Pregnancy is critical window for endocrine disrupting chemical effects on maternal endocrine and metabolic health

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EDC is any chemical that interferes with the hormone activity, including the production, secretion, transportation, metabolism, binding action, and/or excretion of endogenous hormones.
Over a 1,000 xenobiotics have been recognized to have endocrine active properties.
Maternal EDC Exposures Classically Focuses on Fetal Health or Reproductive Capacity

Braun 2017

Catanese et al. 2015
Pregnancy is a Critical Window for Long-term Maternal Health

<table>
<thead>
<tr>
<th>Disease during pregnancy</th>
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Adapted from Rahim et al. 2020 and Yim et al. 2015
Pregnancy is Coordinated by Predictable Shifts in Hormones

![Graph showing hormone levels during pregnancy](https://www.coursehero.com.sg/anatomy-and-physiology/pregnancy/)

- **1st trimester**
  - Human chorionic gonadotropin (hCG)
  - Progesterone

- **2nd trimester**
  - Prolactin
  - Estrogen
  - Relaxin

- **3rd trimester**
  - Delivery
Pregnancy EDC Exposure and Long-term Maternal Health

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Adapted from Rahim et al. 2020 and Yim et al. 2015
The Prevalence of Gestational Diabetes is Rising
EDCs Alter Metabolic Health During Pregnancy

Trimester-Specific Urinary Bisphenol A Concentrations and Blood Glucose Levels Among Pregnant Women From a Fertility Clinic

Yu-Han Chiu,1,2 Lidia Mánguez-Alarcón,3 Jennifer B. Ford,3 Myra Kell-Ellen W. Seely,6 Carmen Messerlian,3 John Petrozza,5 Paige L. Williar Xiao Yun Ye,7 Antonia M. Calafat,7 Russ Hauser,2,3,5 and Tamarra Jar for EARTH Study Team

Pesticide Exposure and Self-Reported Gestational Diabetes Mellitus in the Agricultural Health Study

Tina M. Saldana, PHD1, Olga Basso, PHD1, Jane A. Hoppin, SCD1, Knott, MPA2, Aaron Blair, PHD3, Michael C.R. Alavanja, DRPH3 an

Exposure to Bisphenol a Substitutes and Gestational Diabetes Mellitus: A Prospective Cohort Study in China

Xiaomin Zhang1, Wei Yi1 Wen Yu Liu1, Xin Ping Li1, Jie Hu1, Bin Zhang2, Shuqing Xu1, Yongwei Cai3 and Yuanyuan Li1

Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors

D. Meeker5, Tianyi Huangb, d, Russ Hausera, Kelly K. Ferguson6, c Elrathf, Ellen W. Seelyg

Maternal urinary phthalate metabolites in relation to gestational diabetes and glucose intolerance during pregnancy

Rachel M. Shaffer a, b, Kelly K. Ferguson b, Lianne Sheppard a, c, 1 Suchitra Chandrasekaran b, Shanna H. Swan h, Emily S. Barrett 1, Ru McElrath 1, Sheela Sathyanarayana a, m, the TIDES Study team

Urinary concentrations of parabens mixture and pregnancy glucose levels among women from a fertility clinic

Andrea Bellavia a,b, Yu-Han Chiu c, Florence M. Brown d, Lidia Mánguez-Alarcón a, Jennifer B. Ford a, Myra Keller a, John Petrozza e, Paige L. Williams b, f, Xiao Yun Ye g, Antonia M. Calafat g, Russ Hauser a, e, f, Tamarra James-Todd a, f, g, for the EARTH Study Team
Pregnant Women are Exposed to Numerous EDCs
Multiple Estrogenic Hits

Hypothesis: Multiple EDC hits during pregnancy will disrupt the hypothalamic-pituitary-gonadal axis and increases blood glucose.

- **BPA – ER Ligand** (Washington et al. 2001)
- **ATR – modulates aromatase** (Samardzija et al. 2016)
- **PFOA – decreases estrogen producing enzymes** (Zhao et al. 2012)
- **TCDD – blocks ERα activity** (DeVito et al. 1992)

**CNS**
- Hypothalamus
  - Pituitary
  - Ovaries

**PFOA**
- Decreases estrogen producing enzymes

**TCDD**
- Blocks ERα activity

**BPA**
- ER Ligand

**ATR**
- Modulates aromatase

**PFOA**
- Decreases estrogen producing enzymes

**TCDD**
- Blocks ERα activity

**Fatty acids**
- Glucose
- Insulin

**Elevated blood glucose**
Does MIX exposure decrease estradiol during pregnancy?

Adapted from Brummelte and Galea 2016

Atrazine (ATR): 10 mg/kg
Bisphenol-A (BPA): 50 μg/kg
Perfluorooctanoic acid (PFOA): 0.1 mg/kg
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): 0.036 μg/kg
Pregnant MIX dams had lower serum estradiol

One-sided Student’s t test
Data mean ± standard error
n = 4-9/treatment group, * indicated p < 0.05
Glucose Tolerance Test

- Fasting blood glucose
  - 0 min
- Inject 2 g/kg glucose
- Measure blood glucose
  - 15 min
  - 30 min
  - 60 min
  - 120 min

6 hour fast
Acute MIX exposure induces metabolic dyshomeostasis only in pregnant females

A) and B) Repeated measures ANOVAs
C) and D) Student’s t test
Data mean ± standard error

n = 7/treatment group. * indicated p ≤ 0.05, # indicated p = 0.07
P = Pregnant and NP = Non-pregnant
Elevated weight gain and visceral adipose in only MIX pregnant females

A

Pregnant Non-pregnant

B

Pregnant Non-pregnant

C

Pregnant Non-pregnant

Student’s t test
Data mean ± standard error
n = 6-7/treatment group, * indicated p ≤ 0.05
P = Pregnant and NP = Non-pregnant
Acute MIX exposure altered lipids in pregnant females

Student’s t test
Data mean ± standard error
n = 7/treatment group, * indicated p ≤ 0.05
Pregnancy EDC Exposure and Long-term Maternal Health

Adapted from Rahim et al. 2020 and Yim et al. 2015

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| Mental Health: Anxiety and Depression | • Postpartum depression |
Gestational Diabetes, a Predictor of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Country</th>
<th>T2DM/GDM</th>
<th>T2DM/no GDM</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madaras et al, 21 1995</td>
<td>Hungary 21/68</td>
<td>0/39</td>
<td>24.93 (1.55–400.64)</td>
</tr>
<tr>
<td>Gunderson et al, 22 1985–206</td>
<td>USA 43/166</td>
<td>150/2242</td>
<td>3.87 (2.87–5.22)</td>
</tr>
<tr>
<td>Vambergue et al, 23 1992</td>
<td>France 53/295</td>
<td>1/111</td>
<td>19.94 (2.79–142.47)</td>
</tr>
<tr>
<td>Ferraz et al, 27</td>
<td>Brazil 6/70</td>
<td>7/108</td>
<td>1.32 (0.46–3.78)</td>
</tr>
<tr>
<td>Krishnaveni et al, 25 1997–98</td>
<td>India 13/35</td>
<td>8/489</td>
<td>22.70 (10.09–51.08)</td>
</tr>
<tr>
<td>Morimitsu et al, 26 1999–2001</td>
<td>Brazil 7/23</td>
<td>0/11</td>
<td>7.50 (0.47–120.11)</td>
</tr>
<tr>
<td>Järvelä et al, 5 1984–94</td>
<td>Finland 23/435</td>
<td>0/435</td>
<td>47.00 (2.86–771.65)</td>
</tr>
<tr>
<td>Albareda et al, 27 1966–93</td>
<td>Spain 44/696</td>
<td>0/70</td>
<td>9.07 (0.56–146.25)</td>
</tr>
<tr>
<td>Åberg et al, 28 1991–99</td>
<td>Sweden 21/229</td>
<td>1/61</td>
<td>5.59 (0.77–40.66)</td>
</tr>
<tr>
<td>Linné et al, 16 1964–65</td>
<td>Sweden 10/28</td>
<td>0/52</td>
<td>38.38 (2.33–631.74)</td>
</tr>
<tr>
<td>Bian et al, 29 1964–65</td>
<td>China 15/45</td>
<td>1/39</td>
<td>13.00 (1.80–93.93)</td>
</tr>
<tr>
<td>Ko et al, 30 1988–95</td>
<td>China 105/801</td>
<td>7/431</td>
<td>8.07 (3.79–17.19)</td>
</tr>
<tr>
<td>Osei et al, 31 1990–91</td>
<td>USA 10/15</td>
<td>0/35</td>
<td>47.25 (2.95–757.28)</td>
</tr>
<tr>
<td>Damm et al, 32 1978–85</td>
<td>Denmark 33/241</td>
<td>0/57</td>
<td>16.06 (1.00–258.06)</td>
</tr>
<tr>
<td>Benjamin et al, 33 1961–88</td>
<td>New Mexico 14/47</td>
<td>3/47</td>
<td>4.67 (1.43–15.21)</td>
</tr>
<tr>
<td>O’Sullivan, 34 1954–60 and 1962–70</td>
<td>USA 24/615</td>
<td>18/328</td>
<td>6.64 (4.19–10.52)</td>
</tr>
<tr>
<td>Persson et al, 35 1961–84</td>
<td>Sweden 5/145</td>
<td>0/41</td>
<td>3.16 (0.18–55.76)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3997/31867</td>
<td>6862/643588</td>
<td><strong>7.43 (4.79–11.51)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=0.50$, $\chi^2=126.67$, df=19 (p<0.0001), $P<0.05$ (95% CI 78–90)

Test for overall effect: $Z=9.39$ (p<0.0001)
MIX induces elevated glucose following exposure

A) Repeated measures ANOVAs
B and C) One-way ANOVA followed by student’s t test

Data mean ± standard error
n = 4/treatment group, * indicated p < 0.05
Weight was unaltered by 6 months

Repeated measures ANOVAs
Data mean ± standard error
n = 4/treatment group
MIX elevated serum total cholesterol, LDL, and free cholesterol

Student's t test
Data mean ± standard error
n = 3-4/treatment group, * indicated p ≤ 0.05
Metabolic Health Conclusions

• Metabolic Health During Pregnancy
  • MIX reduces estradiol during pregnancy.
  • Glucose processing is only altered in MIX exposed pregnant dams.
  • MIX increases gestational weight gain and visceral adipose weight.
  • MIX dams had increased VLDL and decreased LDL.
  • Pregnancy is a critical window for MIX exposure.

• Long-term Maternal Metabolic Health
  • MIX alters long-term glucose processing following a glucose tolerance test.
  • Total cholesterol, LDL, and free cholesterol are only elevated in MIX exposed dams cholesterol panels.
  • Weight gain was unaltered in MIX dams.
Future Directions

- Are altered lipid panels due to non-alcoholic fatty liver disease?
- Is body composition altered from MIX exposure?
- Does MIX exposure lead to insulin resistance of organs?
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Questions