# Environmental factors and premature ovarian insufficiency:

Dr Sedigheh Amooee

1402 Winter

- Primary ovarian insufficiency (POI), defined as loss of ovarian activity before the age of 40 years , is a common gynecological endocrine disease that affects approximately 1% to 4% of women.

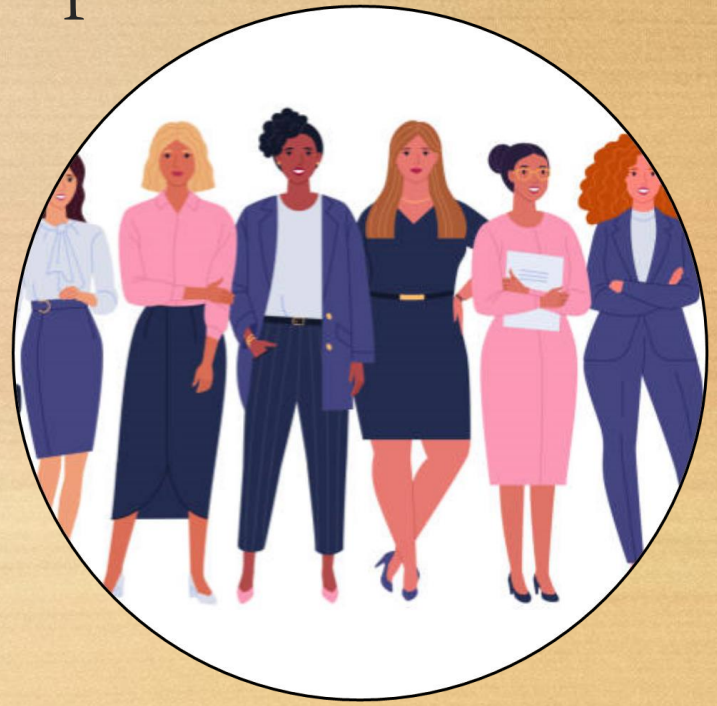
- Over the last few decades, much evidence has been gathered that confirms that certain chemical, physical and biological substances present in our environment produce harmful effects on human reproduction .

- Etiologies of POI are still poorly defined because in more than 75% of cases, the cause is undetermined . Genetic , iatrogenic , immunologic , metabolic and infectious causes have been reported

Four main mechanisms can lead to POI

- Exhaustion of the pool of resting primordial follicles (either constitutive due to default in their assembly, or acquired because of their increased atresia)
- Increased follicular atresia
- An increased activation of primordial follicles
- A blockage of folliculogenesis before the antral stages preventing ovulation

POI shows a complex multifactorial etiology with both genetic and environmental contributions. Recent studies suggest a link between environmental pollutants and POI, although limited corroborative evidence has been reported so far .



- Environmental pollutants refer to all of the exogenic, non-essential factors for humans, which, when released into the environment, can be detrimental to human health and/or to the environment. The industrialization of our society maximizes the use of these substances and poses a real problem for public health.

Persistent organic pollutants(POPs) are ubiquitous compounds that can bioaccumulate because of their persistence in environment and have potential significant impacts on human health.

Common POPs include:

- polychlorinated biphenyls (PCBs)
- organochlorine pesticides (OCPs)
-polybrominated diphenyl ethers (PBDEs)
-polychlorinated dibenzodioxins (PCDDs)
-dibenzofurans (PCDFs)
etc.

Exposure to POPs has been found to be associated with adverse outcomes of female reproduction, such as:

prolonged time to pregnancy
increased spontaneous abortion rates
decreased birth weight in offspring
etc

- Environmental factors seem to be major determinants in the
- ovarian reserve
- In premature menopause acting during the **prenatal period or during the adult life .**

Environmental pollutants can impact ovarian function in three ways that can coexist:

1-Endocrine disrupting chemicals (EDCs)
2-Induction of oxidative stress
3-Epigenetic modifications

Endocrine disrupting chemicals (EDCs): EDCs have been defined by the Endocine Society as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action".

- **Depending on the time of exposure** regarding ovarian ontogenesis, EDCs' **effects** on ovarian functions can be **transitory or permanent.**
- They can influence ovarian reserve by acting mainly on the aryl hydrocarbon receptor (AhR) or estrogen receptors (ERs).

# Aryl hydrocarbon receptor (AhR)

After binding to its exogenous ligand, AhR translocates toward the nucleus, it associates with a nuclear receptor and is able to bind to DNA sequences and modulates them. AhR induces a Bax synthesis, which is a pro-apoptotic factor contributing to follicular atresia.

# Estrogen receptors

ERs play evident roles during the gonadotrophins dependant phase of folliculogenesis.
However arguments for their role from the very early phases of folliculogenesis are given by the fact that they are increasingly expressed from the primordial stage onward in adult human follicles and consistently expressed by oocytes in human fetal ovaries whatever the follicular stage.

# Induction of oxidative stress

This occurs when cell mechanisms regulating the level of reactive oxygen species (ROS) are overwhelmed and responsible for **an imbalance of ROS**.

The accumulation of ROS can harm ovarian function. There is solid proof that ROS, induced by environmental factors, are **involved in the initiation of antral follicle apoptosis.**

It was also highlighted that the anti-oxidant capacities differed depending on the follicle stage.

# Epigenetic modifications

Exposure to environmental pollutants led to **modifications in DNA methylation** altering ovarian function and, if these modifications affect the germline in a stable way, it will **promote transgenerational inheritance of altered ovarian function.**

A cross-sectional study was conducted from 1999 to 2008 on 31,575 women, using NHANES (National Health and Nutrition Examination Survey) data. **The aim was to determine the association between exposure to endocrine disruptors and age at menopause**. Out of 111 analyzed EDCs, 9 polychlorinated biphenyls (PCBs), 3 pesticides, 1 furan and 2 phthalates were significantly associated with an earlier age of menopause from 1.9 to 3.8 years after adjustment for age, race/ethnicity, smoking, body mass index.

**A dose-response relationship was demonstrated** for 14 of them, suggesting to the authors that the increase in the level of exposure to these long half-life chemicals (except phthalates) **could affect ovarian function .**

Grindler NM, Allsworth JE, Macones GA, Kannan K, Roehl KA, Cooper AR. Persistent organic pollutants and early menopause in U.S. women. PLoS One. 2015;10:e0116057.

A review of the literature focused on occupational exposure to chemicals. In total, 1074 articles were selected and 140 chemical substances were analyzed. Twenty agents were retained as likely to induce POI. Eighteen of them, acting via an increase in follicular atresia, including 3 metals (cadmium, lead and chromium), 12 synthetic organic compounds (4 pesticides, 3 solvents, 5 compounds used in industrial chemistry) and 3 belonging to the polycyclic aromatic hydrocarbons (PAHs) family.

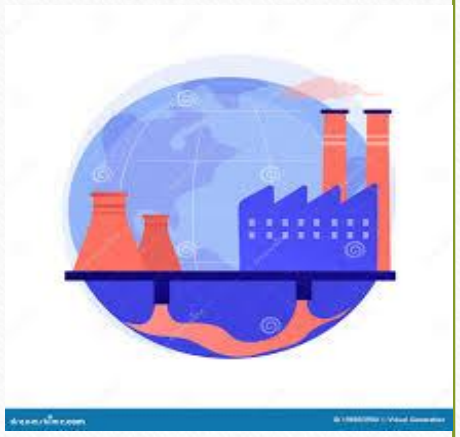
Beranger R, Hoffmann P, Christin-Maitre S, Bonneterre V. Occupational exposures to chemicals as a possible etiology in premature ovarian failure: a critical analysis of the literature. Reprod Toxicol. 2012;33:269–79.

Two synthetic organic compounds (methoxychlor and bisphenol A) acted by **increasing follicular recruitment**.

For 15 additional substances, data was insufficient to draw a direct link; however, these substances seem to lead to a decrease in follicle stocks.

# Phthalates

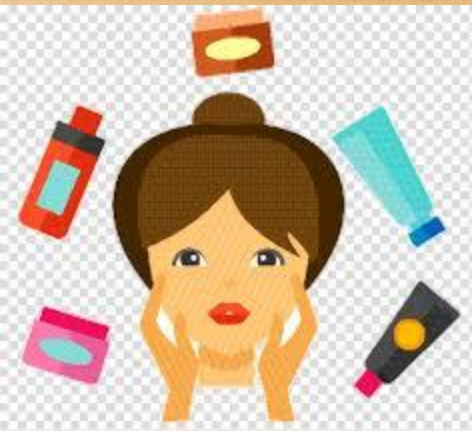
- Phthalates are substances that are currently used in the manufacture of plastics for a very wide spectrum of industrial applications.
  Two types of phthalates can be distinguished.



High molecular weight phthalates (for example, di(2-ethylhexyl) phthalate [DEHP],di-isononyl phthalate [DiNP]), are used as **plasticizers in the manufacture of flexible vinyl (such as polyvinyl chloride) used in consumer products (clothing, children's toys, and household items), flooring and wall coverings, food contact applications and medical devices.** They are produced in high volume because they give materials a certain flexibility and suppleness.

Low molecular weight phthalates (for example, diethyl phthalate [DEP] and dibutyl phthalate [DBP]) are used in **personal-care products (cosmetics), as solvents and plasticizers for cellulose acetate and in making lacquers, varnishes and coatings including the enteric coating of tablets or capsules and for controlled release formulations.**

- The most common one is di(2-ethylhexyl)phthalate (DEHP), and its active metabolite mono(2-ethylhexyl)phthalate (MEHP).
- Human exposure to DEPH is pervasive and ubiquitous through oral ingestion, inhalation or cutaneous contact. It is estimated between 3 and 30 μg/kg/day .



- Phthalates are described in many studies as being endocrine disruptors altering ovarian function.
- The toxic effect of phthalates on the ovary rests on **folliculogenesis and steroidogenesis disorders** with, as a consequence, an alteration in reproductive functions, infertility and POI .

- These substances are stable and remain in the environment for several years.
- When considering foetal development, exposure to MEHP on pregnant mice **leads to premature ovarian senescence in the F1 generation** .
- It led to a depletion of the **primordial-follicle pool in the F1 and F2 generations, according to an acceleration mechanism in follicular recruitment.** The authors concluded to an ovarian toxicity of phthalate with a transgenerational effect.

Zhang XF, Zhang T, Han Z, Liu JC, Liu YP, Ma JY, et al. Transgenerational inheritance of ovarian development deficiency induced by maternal diethylhexyl phthalate exposure. Reprod Fertil Dev. 2015;27:1213–21.

- This multigenerational effect is explained by the effect of phthalates on **DNA methylation of imprinted genes**, not only in fetal ovarian germ cells but also in the F1 and F2 offspring.

- Regarding the neonatal period, exposure of newborn mice to phthalates significantly **decreased the number of primordial follicles at puberty and at the adult age by accelerating follicular recruitment .**
- When exposure to DEHP takes place during the prepubertal period it led to a **significant reduction in the percentage of antral follicles with an increase in messenger RNA quantities of pro-apoptotic genes.**
- DEHP causes oxidative stress and ovarian somatic cell apoptosis.

- A prospective human study on 215 patients recruited between 2004 and 2012 demonstrated a significant decrease in antral follicle count in patients whose urinary phthalate level was high compared to lower concentrations after adjusting for age, BMI and smoking. However, this study was conducted on a population of infertile patients and it is difficult to generalize to the whole population.

Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu YH, et al. Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Hum Reprod. 2016;31:75–83.

- **In summary, we can conclude that phthalates disrupt ovarian function and impact the ovarian reserve by intervening at different stages of folliculogenesis.**

# Bisphenol A(BPA)

Bisphenol A (BPA) is an aromatic organic compound found **in plastics used for food packaging (such as polycarbonates), epoxy resins (interior coating on metal containers and beverage cans) and temperature sensitive papers (receipts).**

BPA is mass produced and found ubiquitously throughout the environment.

# BPA is prohibited

BPA is **an endocrine disruptor** acting notably like an estrogen mimicker on the estrogen receptor α .

- These effects have led French authorities to restrict the use of products containing BPA.
- Since July 2010, the use of baby bottles containing BPA has been prohibited.
- Since January 1, 2014, the manufacture and sale of any packaging containing BPA in contact with foodstuff has been prohibited.

- The animal data support this argument and highlight a negative effect of BPA on ovarian reserve. In fact, exposure to BPA leads to **a decrease in the number of primordial follicles regardless of the exposure window whether it is prenatal , neonatal or at the adult age.**

- In humans, a prospective study on women seeking care for infertility reported that **high urinary BPA concentrations were associated with low antral follicle count after adjusting for age and BMI .**


- Berger A, Ziv-Gal A, Cudiamat J, Wang W, Zhou C, Flaws JA. The effects of in utero bisphenol A exposure on the ovaries in multiple generations of mice. Reprod Toxicol. 2016;60:39–52.
- Zhang HQ, Zhang XF, Zhang LJ, Chao HH, Pan B, Feng YM, et al. Fetal exposure to bisphenol A affects the primordial follicle formation by inhibiting the meiotic progression of oocytes. Mol Biol Rep. 2012;39:5651–7.
- Rodriguez HA, Santambrosio N, Santamaria CG, Munoz-de-Toro M, Luque EH. Neonatal exposure to bisphenol A reduces the pool of primordial follicles in the rat ovary. Reprod Toxicol. 2010;30:550–7.
- Li Y, Zhang W, Liu J, Wang W, Li H, Zhu J, et al. Prepubertal bisphenol A exposure interferes with ovarian follicle development and its relevant gene expression. Reprod Toxicol. 2014;44:33–40.

# Transgeneration effect of BPA

- In utero exposure to BPA alters the **ovarian reserve of the F1 generation** but the results are not significant concerning the F2 and F3 generations; therefore, the negative effect **of BPA does not seem to be transgenerational** .
- Nevertheless, these authors **highlighted a modification in the expression of ovarian genes involved in apoptosis and steroidogenesis in later generations from F1 to F3 after in utero exposure to BPA in favor of a transgenerational effect on ovarian gene expression.**

Berger A, Ziv-Gal A, Cudiamat J, Wang W, Zhou C, Flaws JA. The effects of in utero bisphenol A exposure on the ovaries in multiple generations of mice. Reprod Toxicol. 2016;60:39–52.

# Pesticides

- Pesticides are chemical compounds used in agriculture to fight against organisms that are considered to be harmful to crops. They are composed of different families such as **insecticides, herbicides, fungicides**, etc.
- These organic elements have properties making them stable and **lipophilic**, which makes them slow to degrade over time.
- In this way, they remain in the environment for several years with an extensive presence in soil, food and water. Many pesticides play the role of an **endocrine disruptor in the body, altering reproductive functions and, notably, ovarian function**.

Alterations to cell ultrastructure, which are signs of cell apoptosis, are found in cases of exposure of female rats to permethrin, an insecticide in the pyrethroid family or to methyl parathion, insecticide from the organophosphate family , **leading to an alteration in the total number of follicles.**

Exposure to Simazine , a herbicide from the triazine family, or to Methoxychlor (MXC) an organophosphate pesticide, **led to a decrease in total ovary weight, which is a sign of follicular atresia .**

Prenatal exposure to MXC in rats showed modifications **to DNA methylation, which suggests epigenetic mechanisms .**


Kotil T, Yon ND. The effects of permethrin on rat ovarian tissue morphology. Exp Toxicol Pathol. 2015;67:279–85.

Satar DA, Tap O, Ay MO. Electron microscopic examination of the effects of methyl parathion exposure on the ovaries. Eur Rev Med Pharmacol Sci. 2015;19:2725–31.

Park S, Kim S, Jin H, Lee K, Bae J. Impaired development of female mouse offspring maternally exposed to simazine. Environ Toxicol Pharmacol. 2014; 38:845–51. 54. El-Sharkawy EE, Kames AO, Sayed SM, Nisr NA, Wahba NM, Elsherif WM, et al. The ameliorative effect of propolis against methoxychlor induced ovarian toxicity in rat. Exp Toxicol Pathol. 2014;66:415–21.

Bhattacharya P, Keating AF. Impact of environmental exposures on ovarian function and role of xenobiotic metabolism during ovotoxicity. Toxicol Appl Pharmacol. 2012;261:227–35.

Craig ZR, Hannon PR, Flaws JA. Pregnenolone co-treatment partially restores steroidogenesis, but does not prevent growth inhibition and increased atresia in mouse ovarian antral follicles treated with mono-hydroxy methoxychlor. Toxicol Appl Pharmacol. 2013;272:780–6.

Zama AM, Uzumcu M. Fetal and neonatal exposure to the endocrine disruptor methoxychlor causes epigenetic alterations in adult ovarian genes. Endocrinology. 2009;150:4681–91.

# Pesticide exposure and timing of menopause: the Agricultural Health Study

Sherry L Farr 1, Jianwen Cai, David A Savitz, Dale P Sandler, Jane A Hoppin, Glinda S Cooper
Affiliations expand

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- Abstract

Age at menopause has implications for fertility and risk of hormonally related chronic diseases. Some pesticides disrupt reproductive hormones or are toxic to the ovary, but little is known about the association between pesticide exposure and timing of menopause. Cox proportional hazards modeling was used to examine the association between use of pesticides and age at menopause among **8,038** women living and working on farms in Iowa and North Carolina. Premenopausal women aged 35-55 years were followed from enrollment (1993-1997) to the date of their last menstrual period, or their follow-up interview (1999-2003) if still premenopausal. Women who experienced surgical menopause were censored at the date of surgery. Approximately 62% of the women reported ever mixing or applying pesticides; women who had never used pesticides were the comparison group for all analyses. After control for age, smoking status, and past use of oral contraceptives, the median time to menopause increased by approximately 3 months for women who used pesticides (hazard ratio = 0.87, 95% confidence interval: 0.78, 0.97) and by approximately 5 months for women who used hormonally active pesticides (hazard ratio = 0.77, 95% confidence interval: 0.65, 0.92**). Pesticide use may be associated with a later age at menopause.**

- Analysis of the articles yielded results from other studies that seemed to highlight a link between exposure to pesticides and an impact on the ovarian reserve.

# Cigarette

- The most studied components of cigarette smoke known to influence female fertility are polycyclic aromatic hydrocarbons (PAHs) which, alone, contain more than 100 chemical substances resulting from incomplete combustion. They act on the ovary via the aryl hydrocarbon receptor (AhR) present on the surface of granulosa cells. This receptor belongs to the family of transcription factors and activates the Bax gene, a pro-apoptosic gene, and the expression of cytochrome P450 that converts PAHs into even more toxic molecules .

- Anderson et al. have shown that activation of this receptor could lead to a decrease in germ cells in the ovary of the human fetus .
- According to the meta-analysis by Sun et al. , cigarette smoking in women is an independent factor for earlier age of menopause.
- Analysis of human data reinforced this theory: cigarette smoking led to a decrease in antral follicle count , an increase in serum FSH levels and a decrease in AMH (anti-mullerian hormone) levels in smokers, and this seems to correlate with the number of pack-years .

- The monitoring of a cohort of 410 patients was suggestive of an interaction of genetic polymorphism with the environment. In fact, the risk of POI in cigarette smokers depended on genetic polymorphism.

# Phytoestrogens

- **Phytoestrogens are plant-derived natural substances that have the particularity of mimicking the action of estrogens on their receptors .**
- The primary sources are isoflavones, of which the most common one is genistein, or lignans. An animal study has allowed studying the effect of exposure of the soy isoflavone on female rats from weaning to sexual maturity. This substance altered follicular development by increasing apoptosis of granulosa cells . **Neonatal exposure of mice to genistein seemed to confer early senescence of the ovarian function , over several generations.**

- A review of the literature on phytoestrogens suggested a **disturbance in ovarian function and folliculogenesis** without specifying the effect on the ovarian reserve .
- However the review by Patel et al. specified that genistein was responsible for a decrease in primordial, primary and secondary follicles with an increase in antral follicles.
- This acceleration of follicular recruitment is combined with an increase in apoptosis, and finally, follicular atresia.

Kim SH, Park MJ. Effects of phytoestrogen on sexual development. Korean J Pediatr. 2012;55:265–71.

Patel S, Zhou C, Rattan S, Flaws JA. Effects of endocrine-disrupting chemicals on the ovary. Biol Reprod. 2015;93:20.

# Dioxins

- Dioxins are environmental contaminants belonging to the PAH family. (Polycyclic aromatic hydrocarbons (PAH) are substances resulting from the incomplete combustion of organic fossil or non-fossil materials.)
- They mainly result from waste incineration and act via AhR, for which they are ligands. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic member of the dioxin family .
- It has a long half-life and accumulates in the environment and in the tissues of living organisms.

- The review of Patel et al. specified that the ovary was a clear target for TCDD, altering folliculogenesis.
- Chronic exposure to low doses of TCDD is associated with chronic activation of AhR , a depletion in follicle stock that contributes to premature ovarian senescence in rats .

# Seveso disaster

- The Seveso disaster was an industrial accident that occurred around 12:37 pm on 10 July 1976, in a small chemical manufacturing plant approximately 20 kilometres (12 mi) north of Milan in the Lombardy region of Italy. It resulted in the highest known exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in residential populations, which gave rise to numerous scientific studies and standardized industrial safety regulations, including the European Union's Seveso III Directive.
- This accident was ranked eighth in a list of the worst man-made environmental disasters by Time magazine in 2010.

# Seveso disaster

- An epidemiological study from 616 Italian non menopausal women exposed to the Seveso explosion found a significant trend for an earlier age at menopause in the four first quintiles of level of exposure to TCDD at the time of explosion but not for the 5 quintiles, suggesting a non monotonous dose-related effect .

- Polychlorinated biphenyls (PCB) belong to the PAH family; there are 209 isomers resulting from complex industrial processes. They have been banned since the 1970s, but, because of their stability in the environment, they persist in adipose tissues, living organism fluids and in food
- . They can lead to direct and indirect effects on ovary function . **Maternal exposure to PCB(polycarbonated biphenyls seems to have consequences on offspring, with a decrease in ovary weight in the offspring and follicular atresia .**

# Perfluorinated compounds

- Perfluorinated compounds are a large family of chemical substances present in industry and everyday consumer products, notably for their **anti-adhesive and anti-grease properties**.
- They are very resistant to degradation and persist in the environment and in the food chain . Two large scale epidemiological studies have demonstrated confounders-adjusted associations between exposure to perfluorinated compounds and an earlier age at menopause.

# 2 bromopropane

- A review led in the context of the American National Toxicology Program showed that women exposed to 2 bromopropane are at risk for the early onset of menopause .

- Finally, other toxicants such as **alcohol ,flame retardants ,diesel or anti-UV protectors** seem to influence the ovarian reserve but we have not found sufficient data to conclude this.
- Indeed, only animal studies are available for **flame retardants ,diesel and anti-UV protectors** and discrepancies exist between the two human cross-sectional studies for **alcohol**.

# Discussion

POI is a pathology in young women that can alter their fertility and, more generally, their quality of life.

Its idiopathic etiology (75% of cases) could be explained by the fact that the state of ovarian reserve at a given time seems to reflect a multifactorial influence combining factors that are genetic, epidemiological and environmental in nature.

# Conclusions

Environmental pollutants are a serious threat to human and animal reproduction with harmful effects that disturb endocrine and reproductive functions.

This is a critical public health problem that needs the implementation of protection, prevention and information measures in order to fight against these environmental pollutants.

One of these **preventive activities** may be to help health professionals to better detect patients at risk of POI in order to inform them about their reproductive ability, to limit aggravating factors and to treat them as early as possible through **oocyte cryopreservation**.

# Thanks for your attention

please be careful about every thing that you eat, breath, touch, use, inject and wear!!!!!!!