How Chemicals and Air Pollution Are Harming Fertility: Latest Evidence and What We Can Do

Introductory Remarks on IVF Cohorts
CHE Webinar
December 10, 2020

Linda C. Giudice, MD, PhD, FACOG, FRCOG (hon)

Distinguished Professor,
Center for Reproductive Sciences
Chair, FIGO Committee on Reproductive and Developmental Environmental Health
Member, the Endocrine Society Environmental Clinical Resources Taskforce

Critical Periods of Vulnerability to Disruption by Environmental Factors

The temporal window of cell/tissue reprogramming has been extended to preconception, neonatal, childhood, pubertal, and adult periods.

Ho, et al. Environmental factors, epigenetics, and developmental origins of reproductive disorders. Repro Toxicol 2017; 68:84-105.
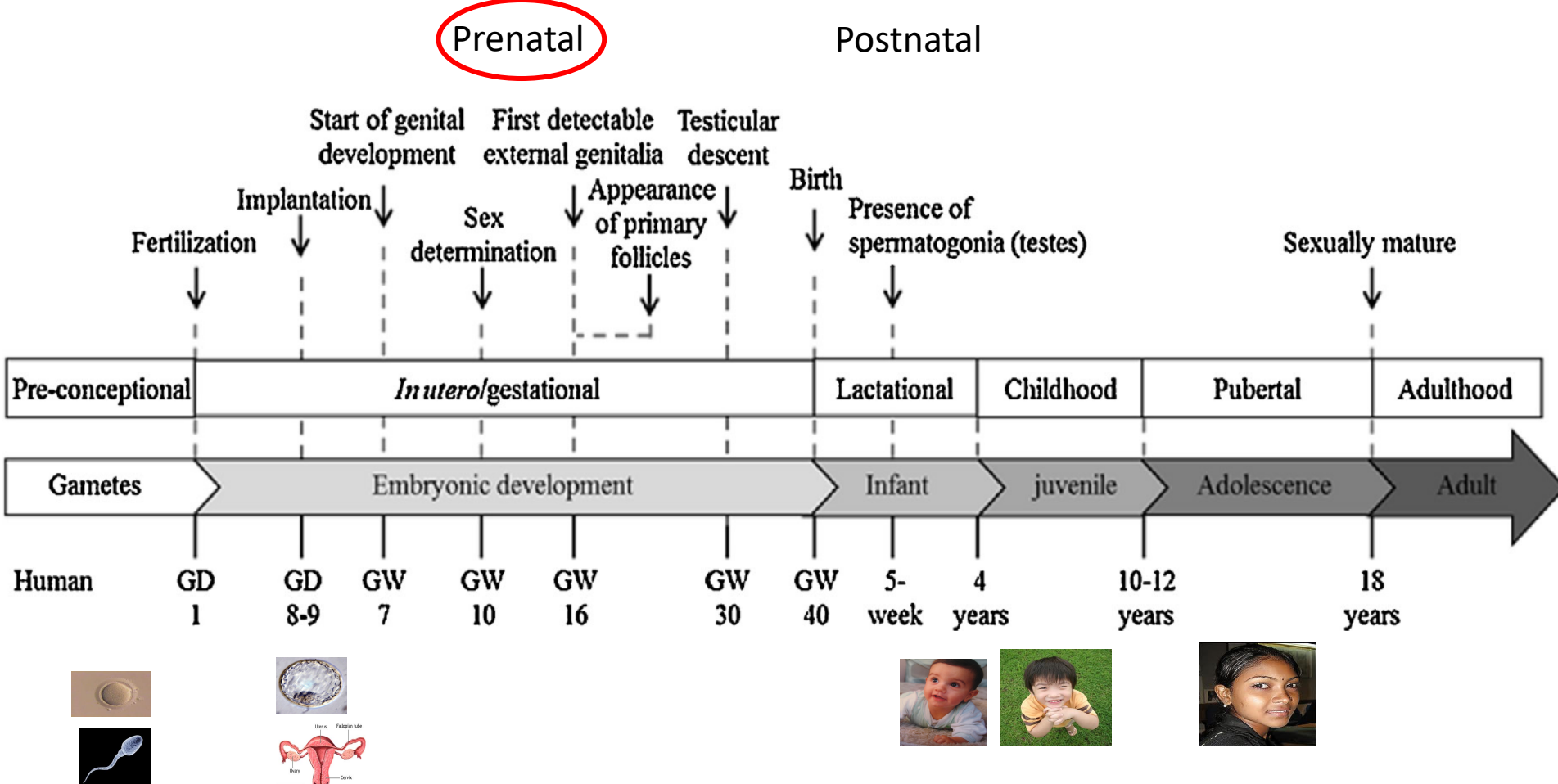
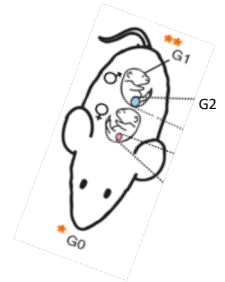# Three generations at once are exposed to environmental conditions

(diet, stress, toxicants, hormones, etc.)

Mother – first generation (F0)

Fetus – second generation (F1)

Reproductive cells – third generation (F2)

To provide a convincing case for transgenerational epigenetic inheritance, an epigenetic change must be observed in the 4th (F3) generation

Perera F, Herbstman J. Reprod Toxicol 2011;31:363–373; Giudice L. Fertil Steril 2016;106:791–794.

How do we arrive at scientific evidence linking environmental toxicants and reproductive dysfunction?

- **Epidemiologic (observational cohort) studies** reveal data *correlating* effects of environmental toxicants on human development and health.
  (no RCTs on toxicants as with pharmaceuticals to test for harm in humans)

- Data from **animal and *in vitro* models** are required to provide mechanistic underpinnings.

- **Wildlife** observations
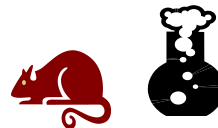
Humans   **Laboratory**   **Wildlife**

Recently IVF and fertility cohorts are giving insights into associations between environmental toxicants and reproductive potential and outcomes

IVF enables scrutiny of the gamete environment *in vivo* and embryo development *in vitro* relevant to environmental exposures (lab and patient).

Some Recent Cohorts:
Environment and Reproductive Health Study (EARTH) Study (*www.hsph.harvard.edu/earth/*) *(Hauser)*
Study of Metals and Assisted Reproductive Technologies (SMART) (*www.albany.edu/sph/bloom*)
Longitudinal Investigation of Fertility and the Environment (LIFE) (*www.nichd.nih.gov*) *(Buck-Louis)*

Assisted Reproduction and Environmental Toxicants

Recently, investigators are using IVF cohorts in response to ART treatments *in the context of environmental exposures and body burdens* (in blood, follicular fluid, hair, urine and seminal plasma) to study:
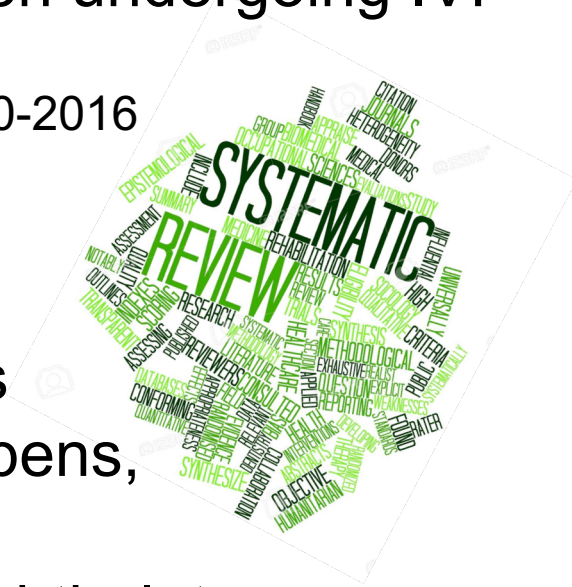
- ovarian reserve
- follicular dynamics
- oocyte quality
- sperm parameters
- peak serum E_2 levels
- endometrial thickness/appearance
- fertilization rates
- embryo dynamics
- aneuploidy rates
- implantation rates
- pregnancy rates/outcomes

Associations between EDC biomarkers of exposure and reproductive potential and outcomes of women undergoing IVF

Well designed, prospective cohort studies 2000-2016

- **Decreased serum E_2 levels**: BPA
- **Decreased serum AMH levels:** PCBs
- **Low antral follicle count:** PGA, parabens, phthalates
- **Poor oocyte quality:** BPA, triclosan, phthalates, PCBs
- **Low fertilization rates:** PFCs, PCBs
- **Low implantation rates:** BPA, phthalates, PCBs
- **Poor embryo quality:** triclosan, PCBs, BPA
- **Low clinical pregnancy and live birth rates:** parabens, phthalates

Krawacka et al. Hum Fertil 2017;1–24

Environmental tobacco smoke affects reproductive health and ART outcomes

- 8 studies reviewed had lower OR for conception of 0.62 (95% CI = 0.47-0.68) among female smokers undergoing ART

- Diminished ovarian reserve was found in smokers vs. non-smokers (OR=2.8 95% CI=1.2-7.99)

- Elevated basal or stimulated FSH levels in smokers versus age-matched non-smokers, and earlier menopause (by 1-4 years)

- Increased miscarriage rate
- Low birth weight
- PTB

Sharara F, et al. Fertil Steril 1998;70:613–622; Genuis SJ. Hum Reprod 2006;21:2201–2208; Andres RL, et al. Semin Neonatol 2000;5:231–241.

Higher consumption of high-pesticide residue fruits and vegetables are associated with lower probability of pregnancy and live birth after ART

Chiu et al. JAMA Int Med 2017;Oct. epub ahead of print

325 women completed diet assessment questionnaire and underwent 541 ART cycles in the EARTH prospective cohort study (2007-2016).

FVs categorized *high* or *low* pesticide residues using a validated method based on surveillance data from the US Department of Agriculture.

RESULTS: *Greater intake of high–pesticide residue FVs was associated with lower probability of clinical pregnancy and live birth.*

Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (2.3 servings/d) had **18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth.**

Negative IVF Endpoints Associated with Air Pollution

Systematic review of animal and human epidemiologic studies 2000-2016 on mean monthly exposures to air pollutants (air quality, O_3, NO_2, SO_2, PM 2.5, PM 10, diesel exhaust, proximity to major roads) 2-4 months before attempting conception and during IVF cycle and associations with IVF and pregnancy outcomes.

Main Findings:
- Decreased fertility for couples living in close proximity to major roads.

- Decreased OR for live birth with NO_2 throughout stimulation to pregnancy outcome.

- High exposures to PM10 not correlated with adverse IVF outcomes, but correlated with increased OR for clinical early pregnancy loss.

Carre et al. Environ Health 2017;16:82–98

Residential proximity to major roadways and traffic in relation to outcomes of in vitro fertilization

Audrey J. Gaskins[a,b,*], Jaime E. Hart[b,c], Lidia Mínguez-Alarcón[c], Jorge E. Chavarro[a,b,d], Francine Laden[b,c,d], Brent A. Coull[e], Jennifer B. Ford[c], Irene Souter[f], Russ Hauser[c,d,f]
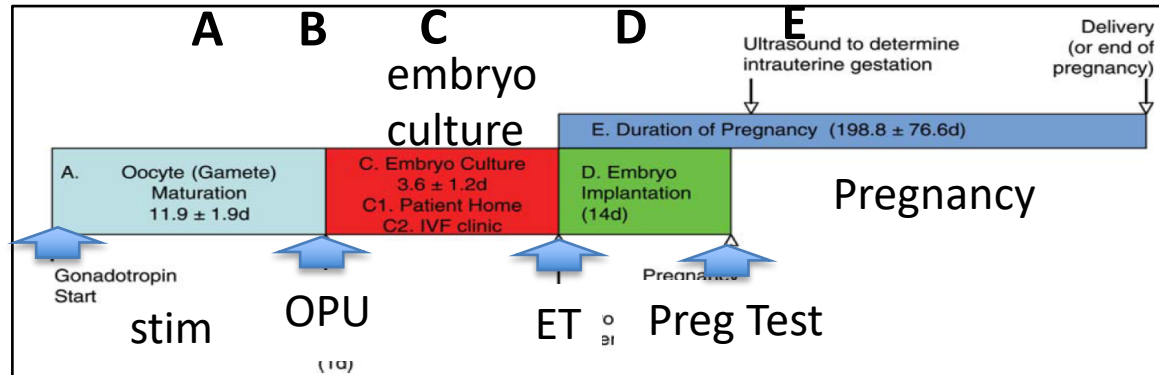
IVF

Closer residential proximity to major roadways significantly associated with lower IR and LBR after IVF:

Adjusted % of IVF cycles resulting in live birth for women living

- **<50 m from major roadway: 33% (95% CI 26-40%)**
- **>400 m from major roadway> 46% (95% CI 36-56%) p<0.04**

Exposure to Ambient Air Pollution During IVF Cycles Influences Outcomes

Timing of sampling A, B, C (C1 (patient home); C2 (IVF clinic), D, E
Measurements: O_3, $PM_{2.5}$, NO_2, SO_2, CO
Outcomes

  Legro[1]:

    NO_2 at C1 & C2 negatively associated with CP and LB all phases: OR 0.76, 95% CI 0.66-0.86
    O_3 at C1 associated with decreased LB from ET to delivery: OR 0.62. 95% CI 0.48-0.81).
    $PM_{2.5}$ at C2 during embryo culture associated with lower PR (OR 0.9, 95% CI (0.82-0.99) but not LBR.

  Qui[2]:

    A→B O_3 associated with lower chance of IUP (adj OR 0.87, 95% CI 0.81,0.98)

  Zeng[3]

    $PM_{2.5}$, NO_2, SO_2, CO negatively associated with biochemical and clinical pregnancy. Longer exposure – higher the odds, irrespective of when in the IVF cycle measurements were made.

[1]Legro et al Hum Reprod 2010; [2]Qiu et al Repro Toxicol 2019; [3]Zeng et al Environ Res 2020

Let's Protect Our Reproductive Health Now For All Generations

Thank you