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## Environmental Agents and their Impact on Placental and Gestational Development

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### Conflicts of Interest

The author declares that there are no conflicts of interest.

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### Outline

- Background
- Birth Outcomes and the Environment
- Environmental Influences on Fetal Health
- Potential Mechanisms
- The Placenta

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“Environmental Agents and their Impact on Placental and Gestational Development”  
Alaeddin Abukabda, PhD

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The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS



**Providing Anticipatory Guidance**  
It is important for health care providers to become knowledgeable about toxic environmental agents that are endemic to their specific geographic areas. Intervention as early as possible during the preconception period is advised to alert patients regarding avoidance of toxic exposure and to ensure beneficial environmental exposure

<https://www.acog.org/~/media/Committee/Opinions/Committee-on-Health-Care-for-Underprivileged-Women/0617n.pdf?i10ncl&no=2018071714531212191>

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**The Faroese Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment – 2007**

“The periods of embryonic, fetal and infant development are remarkably susceptible to environmental hazards. Toxic exposures to chemical pollutants during these windows of increased susceptibility can cause disease and disability in infants, children and across the human lifespan.

Among the effects of toxic exposures recognized in the past have been spontaneous abortion, congenital malformations, lowered birthweight and other adverse effects.”

**2007 Nordic Pharmacological Society. Basic & Clinical Pharmacology & Toxicology. 10273–75**

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**Examples of Environmental Agents**

- Air pollutants (ozone, particulate matter)
- Cigarettes
- Bisphenol-A (BPA), phthalates
- Lead, mercury

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### Environmental Agents and Birth Outcomes

- Exposure of nonsmoking pregnant women to **environmental tobacco smoke** may be a risk factor for preterm birth, low birth weight, fetal death or miscarriage.
- Exposure to **air pollution and particulate matter** may be related to both low birth weight and preterm birth.
- A pregnant woman's exposure to **lead** and pesticides may cause preterm birth, low birth weight, and spontaneous fetal death or miscarriage.
- Environmental contaminants (e.g. lead) can affect **menstruation, ovulation and sperm quality**.
- Exposure to **endocrine disruptors** causes a decline in the sex ratio of males to females at birth.

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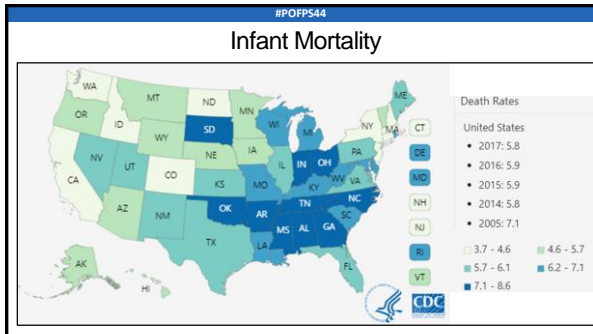
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### Causes of Infant Mortality

- Over 22,000 infants died in the United States in 2017
- Five leading causes of infant death in 2017:
  - 1) Birth defects
  - 2) Preterm birth and low birth weight
  - 3) Maternal pregnancy complications
  - 4) Sudden infant death syndrome (SIDS)
  - 5) Injuries (e.g., suffocation)

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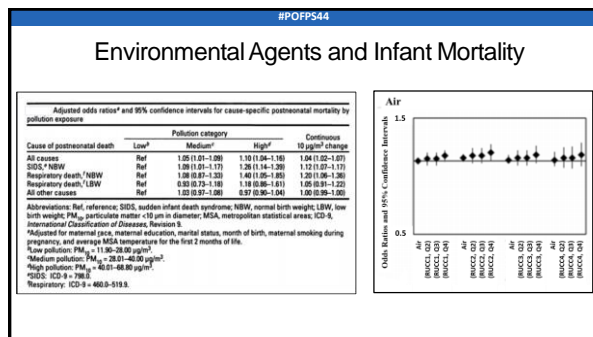
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### Environmental Tobacco Smoke and Birth Outcomes

- Elevates the risk of delivering a low birth weight (LBW), preterm, or small-for-gestational age (SGA) infant
- Exposure for at least 2 hours per day resulted in a mean birth weight reduction of 85 g and a twofold increased risk of LBW among infants of nonsmokers
- Dose-related effects of smoking resulting in a conception delay of approximately 2 months

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### Environmental Tobacco Smoke and Birth Outcomes

Associations between ETS\* exposure and low birth weight, preterm delivery, and small-for-gestational age deliveries, PNSS\*, 1989-1994

	Maternal age (years)							
	Nonsmokers				Smokers			
	<30	95% CI†	OR†	95% CI	<30	95% CI	OR†	95% CI
LBW*	0.97	0.76-1.23	2.42	1.51-3.87	1.39	1.01-1.93	1.69	0.95-3.02
Preterm births	0.92	0.76-1.13	1.88	1.22-2.88	1.00	0.73-1.37	1.42	0.75-2.70
SGA*	0.97	0.75-1.26	1.28	0.76-2.15	1.20	0.83-1.75	0.93	0.51-1.69

\* ETS, environmental tobacco smoke; PNSS, Pregnancy Nutrition Surveillance System; OR, odds ratio; CI, confidence interval; LBW, low birth weight; SGA, small-for-gestational age.  
 † Odds ratios adjusted for ethnicity, education, marital status, parity, state, alcohol use, weight gain, prepregnancy body mass index, and altitude.

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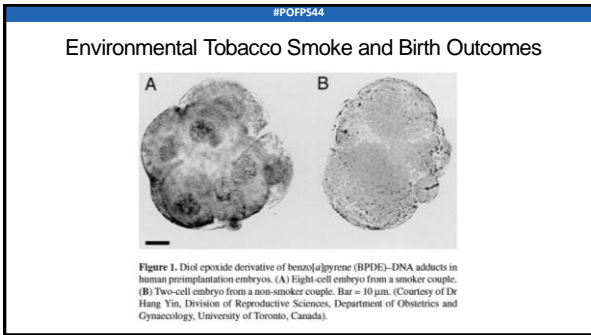
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### Air Pollution and Particulate Matter and Birth Outcomes

- Particulate matter is a complex mixture of extremely small particles and liquid droplets.
- Particle pollution is made up of a number of components, including acids (such as nitrates and sulfates), organic chemicals, metals, and soil or dust particles (<http://www.epa.gov/pm/>).
- Characterized according to size due to the variation of health effects associated with particles of different diameters.

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### Air Pollution and Particulate Matter and Birth Outcomes

- **Decreased placental size and quality**  
Animal studies suggested that volumes of placental compartments and calibers of maternal blood spaces were reduced.
- **Fetal growth delay**  
Studies using ultrasound measurements of fetal growth found strong associations between fetal growth delay and maternal exposure during mid-pregnancy.
- **Small for Gestational Age (SGA)**  
Associated with low birthweight, preterm birth, and SGA births.

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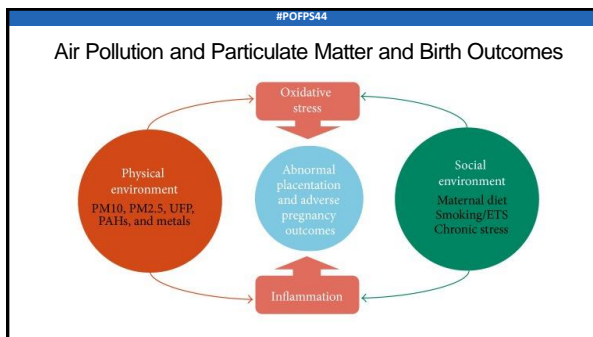
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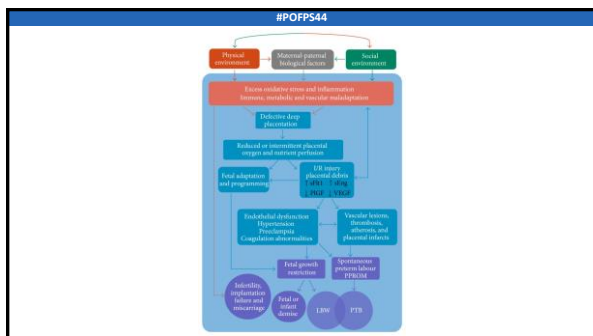
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### Air Pollution and Particulate Matter and Birth Outcomes

Preterm birth rate by PM<sub>2.5</sub> levels in Ohio 2007 – 2010 and trimester of exposure in pregnancy

	PM <sub>2.5</sub> < 15 µg/m <sup>3</sup>		PM <sub>2.5</sub> ≥ 15 µg/m <sup>3</sup>		p-value
	n	% Preterm	n	% Preterm	
First trimester	175,649	8.34	49,272	8.87	<0.001
Second trimester	185,883	8.47	39,038	8.43	0.835
Third trimester	181,665	8.08	43,256	10.05	<0.001
Entire pregnancy	200,259	8.27	24,662	9.99	<0.001

% preterm represents the rate of birth <37 weeks of gestational age among the study cohort of singleton non-anomalous live births

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### Heavy Metals and Birth Outcomes

- Arsenic, cadmium and lead may compromise fetal health even at a low level through trans-placental circulation
- Prenatal cadmium exposure could impair steroidogenesis leading to suboptimal fetal growth and development
- Lead exposure may interfere with calcium deposition in the bone, resulting in decreased fetal bone growth
- Arsenic exposure during pregnancy may contribute to placental insufficiencies leading to intra-uterine growth retardation via oxidative stress

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### Heavy Metals and Birth Outcomes

Comparison of the exposure level with different birth outcomes (n = 419).

Adjusted Urinary Heavy Metal Concentration (µg/g Creatinine)	Preterm Delivery <sup>0</sup>			Low Birth Weight <sup>1</sup>			Preterm and Low Birth Weight		
	Yes (n = 80)	No (n = 339)	p-Value	Yes (n = 26)	No (n = 393)	p-Value	Yes (n = 18)	No (n = 401)	p-Value
Arsenic	73.2	74.2	1.000	89.0	73.8	0.500	84.2	73.9	0.490
Cadmium	0.8	0.8	0.743	1.4	0.8	0.020	1.4	0.8	0.014
Selenium	22.4	22.7	0.949	20.6	22.7	0.998	19.3	22.7	0.324
Lead	1.7	1.8	0.729	1.5	1.8	0.117	1.5	1.8	0.226

<sup>0</sup> Any delivery before 37 weeks of gestation regardless of birth weight. <sup>1</sup> Birth weight < 2500 g regardless of gestational age at birth.

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### Heavy Metals and Birth Outcomes

**Classification of naturally occurring metals by toxicity and hydrologic availability**

[Metals that normally do not exist as dissolved species in natural waters or are very rare in crustal rocks are in italics]

Nontoxic		Low toxicity			Moderate to high toxicity			
Aluminum	Magnesium	Barium	<i>Praseodymium</i>	<i>Actinium</i>	Indium	Polonium	Uranium	
Bismuth	Manganese	<i>Cerium</i>	<i>Promethium</i>	<i>Antimony</i>	<i>Iridium</i>	<i>Radium</i>	Vanadium	
Calcium	Molybdenum	<i>Dysprosium</i>	<i>Rhenium</i>	Beryllium	Lead	<i>Ruthenium</i>	Zinc	
Cesium	Potassium	<i>Erbium</i>	<i>Rhodium</i>	Boron	Mercury	Silver	<i>Zirconium</i>	
Iron	Strontium	<i>Europium</i>	<i>Samarium</i>	Cadmium	Nickel	<i>Tantalum</i>		
Lithium	Rubidium	<i>Gadolinium</i>	Scandium	Chromium	<i>Niobium</i>	Thallium		
	Sodium	<i>Gallium</i>	<i>Terbium</i>	Cobalt	<i>Osmium</i>	Thorium		
		Germanium	Thulium	Copper	Palladium	<i>Titanium</i>		
		<i>Gold</i>	<i>Tin</i>	<i>Hafnium</i>	Platinum	<i>Tungsten</i>		
		<i>Holmium</i>	<i>Ytterbium</i>					
		<i>Neodymium</i>	<i>Yttrium</i>					

U.S. GEOLOGICAL SURVEY CIRCULAR 1133, 1995

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### Phthalates and Birth Outcomes

- Associations have been reported between prenatal and early postnatal phthalate exposures and shorter anogenital distance as well as lower serum testosterone in newborns .
- Pre-natal exposure biomarkers have been associated with reduced gestational age.

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### Endocrine Disruptors and Birth Outcomes

- Chemicals that, at certain doses (high or low), may act on the endocrine system.
- Endocrine disruptors are found widely in contaminated water, air, food, and household products, like plastics.
- BPA binds to estrogen receptor and may disrupt estrogen function

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### Endocrine Disruptors and Birth Outcomes

EXAMPLES OF ENDOCRINE DISRUPTING CHEMICALS

Chemical	Use	Mechanism	Health Effect
Diethylstilbestrol (DES)	Medication	Mimics estrogen	In humans – female – vaginal cancer, reproductive tract abnormalities; male – abnormalities of the penis and testicles, karyenodermatides
Genistein	Naturally occurring in soybeans	Mimics estrogen, blocks testosterone	In adult humans – lowers cholesterol, may decrease breast cancer risk. In animals – infertility.
Bisphenol A	Used in dental sealants, lining of food cans, and polycarbonate plastics	Mimics estrogen	In male mice – affects prostate size, decreases sperm production, affects behavior
Vinorelbine	Pesticide/fungicide	IRIIBs testosterone	In male rodents – feminization, nipple development, abnormal penis development
Polychlorinated biphenyls (PCBs)	No longer made; still found as a pollutant	IRIIBs thyroid hormones	In humans – delayed neurological development; IQ deficits
Dioxin	Byproduct of industrial processes including incineration	Decreases estrogen; decreases testosterone; alters thyroid hormone	In female rodents – delayed puberty, increased mammary cancers. In male rodents – decreased testosterone, penis and testicular abnormalities, feminized sexual behavior. In humans – decreased thyroid hormone levels; decreased testosterone; cancers

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### Potential Mechanisms – Barker Hypothesis

- Fetal origins of adult disease hypothesis.
- Fetal undernutrition in middle to late gestation leads to disproportionate fetal growth, programs later coronary heart disease.
- Not only coronary heart disease, but also diabetes, obesity, stroke and mental illness.

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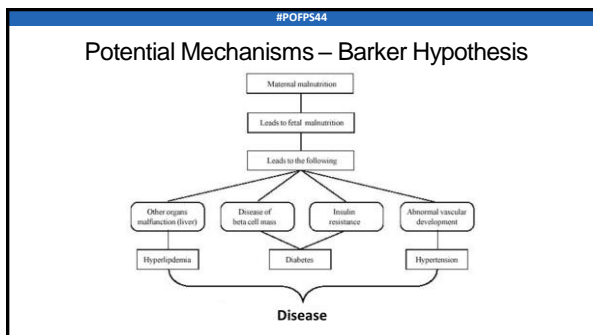
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### Potential Mechanisms – Fetoplacental Epigenome

- Epigenetic marks regulate development
- DNA methylation and histone modifications (acetylation, methylation, phosphorylation and ubiquitination)
- Results in altered gene expression

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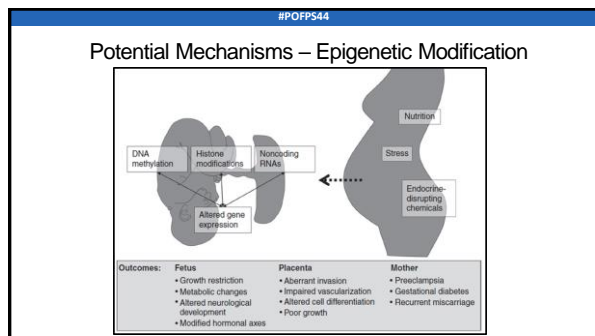
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### Potential Mechanisms – Developmental Plasticity

The ability of a given genotype to produce different phenotypes in response to different environments.

Part of the organism's "adaptability" to environmental cues.

The expressions of suites of genes, particularly during development or life history transitions, probably underlie the fundamental plasticity of an organism.

Provides the best chances of survival and reproductive success to organisms under changing environments.

Environmental conditions that are experienced in early life can profoundly influence human biology, child growth and maturation, and long-term health and longevity.

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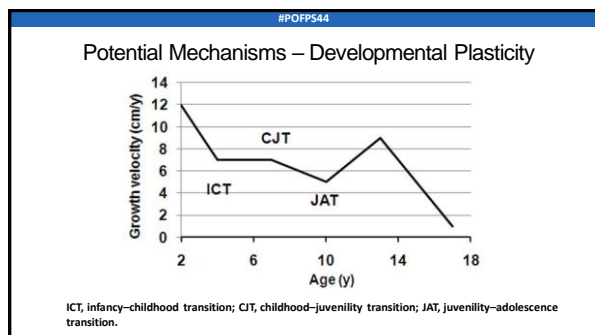
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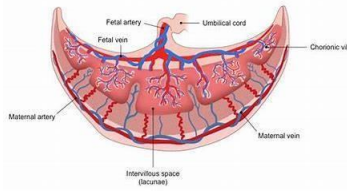
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### Potential Mechanisms – The Placenta

- Transient organ
- Functions in oxygen exchange, immunity, hormone secretion, nourishment and waste removal



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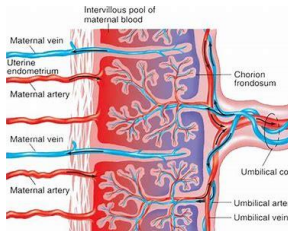
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### Potential Mechanisms – The Placenta

- Exposure to environmental agents linked to reduced placental vascular density, efficiency, size, number
- Altered gene expression and vasoactive sensitivity
- dual biomarker to assess maternal and fetal health



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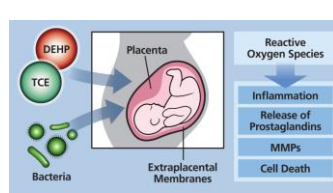
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### Potential Mechanisms – The Placenta

- Environmental agents may penetrate the placenta and disrupt function and efficiency
- Epigenetic markers in placenta may represent exposures from intrauterine and extrauterine environment



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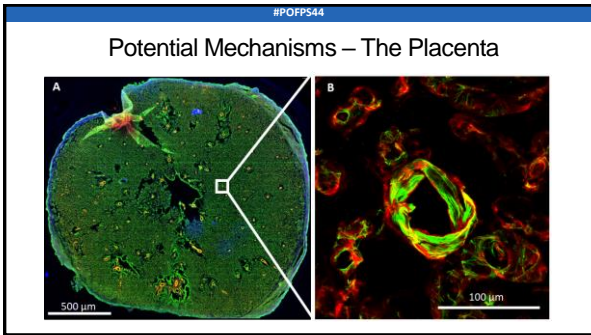
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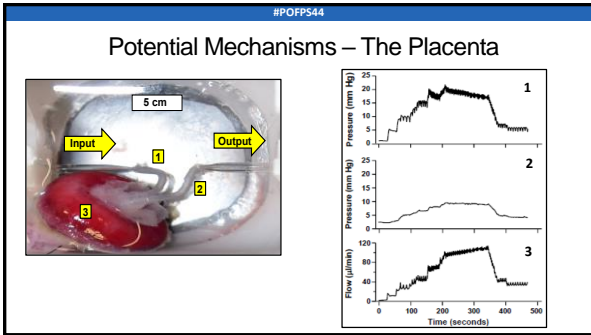
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**Summary**

- Exposure to environmental agents affects birth outcomes
- Several mechanisms may be potentially involved and should be taken into consideration
- The placenta is a critical transient organ and is affected by environmental toxicants/toxins

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### Questions

- Ambient particulate matter is harmless and should therefore not be studied by toxicologists.
  - True
  - **False**
- It is important for clinicians to become knowledgeable about toxic environmental agents.
  - True
  - False
- Since the placenta is a transient organs it should not be a priority for clinicians.
  - True
  - **False**

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### Acknowledgments



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