Risk Factors for Female Infertility in an Agricultural Region

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Agricultural Exposures - Risk

• Male Partner
  – Altered semen parameters
  – Poor fertilization rate
  – Early and late abortions

• Female partner
  – Ovulatory-tubal factor
  – Time to pregnancy
  – Spontaneous abortion
  – Fetal death due to anomalies
# Pesticide Residues in the Male Reproductive Tract

<table>
<thead>
<tr>
<th>Chemical</th>
<th>2,4-D</th>
<th>$p,p'$-DDE</th>
<th>Mirex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/ml (ppb)</td>
<td>ng/ml (ppb)</td>
<td>ng/ml (ppb)</td>
</tr>
<tr>
<td><strong>Seminal plasma</strong></td>
<td>29.8 ± 4.8 (n=97)</td>
<td>0.39 ± 0.43 (n=25)</td>
<td>0.10 ± 0.8 (n=25)</td>
</tr>
</tbody>
</table>
## Pesticide Residues in the Female Reproductive Tract

<table>
<thead>
<tr>
<th></th>
<th>$p,p'$-DDE (ppb)</th>
<th>a-HCH (ppb)</th>
<th>Dieldrin (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular (18)</td>
<td>3.37 ± 0.42</td>
<td>0.34 ± 0.14</td>
<td>0.13 ± 0.13</td>
</tr>
<tr>
<td>Amniotic (41)</td>
<td>0.21 ± 0.17</td>
<td>0.14 ± 0.05</td>
<td>NT</td>
</tr>
<tr>
<td>Placenta (9)</td>
<td>4.7 ± 22.3</td>
<td>17.2 ± 62.4</td>
<td>NT</td>
</tr>
<tr>
<td>Breast Milk (20)</td>
<td>6310 ± 5900</td>
<td>859 ± 2750</td>
<td>48.7 ± 80</td>
</tr>
</tbody>
</table>
Goal

• Case-control study to retrospectively examine relationship between specific agricultural (occupational; residential) exposures and risk of female infertility.
IRB Approval

• Study approved by Clinic IRB
• All subjects gave *verbal,* informed consent
• 3.5 year recruitment period, 6/97-2/01
Infertility

• Unable to achieve pregnancy or bear live child after 12 months of trying.
Cases and Controls

Cases --
• 18-35 years old
• - preg (>12 mo)
• Infertility Care
  OB-GYN at MC and Wausau Med Ctr
• Spouse/partner

Controls --
• 18-35 years old
• + preg (<12 mo)
• Prenatal Care
  OB-GYN at MC and Wausau Med Ctr
• Spouse/partner
Infertility Conditions

• Pituitary-hypothalamic dysfunction
• Anovulation / tubal factor / endometriosis
• Altered menstrual cycle
• Abnormalities of uterus, cervix, vagina
• Recurrent miscarriage
• Unexplained infertility
## Infertility Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained</td>
<td>292</td>
<td>57.6</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>116</td>
<td>22.8</td>
</tr>
<tr>
<td>Anovulation</td>
<td>49</td>
<td>9.7</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>5.1</td>
</tr>
<tr>
<td>Pituitary-Hypothalamic</td>
<td>14</td>
<td>2.8</td>
</tr>
<tr>
<td>Tubal</td>
<td>7</td>
<td>1.4</td>
</tr>
<tr>
<td>Preg – ectopic</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Cervical-Vaginal</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Exclusions

• Couplet Sterility
  – Tubal ligation
  – Hysterectomy
  – Vasectomy

• Endometriosis
  (without mention of infertility)
Survey

• Demographics
• Occupational/Farm/Residential exposures
• Pesticide Use
• Livestock pharmaceuticals
• Source of drinking water
• Diet/reproductive health
• Physical/mental stressors
• Weight and height
• Time reviewing exposure lists
Data Analysis

• Multivariate logistic regression
• Adj OR, 95% CI
  – Confounding variables
    • Maternal level of education
    • Maternal/paternal hours of passive smoke
    • Maternal/paternal time reviewing exposure lists
    • Per capita income
## Recruitment Numbers

<table>
<thead>
<tr>
<th></th>
<th>Screened</th>
<th>Eligible</th>
<th>Ineligible/ Refused</th>
<th>Participation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>1,791</td>
<td>626</td>
<td>73/231</td>
<td>58.2% (322/553)</td>
</tr>
<tr>
<td>Control</td>
<td>822</td>
<td>558</td>
<td>45/191</td>
<td>62.7% (322/513)</td>
</tr>
</tbody>
</table>
% Recruitment to the Fertility Risk Factor Study
Reasons for Refusing

- Lack of interest
- Insufficient time
- Sensitive nature of topic
- Involved in unstable relationship
- Uncomfortable with phone interviews
Interpretation Qualifiers

• Exposures
  – “2 years before trying to conceive”
  – Central Wisconsin population
## Infertile Case Women

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work outside of home</td>
<td>4.8 (2.6 - 8.5)</td>
</tr>
<tr>
<td>HS graduate</td>
<td>1.7 (1.1 - 2.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.6 (0.9 - 2.9)</td>
</tr>
<tr>
<td>1-5 hr passive smoke</td>
<td>1.8 (1.2 - 2.5)</td>
</tr>
<tr>
<td>&gt;1 alcoholic drink/wk</td>
<td>1.8 (1.2 - 2.8)</td>
</tr>
<tr>
<td>Steady wt gain as adult</td>
<td>3.5 (2.0 - 6.1)</td>
</tr>
<tr>
<td>Male partner &gt; 41 yr</td>
<td>4.5 (1.2 - 16.3)</td>
</tr>
</tbody>
</table>
### Agricultural Factors

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mix-apply herbicides</td>
<td>26.9 (1.9 – 384.8)</td>
</tr>
<tr>
<td>Ever-use fungicides</td>
<td>3.3 (0.8 – 13.2)</td>
</tr>
</tbody>
</table>
Pesticide Use

• Mix and apply herbicides
  – Case: unk > glyphosate > 2,4,5-T > atrazine
  – Control: unk > glyphosate > 2,4,5-T > atrazine

• Use of fungicides by either partner
  – Case: unk > chlorothalonil > captan > benomyl = maneb = zineb = dicofol
  – Control: Chlorothalonil > captan = maneb = unk
# Fertile Control Women

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live on farm, ranch or rural home</td>
<td>0.5 (0.4 – 0.8)</td>
</tr>
<tr>
<td>Drink Central WI groundwater</td>
<td>0.6 (0.4 – 0.9)</td>
</tr>
<tr>
<td>Consume ≥3 glasses milk/day</td>
<td>0.3 (0.1 – 0.7)</td>
</tr>
</tbody>
</table>
Summary of Findings

• Significant Risks
  – Mix-apply herbicides
  – Ever-use fungicides
  – Alcohol, smoke, passive smoke, steady weight gain
  – Partner’s age

• Protective Factors
  – Residing on farm, ranch, rural area
  – Private well water for drinking
  – 3 glasses of milk per day
Possible Mechanisms

- Hormone signaling “endocrine” disruption
- Age-related decline in gamete quality
- Private well water vs. municipal water – disinfection by-products
- Milk – no direct benefit: healthy choice; conjugated linoleic acids
Strengths and Limitations

• **Strengths**
  – Females and male partners participated
  – Participation rate ~ 60%
  – Behavior can be modified

• **Limitations**
  – Self-reported information
  – Individual pesticides not analyzed
  – Pesticide exposure – subcategory of infertility
Future Studies

- Exposures vs. subcategories of infertility
- Job matrix variables – protective gear
- Intervention effectiveness - smoking
Publications

• Poster (ISEE, Vancouver, BC; 2002)
• Epidemiology (July, 2003)
• Presentations
  – Morgantown, WV, 1998
  – Cooperstown, NY, 2000
  – Little Amana, IA, 2002
  – Marshfield, WI, 2002
Thank You!

• NIOSH
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• Lorelle Benetti

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• Frank Baker, MD, PhD