FETAL/ENVIRONMENTAL ORIGINS OF ADULT DISEASE

Children's Health and the Environment
WHO Training Package for the Health Sector
World Health Organization
www.who.int/ceh

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WHAT IS THE ENVIRONMENT?

"Everything that surrounds anything"
web.mala.bc.ca

All the physical, chemical, biological and social factors that may affect the origin, growth, development and survival of an organism in a given setting.
Causes and estimated number of deaths/year in children 0 to 4 yrs

<table>
<thead>
<tr>
<th>Cause</th>
<th>Estimated Deaths/Year</th>
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<tbody>
<tr>
<td>Acute respiratory infections:</td>
<td>1 000 000</td>
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<tr>
<td>Diarrhoeal diseases:</td>
<td>1 600 000</td>
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<tr>
<td>Malaria and other vector-borne:</td>
<td>1 000 000</td>
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<tr>
<td>Injuries (non-intentional)</td>
<td>300 000</td>
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<tr>
<td>Poisonings</td>
<td>16 000</td>
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www.who.int/evidence 2002 data
The environment and health for children and their mothers, Fact sheet WHO/284, 2005

Diseases strongly linked to environmental threats are present in places where children grow, live, learn and... work

WHO ACTIVITIES ON CHILDREN'S HEALTH & THE ENVIRONMENT
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WE KNOW MORE! New recognition of:

- Special vulnerability of child/fetus to environmental influences
  - Chemicals, radiations, noise, climate change,…

- Effects related to toxicity, dose, type of exposure and timing

- Effects exacerbated by:
  - Poverty
  - Malnutrition
  - Urbanization
  - Degraded environments
  - Stressful circumstances
  - Ignorance
Main Global Environmental Health Risks

- Poor hygiene and sanitation
- Household water insecurity
- Air pollution – indoor and outdoor
- Disease vectors
- Chemical hazards
- Injuries and accidents
- …. Emerging Issues!

Over 5,000,000 children under 14 years die every year from diseases that relate to environmental conditions, mainly in the developing world.

www.who.int/world-health-day/2003
HEALTH EFFECTS OF GLOBAL WARMING:

- **Direct Effects**
  - Thermal extremes: heat stroke
  - Weather disasters: drowning, and psychological trauma
  - Dehydration and diarrhoeal disease

- **Indirect Effects**
  - Food availability: malnutrition, growth retardation, and developmental delay
  - Increased aeroallergens: allergies
  - Malaria, dengue fever, and other vector-borne diseases
COMBINATION OF ENVIRONMENTAL RISK FACTORS

Heavy traffic
  +
Toxic waste site, industrial effluent
  +
Contaminants (in water, food, objects)
  +
Malnutrition
  +
Genetic predisposition

1. No effects
2. No obvious effects – *disease later in life*
3. Developmental problems
4. Disease
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**RISKS**
Physical
Chemical
Biological
Social

**MEDIA**
Water, Air, Food
Soil, Objects

**SETTINGS**
Rural/urban
Home, Park, Field, Street, Work

**ACTIVITIES**
Eating, Drinking, Working, Hobbies, Habits, …

**SUSCEPTIBILITY**
Critical windows
Nutrition
Poverty
Ethnic minorities

**EFFECTS ON**
Organs
Systems
Functions
Well-being
Development
Survival

**COMPLEX ENVIRONMENTS, MULTIPLE PROBLEMS, STRATEGIC APPROACHES**
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ARE ENVIRONMENTAL THREATS SIMILAR AROUND THE WORLD?

KEY GLOBAL RISK FACTORS (WHO)

- Water safety
- Hygiene and sanitation
- Air pollution
- Disease vectors
- Chemical hazards
- Injuries and accidents
- **EMERGING ISSUES!**

CEH CONCERNS IN INDUSTRIALIZED COUNTRIES

- Respiratory disease and air quality
- Obesity/nutrition/diabetes
- "Built" environment
- Neurological impairment
- Birth defects
- Autism
- Fetal origin of adult disease
- Childhood cancer
- Endocrine disruption
1. Eradicate extreme poverty and hunger
2. Achieve universal primary school education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development
BARKER HYPOTHESIS

Low birthweight linked to hypertension, cardiopathy, type II diabetes and osteoporosis later on in life

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**FETAL ENVIRONMENT**

- Intrauterine Env
- U-Placental Unity

**MATERNAL ENVIRONMENT** + **MATERNAL & PLACENTAL PHYSIOLOGY**

**GENOME**

**RESPONSES TO ADVERSE ENVIRONMENTS:**

1. Accelerated maturation (↑ G-corticoid level)
2. Keeps nutrients (↓ growth & nutrition)
3. Pregnancy termination (abortion, prematurity)

**FETAL ORIGIN OF DISEASE** ➔ IMPACT ON PUBLIC HEALTH

**ALTERATIONS:**

- FETAL GROWTH
- INTERACTION PRE-AND POST-NATAL ENVIRONMENTS
GENETIC MODIFICATIONS

Epigenetics:
Heritable changes in gene function that cannot be explained by changes in chromosomal system

3 Main types of epigenetic information:
- DNA methylation
- Genomic imprinting
- Histone modification

- Changes can be permanent or transient
- Some of them are part of normal development
- Some are affected by environment → altered gene expression (suppression/activation of genes)
THRIFTY PHENOTYPE HYPOTHESIS

How does the fetus respond to an adverse environment?
By making irreversible changes in its development

- Abnormal insulin secretion/action
- Reduced vascularity
- Reduced number of nephrons

The developing organism predicts its future environment

Embryo/fetus depend on the information transmitted by the mother/placenta to evaluate/predict the present and future environments.

**PARs:** decisions to change the course of development for future advantages

- Appropriate PARs
- Inappropriate PARs

Key concept: match/mismatch PARs
Relationship between real and predicted postnatal environments determines disease risk

- Match: low risk of disease
- No match: higher risk of disease

Nutritional signals:
low food availability → insulin resistance

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- Very adverse environment → Death
- Less adverse environment → Alterations of
  - Maturity
  - Size
  - Growth
  Small newborn
  (Prematurity)

Other factors:
- Infections
- Genetics

Long-term consequences

Compensatory growth
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IMPLICATIONS OF THESE MODELS

- "Lifestyle" disease
- Improve maternal and child health
- More research needed in:
  - Genetic changes
  - Windows of opportunity during plasticity periods?
  - Peri-conception period
  - Father and mother's exposure
  - Women's nutrition
  - Metabolic, cardiovascular, skeletal & other systems

BUT THE TIME FOR ACTION IS NOW
EXAMPLE OF AN INORGANIC CHEMICAL ARSENIC (AS)

- From natural erosion, pesticide run-off, coal burning, smelting, glass and electronic production waste

- Skin lesions and cancer, vascular and neurological disease, increased risk of cancer

- WHO guideline: 0.01 mg/L (ppm)

- Arsenic crosses the placenta

- Previous studies: *In utero* exposure to Arsenic linked to increased risk for stillbirth, and spontaneous abortion
EXAMPLE: ARSENIC AND THE ANTOFAGASTA STUDY

- High Arsenic exposure in Antofagasta (Chile) from 1958 to 1970

- Study of exposed children (1958 – 1971): Increase in mortality from lung cancer and bronchiectasis when \textit{in utero} + childhood exposure to arsenic in drinking water

- Exposure in:
  - Early childhood
  - \textit{In utero} and early childhood

- Mortality due to:
  - cancer SMR=7
  - bronchiectasis SMR=12
  - SMR=6.1
  - SMR=46.2

Smith. A. Increased Mortality from Lung Cancer and Bronchiectasis in Young Adults after Exposure to Arsenic in Utero and in Early Childhood, EHP 114 (8), August 2006.
EXAMPLE: TOBACCO SMOKE

Lung development is a multievent process that begins at the first month of gestation and continues postnatally.
- Toxicants to developing lungs: ETS, bioactivated compounds and oxidant gases
- Targets: epithelial cells that are maturing and/or proliferating

Developing fetus more susceptible than adult to PAHs carcinogenicity:
- Increased susceptibility of the fetus to DNA damage
- Reduced ability to clear ETS constituents

Tobacco metabolites in the fetus: toxic effects.

Perera, Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage, EHP (2004) 112 (10)
Pinkerton, The mammalian respiratory system and critical windows of exposure for children’s health, EHP (2000) 108 (S3).
Jaakkola, Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration, EHP (2001) 109 (6).
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EXAMPLE: TOBACCO SMOKE

Maternal smoking is risk factor for:
- low lung function, low birth weight, pre-term delivery,
- sudden death, lower respiratory illness, wheezing and asthma in children, debilitating asthma, obstructive pulmonary disease, cancer in adults.

Effects on lung development:
- diminishing airway and alveolar growth
- Structural alterations
- Interference with control of respiration and developing immune system
- Reduction in fetal breathing movements: exposure to hypoxia even 1 hr after cigarette was smoked
- Changes in CNS sensitivity to blood gases = impaired control of breathing
- Reduced placental blood flow, reduced supply of nutrients and oxygen to the fetus and growth retardation: Fetal origins of disease

EXAMPLE: TOBACCO SMOKE

- Secondhand smoke + urban air pollutants:
  - Effect greater than the sum of individual effects
  - Reduced fetal growth, lower birth weight
  - Problems in learning and school performance

- Women who quit smoking during pregnancy and who are exposed to second-hand smoke: babies born with more gene mutations (umbilical cord blood studies)

- High doses of vitamin C can be beneficial

Grant, Qualitatively and Quantitatively Similar Effects of Active and Passive Maternal Tobacco Smoke Exposure on In Utero Mutagenesis at the HPRT Locus, BMC Pediatrics (2005), 5 (20).

Proskocil, Vitamin C prevents the effects of prenatal nicotine on pulmonary function in newborn monkeys. Am J Respir Crit Care Med. (2005) 171(9):1032
OTHER EXAMPLES

- **Radiation**: exposure *in utero* in Nagasaki led to mental retardation and small head size.

- **Ethyl alcohol**: array of congenital malformations in children of heavily alcoholic mothers:
  - Mental retardation
  - Microcephaly
  - Short palpebral fissures
  - Intrauterine and postnatal growth retardation.

- **Noise, heat**: impacts that harm mother's health can indirectly have detrimental effects on fetus.

WHAT IS AN ENDOCRINE DISRUPTING CHEMICAL? (EDCS)

Exogenous substance or mixture that alters the function(s) of the hormonal system and consequently causes adverse effects in an intact organism, or its progeny or its sub-population.

**Natural**
- Phytoestrogens
- Fungal estrogens

**Synthetic**
- Hormones
- Some pesticides
- Industrial by-products ("dioxin-like")
- Pharmaceuticals
- Some persistent organic pollutants (POPs)
EXAMPLES OF EFFECTS ON WILDLIFE

REPTILES: decline in alligator population by 90% after difocol, DDT, DDE chemical spill

- Smaller penis size
- Abnormal gonad morphology
- Altered sex steroid concentrations

FISH: reproductive alterations when exposed to sewage treatment waste
Another type of cancer: Diethylstilbestrol as a model for environmental estrogens

- DES administered to pregnant women 1940-1960 for high-risk pregnancies but later to promote "healthier babies" as well.

- Female offspring developed clear-cell carcinoma of the vagina, vaginal adenosis, cervical ectropion, and other abnormalities.

- Males: reproductive tract abnormalities.

*Has human cancer incidence resulting from DES exposure peaked? DES daughters are reaching post-menopause, the age of endometrial carcinoma…*

- DES may be a model compound for other environmental agents with estrogenic potential.
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PLASTICS

- Phthalates: solvents, soft plastics, and cosmetics
- Most US population exposed to phthalates
- Special population highly exposed
- Animals: reproductive and developmental toxicities
- Human studies: possible associations with
  - Altered semen quality
  - Shortened gestation
  - Reduced anogenital distance in baby boys
  - Premature breast development
  - Obesity
REPORT DETAILS ENVIRONMENTAL HARM TO FETUSES

- Study by the Environmental Working Group and Commonweal on 10 babies born in 2004 (USA)

- **Findings:**
  - 287 chemicals found.
  - 200 industrial chemicals and pollutants found in umbilical cord blood, on average.
  - Among them: pesticides, consumer product ingredients and wastes from burning coal, gasoline and garbage.
  - 180 cause cancer in humans or animals.
  - 217 are toxic to the brain and nervous systems.
  - 208 cause birth defects or abnormal development in animal tests.

*Houlihan, Body Burden, The pollution in newborns, EWG, 2005*
Many pregnancy/birth problems could be avoided through:

- Family planning,
- Balanced, organic diet
- Management of maternal health problems
- Avoiding maternal infection

Usual advice:

- Folic acid in flour to prevent neural tube defects,
- Iodine in salt to prevent congenital hypothyroidism,
- Vit B12 (methyl donor important for DNA and protein modification) around conception
- Rubella vaccinations prevents congenital rubella syndrome.
HOW TO REDUCE EXPOSURE?

- Don't smoke! Nor stay near smokers
- Eat food without additives
- ...organic (without pesticides and preservers)
- Eat less meat and fat products
- Avoid fish rich in POPs and Hg (salmon, tuna,...)
- Avoid microwaving plastics
- Filter water at home
- Use few cosmetics and fragrances
- Don't use solvents
- Reduce the number of chemical cleaners at home
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CHILDREN'S HEALTH AND THE ENVIRONMENT

WHO - Tools and mechanisms available to promote CEH

- Training Package for the Health Sector
- National Profiles on the status of CEH
- CEH Indicators
- Promotion of the Environmental History taking: "Green page"
- EH components into the IMCI
- Guidelines for setting up CEH Centres
- Technical assistance to countries
- Collaborative research: Longitudinal Cohort Studies on CEH

Through: Partnerships and alliances with NGOs and IGOs
Applying a PREVENTIVE AND EDUCATIONAL APPROACH
Improving the capacity to diagnose, prevent and manage paediatric diseases linked to the environment

New training materials:

- Reproductive health and the Environment
- Environmental Health Criteria 237: Principles for Evaluating Health Risks in children Associated with Exposure to Chemicals

HECANET NEWSLETTER

- HECANET is an international mailing list dedicated to promoting healthy environments for children.
  - The list provides updates on:
  - the activities in the area,
  - advocacy tools and information resources,
  - relevant meeting announcements,
  - and reports on technical research and monitoring related to environmental risks to children's health


- To subscribe, send an email to: heca@who.int
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CEH WEBSITE

www.who.int/ceh
"Improving children and mothers' (and fathers') environmental health by addressing and tackling issues affecting their health, presents an essential contribution towards the achievement of the Millennium Development Goals (MDGs)"