγ and ER[55,76], which may promote the expression of adipogenic genes[77] and may enhance adipocytes differentiation[78].

ENVIRONMENTAL TOXINS EXPOSURE AND OC

Several studies have given substantial evidence concerning the link between EDCs/AGEs and OC development (Figure 2). Human exposure to different EDCs (e.g. pesticides, triazine herbicides, organophosphate diazinon, triclosan, methoxychlor (MXC)) has been proven to increase the risk of OC[79-83] and many studies conducted on animal models support this hypothesis. Mice exposed to BPA and 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) have shown an increased incidence of ovarian cysts and ovarian adenomas, along with an enhanced OC cells proliferation[84,85]. Additionally, BPA has also been reported to interfere with sex steroid hormones synthesis, leading to hormonal imbalance[86].

Hormonal effects

The role of E in the development and progression of OC is still debated, but a possible involvement in the early stages of malignancy seems plausible. Several studies conducted on postmenopausal women have linked hormone replacement therapy to an increased risk of OC[87-89] and recent studies have reported that both E and E+P preparations are equally associated with OC[90]. Given the fact that some EDCs exhibit estrogenic properties, the environmental exposure may thus activate ER signalling, favouring cancer development[91]. Some in vitro studies support this hypothesis: plasticizers and pesticides have been shown to promote OC cells proliferation via E pathways activation[83,92] and DDT via nuclear receptor binding[93]. Also EDCs with antiestrogenic properties might disrupt the hormonal milieu. The perimenopausal phase is characterized by increased levels of gonadotropins (hypergonadotropic condition) that are able to activate different molecular pathways involved in cellular growth and invasion and EDCs exposure may enhance this process, further increasing gonadotropins levels and consequently the risk of OC[94]. It has been reported that chlorpyrifos and MXC might be able to alter gonadotropin-releasing hormones production[95,96] and that DDT might disturb the normal functioning of gonadotropins via the expression of FSH and LH[97].

The overexpression of androgen receptor in OC cells[98] suggests that A may also play a role in the tumorigenic process. Androgens are involved in the regulation of cells proliferation and, in particular, are able to decrease cell death[98]. Some authors have depicted a possible link between the use of exogenous A and an increased risk of OC[99,100] and some studies conducted on animal models have shown that the exposure to EDCs with androgenic properties (e.g. 4-Nitro-3-phenylphenol) is associated with hormonal disruption[101].

Epigenetic effects

Long-term exposure to environmental toxins may also be associated with changes in gene expression (epigenetic modifications)[102]. Several epigenetic markers have been taken into account, including histone modifications, non coding RNAs transcription and changes in DNA methylation[103]. The latter is the most studied and consists in the transfer of a methyl group(s) to a DNA molecule by DNA methyl transferases (DNMTs) activation[104]. This process is essential for normal cellular development, but it is also believed to play a key role in carcinogenesis[105]. Chemicals and environmental toxins may interfere with the methylation of CpG islands (DNA regions where a cytosine nucleotide is followed by guanine nucleotide, separated only by a phospahte group) which can cause permanent silencing or activation of particular genes[105]. The epigenetic effect of EDCs in case of reproductive cancer has been observed[106,107], but only few studies have examined the EDC-related epigenetic changes in the ovary. It has been reported that EDCs may alter the expression of E responsive genes by promoting hypermethylation in the promoter region of hormone receptor genes, leading to gene silencing[108,109]. In addition, studies on animal models have shown that high doses of MXC are associated with hypermethylation of ER **β**, DNA methyltransferase 3 **β** and pregnancy associated plasma protein A genes in rats[110]. Reduced expression of ER **β** gene and increased activity of DNMT gene under the influence of EDCs have also been observed[108].

POSSIBLE OVARIAN NEOPLASTIC REPERCUSSION IN PCOS WOMEN EXPOSED TO EDCs

The previous sections explored the effects of environmental toxins exposure in the pathogenesis of both PCOS and OC, considered separately. The current section pertains to the possible neoplastic ovarian repercussion after environmental toxins exposure in patients with PCOS.

The possible association between PCOS and increased cancer risk was first hypothesized in 1940[111] and, more recently, concerns that women with PCOS might be at increased risk of OC have been raised[112]. PCOS has been postulated to promote OC development mainly through excessive A stimulation[98,113]. Normal ovarian cells as well as borderline ovarian tumours cells express androgen receptors on their surface, and increased A levels positively correlate with an increased risk of borderline serous and invasive mucinous tumours[114,115]. Only few studies examined the possible link between PCOS and OC with inconsistent results[98,99,116-123]. Many of these studies had small cohort sizes and different diagnostic criteria for PCOS were used, limiting the power of the study and introducing selection bias. A recent review published by Harris et al. failed to identify a clear association between PCOS and OC and several potential confounders have been pointed out[126]. Firstly, obesity is a common finding in PCOS women who are also, as stated before, at higher risk of T2DM, IR and metabolic syndrome[27,29,125]. All these conditions have been associated with ovarian cancer[126,127] and, in case of PCOS women, could act as potential intermediate variables. Few studies adjusted their results for these confounders, resulting in an attenuation of the true association[120]. In addition, oral contraceptives are often a first-line treatment in PCOS women not seeking for pregnancy, which use seems to play a protective role in ovarian neoplasms development by decreasing the number of potentially damaging ovulations[128,129]. Furthermore, metformin is frequently prescribed in PCOS patients in order to improve IR and reduce the risk of T2DM. Laboratory studies have advised a possible anti-cancer activity of metformin[130] and several studies have confirmed its influence on ovarian cells growth and proliferation[131,132]. One study reported a decreased risk of OC in patients treated with metformin[118]. Age represents another possible confounding factor. Given the fact that postmenopausal women are more likely to be diagnosed with OC, in a recent meta-analysis published by Barry and colleagues only PCOS patients <54 years of age (premenopausal women) were considered and even in this case, no robust association between PCOS and OC was found[119].

Although there may be several confounding factors, environmental toxins exposure in patients with PCOS may exacerbate some PCOS features (hormonal, metabolic, genetic) that in the end may favour the neoplastic process.

Hormonal pathways

Cells within the ovaries and on their surface are responsive to A, which have antiapoptotic effects and induce cells proliferation, thus promoting cell survivability, mutations' accumulation and, eventually, neoplastic transformation. Moreover, once ovarian cells turn malignant, they possess the enzymatic capabilities to synthesized A with greater biological effects and tend to overexpress androgen receptors[133-135]. Both PCOS and BPA synergically increase not only A levels, but also free A levels, since BPA manages to unbind T from SHBG[58]. BPA plasmatic concentrations positively correlate with T, free T, androstenedione and DHEA levels in PCOS women[45,46]. Considering the above-mentioned premises, this hormonal disruption can furthermore increase ovarian cancer growth both directly, acting on A receptors, and indirectly, providing weaker A to the tumour enzymatic machinery, which in turn will convert them into more biologically active ones[52,136]. Additionally, elevated A levels impede the hepatic clearance capacity of BPA, creating a vicious circle that promotes A production and in the end tumour mass growth[137].

Oestrogens effects on ovarian cancer cells are somewhat less clearly defined, considering that OC is typically found in postmenopausal women. Still, both ER α and β are found in more than half of all ovarian tumours[138]. Alfa receptors support cellular growth and are counterbalanced by β receptors. In time, ovarian malignant cells that only express α receptors are selected[139,140]. PCOS patients are usually overweight/obese[141]. The hypertrophic fatty tissue is the production site of estrone, an E with low biological effects, but still a proliferative stimulus to ovarian cells. Additionally, the hyperandrogenic condition typical of PCOS provides other substrates to the aromatase located in adipocytes, favouring A conversion to E. EDCs in general can act either with estrogenic effect or with antiestrogenic effect, depending on the substance(s), on its dose and on possible synergic effects with other EDCs[142]. When the net effect tips toward the estrogenic effect, PCOS and EDCs could act directly toward premalignant and malignant cells proliferation by binding to ER, while when the net effect is rather antiestrogenic, we may occur in a negative feedback at hypothalamic level, with subsequent gonadotropins release, which, in turn,

will stimulate gonadal cells proliferation and hormones synthesis, still concurring in tumour proliferation[92,93,142-144].

Metabolic disruption

The low-grade systemic inflammation typical of the metabolic syndrome of PCOS women is bolstered by EDCs, as stated above. This meta-inflammation promotes tumour growth through, at least, two major mechanisms: oxidative stress and IR.

Oxidative stress, a known carcinogenetic stimulus, is a by-product of chronic metainflammation mainly sustained by TNF-α and IL-6, powerful cytokines produced by adipose tissue and its residing macrophages[145,146]. TNF-α leads to lipolysis and subsequent IL-6 secretion. In the liver, IL-6 is responsible both for acute phase proteins synthesis (further promoting systemic inflammatory response) and, also, for IR, not only in hepatic cells but also in peripheral tissues (skeletal muscles cells). EDCs (namely organochlorines) increase adipogenesis and maturation of mesenchymal stem cells into adipocytes through growth factors expression (BMP, EGF, IGF-1), leading to deposition of fatty tissue, both visceral and peripheral[147,148]. IR comes from EDCs-derived TNF-α activity, which impedes glucose uptake at cellular level by downregulating GLUT-4 transporters function[149]. EDCs exposure (BPA and diethylhexyl phthalate) during gestation and during the immediate post-natal period, could cause reduced insulin secretion, hyperglicemia and pancreatic insulitis in adult life[150-152]. In addition, EDCs alter the surrounding environment of pancreatic islets, adipose muscle and hepatic cells by affecting the extracellular matrix[153]. Inflammation, deposition of connective tissue and angiogenesis are finally promoted, altering the blood flow in metabolically active tissues and causing chronic low grade ischemic damages, further stimulating the inflammatory response and decreasing hormonal secretion capability via a multitude of pathways (hormonal receptor, intracellular second messenger, growth factors)[154-156]. The result is an important disruption in the ability of insulin to exert its effects favouring hyperglycaemia and compensatory hyperinsulinemia. Hyperglycaemia leads to AGEs formation. Considering AGEs pro-inflammatory effects, we circle back to reactive oxygen species (ROS) and their oxidative stress, amplified not only as a local ischemic-derived damage to adipose tissue and skeletal muscle, but as systemic insults, especially in ovarian pre-malignant and malignant cells, where DNA strands get damaged, steroidogenesis is impaired and overall ovarian disfunction is found[74]. AGEs alter insulin sensitivity and glucose uptake directly in granulosa cells[68] and in adipocytes[67]. Finally, PCOS derived hyperandrogenism further impairs the body capacity of AGEs clearance, amplifying their effects. Hyperinsulinemia (derived from PCOS, EDCs and AGEs) promotes A production in the ovaries, thus providing a proliferative stimulus, also sustained by IGF-1, a molecule capable of sustaining cellular mitosis and of dampening cisplatin pro-apoptotic effects when neoplastic transformation has already taken place[157].

Epigenetics

EDCs can cause epigenetic modifications, especially during pre- and peri-natal exposition[158]. These “subtle” epigenetic alterations accompany the individual throughout its life and can concur to carcinogenesis. The data available on epigenetic changes and ovarian cancer mainly show that ER are involved, particularly downregulating suppressor receptors (ER β), through gene promoter hypermethylation, resulting in silencing gene activity[109]. In the context of PCOS and EDCs exposure, the shift toward ERα-only expression may be included in a pro-estrogenic milieu granted by abundant adipose tissue (PCOS), xenoestrogens (EDCs) and a spontaneous receptor selection already undertaken by the ovarian neoplasm striving to grow. Many xenoestrogen can only exert a modest estrogenic effect, but they have greater bioavailability (almost complete) when compared to endogenous oestrogens. Moreover, xenoestrogens of different kind can work synergically with one another and with endogenous oestrogens[159-162].

CONCLUSION

In conclusion, the molecular similarity of environmental toxins to endogenous steroids hormones may lead to hormonal and metabolic disruption, favouring both PCOS and OC development. In addition, patients diagnosed with PCOS who are exposed to environmental toxins may be at higher risk of OC. Several mechanisms seem to play a role in this process:

- hyperandrogenism, a key feature of PCOS patients, seems to be further boosted by EDCs exposure, finally promoting cells proliferation and in the end tumour mass growth;
- some EDCs show estrogenic properties and especially in overweight/obese patients with PCOS (where the hypertrophic fatty tissue represents the production site of estrone and the conversion site of A to E) may promote tumour proliferation by binding to ERα present in more than half of all ovarian tumours;
- the low-grade systemic inflammation typical of the metabolic syndrome of PCOS women is bolstered by EDCs by two major mechanisms, oxidative stress and insulin-resistance, which may lead to DNA strands damage and impaired steroidogenesis, finally providing a proliferative stimulus;
- EDCs may be responsible for epigenetic modifications, in particular for the shift toward ERα-only expression, which may intensify the pro-estrogenic milieu granted by abundant adipose tissue, typical of PCOS women, favouring carcinogenesis.

From a public health perspective a possible association between PCOS, EDCs exposure and OC would be highly important. Indeed, it would allow to recognise women at risk, to monitor them properly and to offer preventive treatment(s). This lack of recognition further delays the diagnosis of pre-malignant/malignant ovarian diseases (which is already delayed in OC because of the nature of the cancer itself). However important, the association between PCOS, EDCs and OC remains challenging for several reasons:

- PCOS still has a poorly understood aetiology and it is often encased in patient with other metabolic abnormalities;
- the list of EDCs is growing, and a single EDC can exert different effects according to:
  - timing of exposure (pre-natal life/post natal/pre-pubertal…),
  - length of exposure,
  - total dose,
  - latency between exposure and effects,
  - possible synergic effects with other molecules.

Further research, although difficult, is needed in this field. The identification of possible cancerogenic molecules would allow to prevent further diffusion of these substances in the environment, or at least to provide adequate information to the population considered at risk.

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Figure Legend

Figure 1: Mechanisms by which EDCs/AGEs exposure may favor PCOS (PPARγ: peroxisome proliferator-activated receptors; IR: insulin resistance; CVD: cardiovascular disease; T2DM: diabetes mellitus type 2; HPO axis: hypothalamic-pituitary-ovarian axis; SHGB: sex hormone-binding globulin)

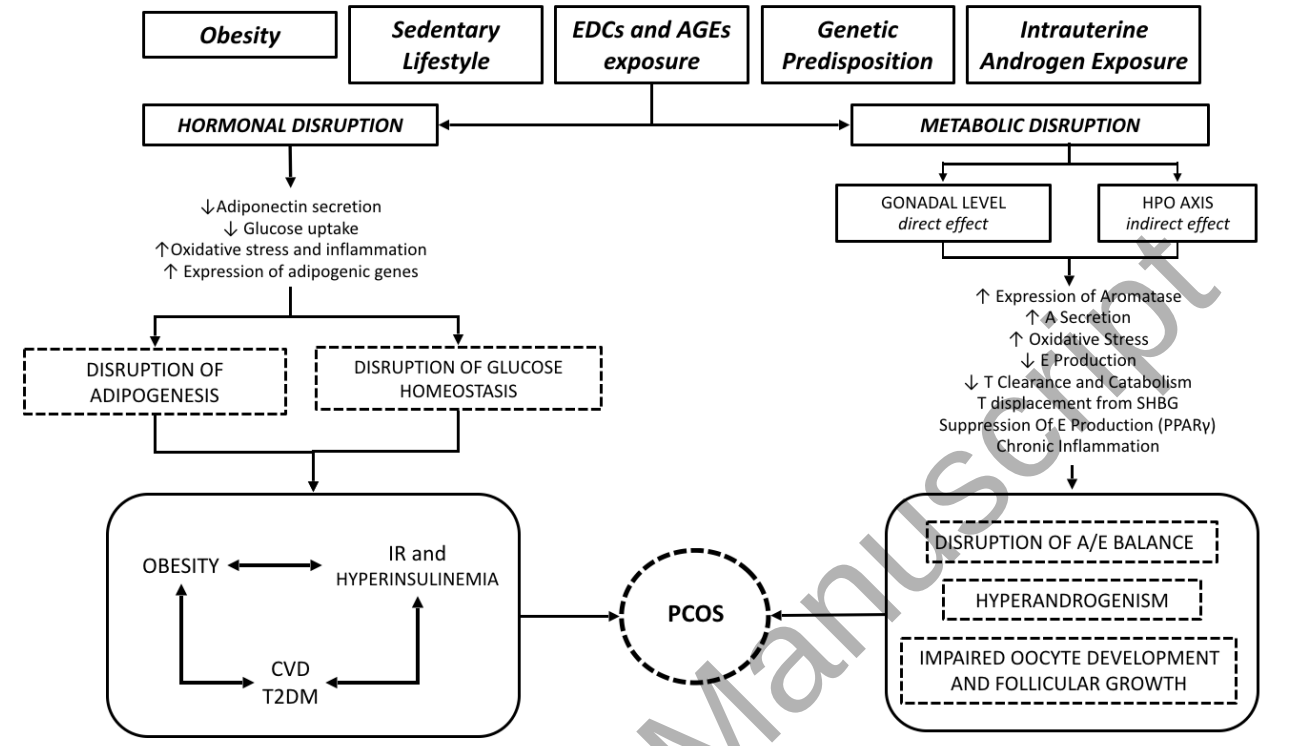

Figure 2: Mechanisms by which EDCs/AGEs exposure may favor OC