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

Chemical	**2,4-D** ng/ml (ppb)	***p,p′*-DDE** ng/ml (ppb)	**Mirex** ng/ml (ppb)
Seminal plasma	**29.8 ± 4.8** (n=97)	**0.39 ± 0.43** (n=25)	**0.10 ± 0.8** (n=25)

Pesticide Residues in the Female Reproductive Tract

	p,p′-DDE (ppb)	a-HCH (ppb)	Dieldrin (ppb)
Follicular (18)	3.37 ± 0.42	0.34 ± 0.14	0.13 ± 0.13
Amniotic (41)	0.21 ± 0.17	0.14 ± 0.05	NT
Placenta (9)	4.7 ± 22.3	17.2 ± 62.4	NT
Breast Milk (20)	6310 ± 5900	859 ± 2750	48.7 ± 80

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

	Frequency	%
Unexplained	292	57.6
Endometriosis	116	22.8
Anovulation	49	9.7
Other	26	5.1
Pituitary-Hypothalamic	14	2.8
Tubal	7	1.4
Preg – ectopic	2	0.4
Cervical-Vaginal	1	0.2

Exclusions

- **Couple Sterility**
  - **Tubal ligation**
  - **Hysterectomy**
  - **Vasectomy**
- **Endometriosis**
  (without mention of infertility)

Survey

- Demographics
- Occupationa/Farm/Residential exposures
- Pesticide Use
- Livestock pharmaceuticals
- Source of drinking water
- Diet/reporductive health
- Physical/mental stressors
- Weight and height
- Time reviewing exposure lists

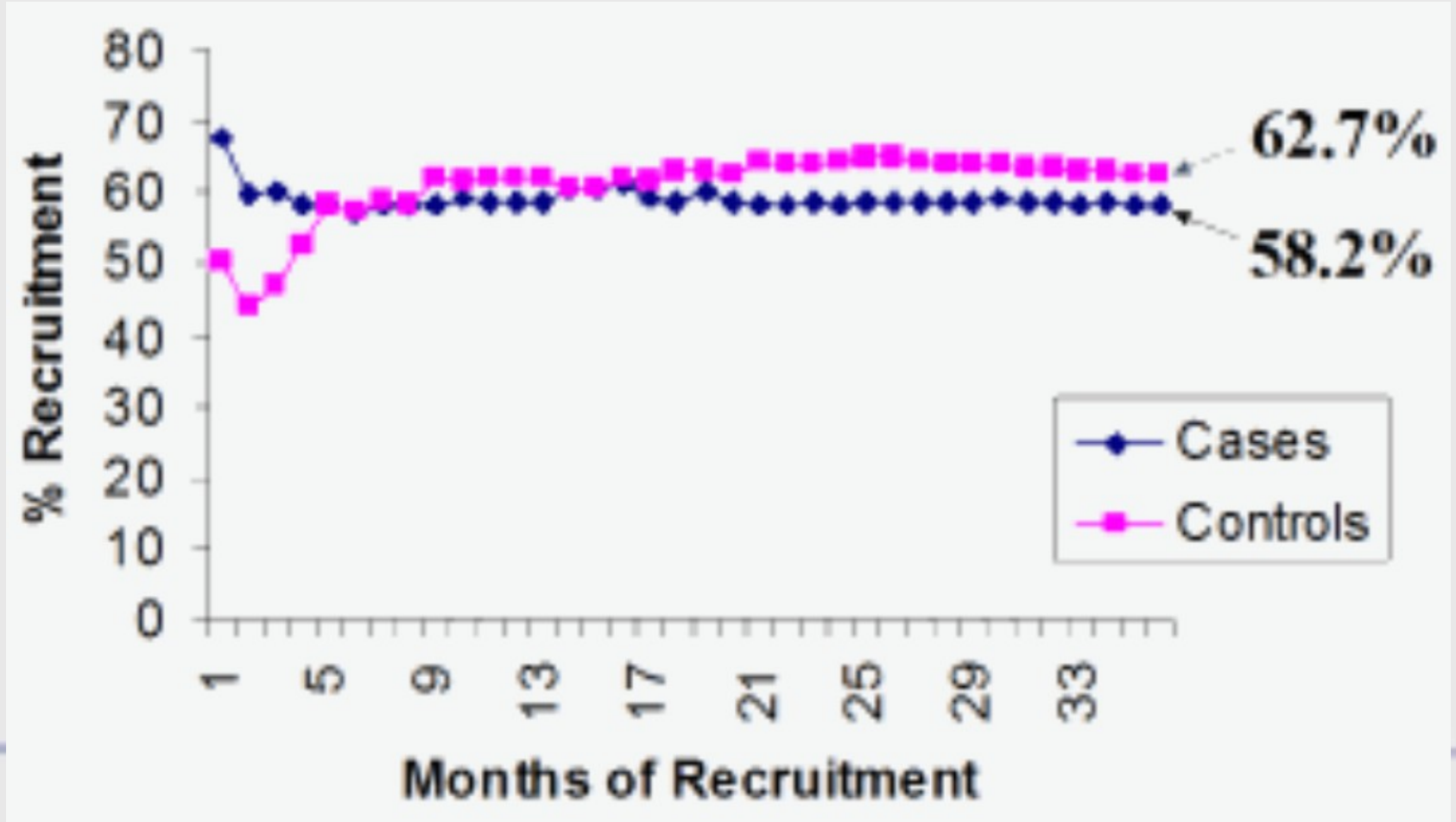
Data Analysis

- 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

	Screened	Eligible	Ineligible/ Refused	Participation Rate
Case	1,791	626	73/231	58.2 (322/553)
Control	822	558	45/191	62.7% (322/513)

% 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

	OR (95% CI)
Work outside of home	4.8 (2.6 - 8.5)
HS graduate	1.7 (1.1 - 2.6)
Current smoker	1.6 (0.9 - 2.9)
1-5 hr passive smoke	1.8 (1.2 - 2.5)
>1 alcoholic drink/wk	1.8 (1.2 - 2.8)
Steady wt gain as adult	3.5 (2.0 - 6.1)
Male partner > 41 yr	4.5 (1.2 - 16.3)

Agricultural Factors

	OR (95% CI)
Mix-apply herbicides	26.9 (1.9 – 384.8)
Ever-use fungicides	3.3 (0.8 – 13.2)

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

Live on farm, ranch or rural home	0.5 (0.4 – 0.8)
Drink Central WI groundwater	0.6 (0.4 – 0.9)
Consume ≥3 glasses milk/day	0.3 (0.1 – 0.7)

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!

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