Preconception Omega-3 Fatty Acid Supplementation and the Prevention of Toxicant-Associated Preterm Birth in a Mouse Model

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Dioxin or TCDD
(2,3,7,8-tetrachlorodibenzo-p-dioxin)

- By-product of industrial processes
- Known endocrine disruptor
  - Mimics estrogen; inhibits progesterone action
- “Agent Orange”—herbicide contaminated with TCDD
- Vehicle fuel combustion
- Bioaccumulates within the food chain
  - In utero and neonatal exposure
Impact of in utero TCDD

Pregnant C57/bl6 mice exposed E15.5 (in utero/lactational) → Pups born on E20

<table>
<thead>
<tr>
<th>Uterine Phenotype</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced uterine PR mRNA/protein</td>
<td>Reduced fertility PTB common</td>
</tr>
</tbody>
</table>

10 μg/kg TCDD in corn oil

Nayyar et al, 2007; Bruner-Tran and Osteen, 2011
A History of Fetal Exposure to TCDD is Associated with Preterm Birth in a *Subsequent* Adult Pregnancy

<table>
<thead>
<tr>
<th>Mating Scheme</th>
<th>Pregnancy</th>
<th>Pregnancy Outcome</th>
<th>Full-term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Female / Control Male</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>F1 Female / Control Male</td>
<td>39%</td>
<td>64</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Control Female / F1 Male</td>
<td>47%</td>
<td>61</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>F1 Female / F1 Male</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Preterm birth was defined as spontaneous parturition >24 hrs prior to E20.*

Ding et al, 2011
Placental Inflammation and Timing of Human Parturition

- Placental inflammatory signals may regulate timing of parturition
- Placenta is largely derived from *paternal* genes
- Normal human placenta at end of pregnancy
  - Increased expression of multiple TLRs
  - Decreased expression of PR
Impact of Developmental TCDD Exposure on PR Expression at the Maternal-Fetal Interface

Placenta

<table>
<thead>
<tr>
<th>E18.5</th>
<th>E17.5/18.5</th>
<th>E18.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Female</td>
<td>Control Male</td>
<td>Control Female</td>
</tr>
</tbody>
</table>

- PR A/B
- PR B

* * *

Placenta

<table>
<thead>
<tr>
<th>E18.5</th>
<th>E17.5/18.5</th>
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<tr>
<td>Control Female</td>
<td>Control Male</td>
<td>Control Female</td>
</tr>
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</table>

- TLR-4
- p65
- p105

* * *
Our data indicate that TCDD-mediated preterm birth in mice is associated with a hyper-inflammatory response within the placenta, regardless of which parent was exposed.

Can we reduce the inflammatory response? Limited options for pregnant patients.

Nutritional Intervention
- anti-inflammatory
- membrane fluidity
- brain development
Omega-3 Fatty Acid Supplementation During Pregnancy

- 200-300 mg/day DHA/EPA recommended for all pregnant women
- Women “at risk” of PTB:
  - DHA/EPA supplementation should be initiated at 20-24 weeks
  - 1.5-3.0 g/day/DHA/EPA
  - Results from studies to date are inconclusive

*Our data suggests omega-3 fatty acid supplementation prior to establishment of the maternal-fetal interface may be more effective.*
Preconception Fish Oil

Pregnant C57/bl6 mice exposed E15.5 (in utero/lactational)

Pups born on E20

6-8 wk old males

10 μg/kg TCDD in corn oil

Standard diet               5% Fish oil diet

Mated at 9-10 weeks

Pregnancy Outcomes

Modified from Jirtle and Skinner, 2007
## Pregnancy Outcomes following Preconception Fish Oil Supplementation of Male F1 Mice

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pregnancy Rate</th>
<th>Pregnancy Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Full-Term</td>
</tr>
<tr>
<td>Vehicle Only</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Vehicle + Fish Oil</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F1 male</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>F1 male + Fish Oil</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

McConaha et al, 2011
Impact of Fish Oil Supplementation on Placental PR and TLR-4 mRNA Expression

McConaha et al, 2011
Conclusion

- Dietary modification prior to the establishment of the maternal-fetal interface and which *includes both parents* should be examined for the prevention of preterm birth in women.
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- Joe Arosh, PhD

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- NCCAM
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