Early exposure to Endocrine Disruptors.

Case studies of selected health effects later in life: implications for research and for policy

Juan Gabriel Ruiz P. MD MMedSci

Kangaroo Foundation
Bogotá, Colombia

AND

Department of Medical and Population Health Sciences Research
Herbert Wertheim College of Medicine
Florida International University
Miami, FL, USA
Presented at

«ETTORE MAJORANA» FOUNDATION AND CENTRE FOR SCIENTIFIC CULTURE

ERICE INTERNATIONAL SEMINARS ON PLANETARY EMERGENCIES
49th Session
The New Manhattan Project
Nota Bene:

- The original review is about early exposure to endocrine disruptors, poor nutrition or impoverish environment.
- Case studies of selected health effects later in life are been reviewed:
  - Endocrine Disruptors
  - Preterm Birth disruption of maturation
  - LBW and Intrauterine growth restriction
  - Primary antenatal and postnatal malnutrition
  - Severe social and emotional deprivation
  - Poverty, SES, health habits and performance in life.
Nota Bene:

The current presentation will address two case studies on Endocrine Disruptors

These cases are intrinsically very important

Also, they illustrate our proposed analytical and decision-making approach, for producing concrete recommendations
Contents

- Background and basic assumptions
- Case studies
  - Diethylstilbestrol
  - Bisphenol A
- Implications
  - Proposed Conceptual framework for identifying implications
  - Research implications
  - Policy implications
BACKGROUND AND BASIC ASSUMPTIONS
Background and basic assumptions

- Dose-response relationships
  - Debate between monotonic vs. non-monotonic
  - Implications on “safe” levels of exposure
- Transgenerational epigenetic inheritance
  - Risk of deleterious effects being passed to descendants
A model for gene-environment interplay in development

- Gene-driven development
- Experience expectant development
- Experience-dependent development
Neurodevelopment as a model for development

- Gene-driven development
  - Relatively insensitive to experience
  - Environmental significant injury or faulty gene expression, can impair development
  - Necessary but not sufficient
  - Neurogenesis, migration, differentiation, synaptogenesis

- Example: Initial myelination of optic nerve
Neurodevelopment as a model for development

- Experience expectant development
  - Sensitive periods (windows of opportunity) of phenotype (neural) plasticity
  - If appropriate stimuli are present, and underlying structures and genes are OK (Brain “readiness”), the process develops.
- General or selective deprivation disrupts the process
- Example: Visual cortex integration – Amblyopia
Neurodevelopment as a model for development

- Experience-dependent development
  - Unique for each individual
  - Does not have definite sensitive periods
  - Usually depends on previous developments
  - Example: Language development
    - Initial universal sensitive period (experience expectant)
    - Followed by idiosyncratic expansion on language command (learning, experience dependent)
Biological and socio-cultural mediators

- Causality of developmental events and effects is multiple, complex and non-linear
- Example: Neurodevelopmental status at 1 year and KMC
  - Preterm infant’s brain synaptogenesis and pruning at jeopardy, because preterm delivery
  - KP at a sensitive period partially remediates (microenvironment, biological effect)
Biological and socio-cultural mediators

- KP Promotes healthy bonding-attachment
- Kangaroo Parents provide a better, more stimulant environment, irrespective of SES and education (socio-emotional effect)
- The more vulnerable prematures do better at 1 year when exposed to KMC
Case studies

ENDOCRINE DISRUPTORS
Case study 1: DES, “proven guilty”

- DES use in pregnant women (3 million in US between 1941 and 1971)
- First Generation /pregnant women DES
  - Breast Cancer > 40 years RR 1.91 (95%CI, 1.09-3.33)
  - Cervical Cancer > 45 years HR 2.1 (95%CI 1.4-4.0)
Case study 1: DES, “proven guilty”

- Second generation
  - DES Daughters
    - Vaginal Clear cells CA in premenopausal women: Transplacental carcinogen (4000% risk increase)
    - Teratogen: Reproductive system anomalies
  - DES Sons
    - Urinary tract Malformations
    - Hypogonadism
    - Sexual identity and gender dysphoria
    - Left handedness
Case study 1: DES, “proven guilty”

- Third Generation effects
  - Female infertility?
  - Male hypospadias?

- Animal studies:
  - Obesity and feminization of males (behavior)

- Convincing evidence of
  - Causal association
  - Epigenetic transgenerational transmission
Case study 1: DES, “proven guilty”

- Sources of evidence
  - Compelling case reports and case series
  - Observational comparative studies
    - Case control
    - Cohort studies
  - Animal models

- Quality of evidence
  - Moderate to High and homogeneous
Case study 2: BPA health effects in health in adults

- Studies in Humans: review 1 (Reproductive Toxicology 42 (2013) 132–155)
  - non systematic but extensive review
  - No search strategy
  - No selection criteria
  - No attempt to assess studies’ quality
  - Reports a score of associations of BPA and human health
Case study 2: BPA health effects in health in adults

- Reproduction
  - Fertility
  - Male sexual function
  - Reduced sperm quality
  - Sex hormone concentrations
  - Polycystic ovary syndrome
  - Endometrial disorders
  - Breast cancer
  - Miscarriage
  - Premature deliveries
Case study 2: BPA health effects in health in adults

- Development
  - Birth weight
  - Male genital abnormalities
  - Childhood behavior/neurodevelopment
  - Childhood asthma/wheeze
Case study 2: BPA ubiquitous and under trial

- Metabolic disease
  - Type-2 diabetes
  - Cardiovascular disease, hypertension, and cholesterol levels
- Liver function
- Obesity
Case study 2: BPA health effects in health in adults

- Other health effects
  - Thyroid function
  - Immune function
  - Albuminuria
  - Oxidative stress and inflammation
  - Epigenetics, gene expression, and sister chromatid exchange
Case study 2: BPA Metabolic effects in adults

  - Systematic review
  - Explicit comprehensive search strategy
  - Explicit selection criteria
  - Description of studies’ quality, including adjustment for potential confounders
  - Most reported associations come from cross sectional studies
Case study 2: BPA Metabolic effects in adults

- Main findings
  - Prevalence ORs Low vs High uPBA levels
    - Diabetes 1.47 (95 % CI: 1.21–1.80)
    - Overweight 1.21 (95 % CI: 0.98–1.50)
    - Obesity 1.67 (95 % CI: 1.41–1.98)
    - High WC 1.48 (95 % CI: 1.25–1.76)
    - Hypertension 1.41 (95 % CI: 1.12–1.79)
  - 3/5 Longitudinal studies suggest association with incident CVD, Diabetes and weight gain
Case study 2: BPA perinatal exposure and child behavior

- Studies in Humans: review 3 (Journal of Exposure Science and Environmental Epidemiology (2016), 1–9)
  - Systematic review
  - Explicit comprehensive search strategy
  - Explicit selection criteria
  - Description of studies’ quality, including adjustment for potential confounders
  - Most reported associations come from the same cohort
Case study 2: BPA perinatal exposure and child behavior

Main findings:

- No meta-analysis feasible (heterogeneity)
- Pre-natal exposure associated with differential effects in boys and girls
- Inconsistent results
- Postnatal exposure associated with attention deficit (boys) and depression anxiety in both genders
- Again, inconsistent results
- No evidence of autistic disorders
Table 3. Association between prenatal and childhood BPA exposure and children’s behavior.

<table>
<thead>
<tr>
<th>Source</th>
<th>Prenatal BPA exposure</th>
<th>Childhood BPA exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun et al.(^{36})</td>
<td><strong>Overall: No statistically significant association on the SRS</strong></td>
<td><strong>Overall: No statistically significant associations on the BASC-2</strong></td>
</tr>
<tr>
<td>Braun et al.(^{35})</td>
<td><strong>Girls: Higher levels of anxiety, depression, and hyperactivity on the BASC-2; lower emotional control and inhibition on the BRIEF-P</strong></td>
<td></td>
</tr>
<tr>
<td>Braun et al.(^{37})</td>
<td><strong>Girls: Higher scores on externalizing behaviors on the BASC-2</strong></td>
<td></td>
</tr>
<tr>
<td>Evans et al.(^{38})</td>
<td><strong>Overall: Higher levels of externalizing and aggressive behaviors on the CBCL</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Boys: Higher levels of internalizing and externalizing behaviors, withdrawn/depressed behaviors, somatic problems, and oppositional/defiant disorder behaviors on the CBCL</strong></td>
<td></td>
</tr>
<tr>
<td>Harley et al.(^{39})</td>
<td><strong>Boys: Higher levels of internalizing including depression behaviors on the mothers’ BASC-2 reports</strong></td>
<td><strong>Girls: Higher levels of externalizing behaviors, including conduct and attention problems on mothers’ BASC-2 reports</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Higher levels of internalizing, anxiety, depression behaviors on the BASC-2 teachers’ reports</strong></td>
<td><strong>Higher levels of internalizing behaviors, depression, hyperactivity on teachers’ BASC-2 reports</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Higher levels of inattention, hyperactivity and ADHD on the mothers’ CADS reports</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Higher levels of hyperactivity and ADHD on the teachers’ CADS reports</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Boys: Higher levels of inattention and anxiety on the teachers’ BASC-2 reports</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Higher levels of inattention on the teachers’ CADS reports</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Overall: Higher levels of anxiety and depression on CBCL</strong></td>
</tr>
<tr>
<td>Hong et al.(^{40})</td>
<td><strong>Overall: No statistically significant association on SRS</strong></td>
<td><strong>Overall: No statistically significant association on the CBCL</strong></td>
</tr>
<tr>
<td>Miodovnik et al.(^{41})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perera et al.(^{42})</td>
<td><strong>Boys: Higher levels of emotional reactivity and aggressive behavior on the CBCL</strong></td>
<td><strong>Overall: Higher levels of anxious/depressed symptoms, rule-breaking behavior, aggressive behavior, and internalizing and externalizing problems on the CBCL</strong></td>
</tr>
<tr>
<td>Roen et al.(^{43})</td>
<td><strong>Girls: Higher levels of withdrawn/depressed symptoms and internalizing problems on the CBCL</strong></td>
<td><strong>Boys: Higher levels of anxious/depressed symptoms, somatic complaints, thought problems, rule-breaking behavior, aggressive behavior, and total internalizing and externalizing behavior on the CBCL</strong></td>
</tr>
<tr>
<td>Stein et al.(^{44})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yolton et al.(^{45})</td>
<td><strong>Overall: No statistically significant association on the NNNS</strong></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; BASC-2, Behavioural Assessment System for Children, Second Edition; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool; CADS, Conner’s ADHD/DSM-IV Scale; CBCL, Child Behavior Checklist; NNNS, NICU Network Neurobehavioral Scale; SRS, Social Responsiveness Scale.
Case study 2: BPA ubiquitous and under trial

- Quality of Primary studies:
  - poor to moderate
  - Significant risk of confounding and “reverse causality” bias (obese eat more, therefore, are more exposed to BPA).

- Overall quality of evidence
  - Animal studies of high quality
  - Human (epidemiological studies) moderate to poor
  - Association plausible but not fully demonstrated?
IMPLICATIONS

Diagram showing the process flow from 'Before test', through 'Bayes’ theorem', to 'After test'.
Implications

- Proposed Conceptual framework for identifying implications
  - Conditional Probability and study results (Bayes’ Theorem)
  - Post hoc confidence and validation of knowledge (implications for research)
  - Post hoc confidence and policy decision making: cost-risk-utilities and decision thresholds

- Research implications
- Policy implications
Representation of the degree of confidence in a scientific hypothesis

A priori probability
Of being correct
(Plausibility)

Rejected

Uncertainty = Scientific studies

Levels of certainty (confidence)

Threshold for rejection

Threshold for acceptance
Representation of the degree of confidence in a scientific hypothesis

Hypothesis

Study results
Imperfect discriminant ability

A priori probability

Levels of certainty (confidence)

Threshold for rejection

Threshold for acceptance

0

1
Representation of the degree of confidence in a scientific hypothesis

Study results do not replace
But modify the *a priori* probability
(Conditional probability on study results)

Levels of certainty (confidence)

Threshold for rejection

Threshold for acceptance
Determination of the thresholds

- Theoretically, thresholds should be placed at certainty levels that maximize expected utility.
- In formal decision analysis, are determined by threshold analysis (sensitivity analysis)
  - Acceptance threshold: probability at which the utility of accepting or rejecting a hypothesis is the same.
  - Rejection threshold: probability at which the utility of rejecting a hypothesis or continuing research is the same.
Determination of the thresholds for Research

- The opportunity cost of further hypothesis testing (cost of information) is compared with the utility of gained information
  - Rejection and acceptance levels usually placed at very extreme probability levels (Curiosity drive, intrinsic value of knowledge)
  - Affected by Politics, believes, and competing research needs
Determination of the thresholds for Research

Levels of certainty (confidence)

Threshold for rejection

Threshold for acceptance
Determination of the thresholds, Decision Making

- Rejection: Risks and costs of a false negative.
  - If perceived consequences of a false negative are low, it leads to dismissing associations at relatively high levels of posterior probability.
  - Highly dependent on perspective
    - Who suffers the risks and direct costs
    - Who gains or looses money
    - Conflicting interests.
Determination of the thresholds, Decision Making

- Acceptance: Risks and costs of a false positive
  - If the decision is drastic (ban a product), interested parties press for high levels of certainty.
  - When society at large is at risk, or when there are vulnerable minorities, acceptance (at least provisional) should occur at low levels.
  - Other considerations are important
Determination of the thresholds, Decision Making: risk factors

Levels of certainty (confidence)

Threshold for rejection

Threshold for acceptance
Health perspective

Impact on individual and collective health status

Social-political perspective

Societal values and equity in access

Effectiveness
Safety
Sustainability
Profitability

Budgetary impact and overall impact on available resources

Contrast between value of invested resources and value of outcomes

Financial perspective

Economics perspective

Policy Decision Making

Ethics
Equity
Efficiency
Case studies

CLOSING REMARKS, IMPLICATIONS FOR RESEARCH AND POLICY
Implications for research

- Experimental comparative research can only be conducted in non-human models.
- More good quality observational comparative longitudinal research in humans is needed.

Critical issues
- Meaningful measurement of exposure.
- Clarification of dose-response relationships, mediators and modifiers.
- Development of safe alternatives.
Implications for Policy

- There is enough evidence for decision making
- Concept of safe levels must be revised allowing for ample safety margins
- Banning of applications and uses that favor exposure to vulnerable subjects and/or susceptibility windows
- Integral policy for substitution-replacement and its economic consequences
Implications for Policy

- Burden of proof should be reversed.
  - Prior to licensing, every potential ED is guilty until proved reasonably safe.
- Promote rational, explicit and transparent decision making process regarding policies and regulations.
Early exposure to Endocrine Disruptors.

Case studies of selected health effects later in life: implications for research and for policy

Thanks