Couple-Based Approaches for Assessing Human Fecundity & Fertility
(males matter)

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Today’s Seminar

- Why human fecundity & fertility?
  - Data gaps underlying human reproduction
  - Conceptual & methodologic challenges
- Overcoming challenges — LIFE Study

Lots of opportunities for trans-disciplinary collaboration!
Motivation for today’s seminar...

- Basic lack of understanding of human reproduction & development
  - Folklore, myths & urban legends

- Under-appreciated endpoint
  - Reproductive health \( \rightarrow \) pregnancy

Data Gaps - Reproduction

- Inefficiency of human reproduction
  - Monthly probability of conception \( \approx 20\% \) (Robert & Lowe 1975)
  - Post-implantation pregnancy loss rate \( \approx 12-40\% \) (Louis 2011)
  - Human sperm production 4.4 million/gm testis; bulls & stallions have 3-4 times amount (Sharpe 1995)

- What’s normal?
  - Do women ovulate every cycle? Which day?
  - Is there only one fertile window?
  - What is the probability of conception, pregnancy loss or live birth per cycle? What if she’s a little off? What if he is? What if they are?
  - Why isn’t semen quality predictive of conception, implantation or birth?

Fecundity & fertility may be informative for health & disease across the lifespan...
Persistent Misconceptions

- Prospective cohort designs with preconception enrollment not feasible
  - Hard to recruit; burden too much
- Selection bias
  - Women with fertility problems will be disproportionately over-represented
  - Women will under-report time already trying
- Men will not participate
  - Men will not keep diaries or provide semen samples
Conceptual & Methodologic Challenges

- **Conceptual**
  - Series of highly timed, interrelated & conditional outcomes, some of which are "hidden"
  - Couple dependent

- **Methodologic**
  - Hierarchical data structure
  - Correlated outcomes (& exposures)
  - Conditioning on intermediates
  - Missingness & censoring

Hidden Reproductive Endpoints

- Ovulation
- Fertilization
- Development

Involves both partners of the couple...
Motivation for LIFE Study

- Fecundity may be informative about health across lifespan
- Evidence suggesting human fecundity may be diminishing... environmental chemicals associated with
  - Longer time-to-pregnancy
  - Declining semen quality
  - Diminished ART success

Data Gaps (couple fecundity)

- Prospective cohorts
  - Preconception recruitment of couples followed while trying & during sensitive windows for the quantification of partners’ exposures
    - Chemical mixtures
    - Lifestyle

LIFE Study

- Do persistent environmental chemicals affect human reproduction & development in the context of couples’ lifestyles?
  - Which chemical
  - Which partner
  - Can lifestyle mediate effect
Challenges – LIFE Study

- Is population-based recruitment feasible?
- Can couples be recruited & retained?
- Can the home be used as the lab?
- Can a web based data management system handle hierarchical data structure & multiple remote users?

Study Design & Methods - LIFE Study

- Prospective cohort comprising 501 couples recruited upon stopping contraception in two targeted geographic areas
  - Committed relationship; females 18-44 years; English or Spanish; 21-42 day menstrual cycles; no infertility
- Longitudinal data & biospecimen collection
  - Baseline interview & anthropometric assessment
  - Daily journal reporting
  - Blood & urine at baseline; semen & saliva cycles 1 & 2

LIFE Study

- Environmental chemicals
  - Persistent compounds: DCPs, PBBS, PBDEs, PCBs, PFCs, metals
  - Short-lived compounds: BPA, phthalates, UV filters
- Lifestyle
  - Alcohol, caffeine, exercise, fish, smoking, stress, vitamins
- Outcomes
  - 1st TTP, infertility, pregnancy loss, gestation, birth size
  - 2nd libido, menses, ovulation, semen quality, sex ratios
Question 1:
Is population based sampling feasible for preconception recruitment?

Weight of Evidence

**Convenience**
- Miller et al., 1980
- Whittaker et al., 1983
- France et al., 1984
- de Mouzon et al., 1988
- Wilcox et al., 1988
- Varilainen et al., 1994
- Zinaman et al., 1996
- Columbo et al., 2000

**Population Based**
- Sweeney et al., 1989
- Hakkin et al., 1995
- Ellish et al., 1996
- Brown et al., 1997
- Bonde et al., 1998
- Buck et al., 2002
- Wang et al., 2003
- Bonde, Louis, Colombo, de Mouzon, & Zinaman

Recruitment yield 0.1% - 4.0% for studies with denominator

-1% population planning pregnancy (Buck et al., 2004)
Recruitment Strategy – LIFE Study

<table>
<thead>
<tr>
<th>Michigan</th>
<th>Texas</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 counties</td>
<td>12 counties</td>
</tr>
<tr>
<td>InfoUSA®</td>
<td>Texas Parks &amp; Wildlife Registry</td>
</tr>
<tr>
<td>Mailing with telephone follow up</td>
<td>Mailing with telephone follow up</td>
</tr>
</tbody>
</table>

OMB required that each partner be individually contacted & screened.

Question 2:
Can couples be recruited and retained, and at what cost?
Considerations

- Couple-based
  - Inclusive or exclusive
- Burden & remuneration
  - OMB approval
  - $25 blood; $5 urine; $20 saliva; $20 semen

Inclusion Criteria - Couples

- Ages 18-44 years; males aged >18 years
- Able to communicate in English or Spanish
- In committed relationship
- Wishes to conceive in next 6 months
- Planning to stop contraception to become pregnant

Recruitment

<table>
<thead>
<tr>
<th></th>
<th>Letters Mailed (N)</th>
<th>Recruited n (%)</th>
<th>Enrolled n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas</td>
<td>355,087</td>
<td>981 (3%)</td>
<td>397 (40%)</td>
</tr>
<tr>
<td>Michigan</td>
<td>69,336</td>
<td>203 (1%)</td>
<td>104 (51%)</td>
</tr>
</tbody>
</table>

84% couples not screened
36% refused screening
0.1% recruitment yield
Sampling Frameworks – LIFE Study

- Few differences by sampling framework and completion status
  - No difference by site or study completion for: partners’ ages, education, health insurance, or women’s gravidity & parity
  - Couples completing study were more likely to be white & have higher household incomes irrespective of site than couples withdrawing

Data Collection

hCG pregnancy or 12 months

Baseline

Trying - Daily

Pregnancy - Daily

8 wks.

Monthly

Blood, urine, saliva & semen

Urine

Data Completion

<table>
<thead>
<tr>
<th>Card</th>
<th>Male %</th>
<th>Female %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Journal</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Early pregnancy (daily)</td>
<td>--</td>
<td>80</td>
</tr>
<tr>
<td>Pregnancy (monthly)</td>
<td>--</td>
<td>76</td>
</tr>
<tr>
<td>Texas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Journal</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Early pregnancy</td>
<td>--</td>
<td>82</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>--</td>
<td>81</td>
</tr>
</tbody>
</table>
Question 3:
Can the home be used as a lab?

Considerations
- Ability to capture both partners for blood & urine collection
- Compliance with fecundity monitoring & future biospecimen collection
- Tracking of biospecimens from home-lab

Biospecimen Collection
Fertility Monitor

hCG Pregnancy Measurement

Biospecimen Completion

<table>
<thead>
<tr>
<th>Biospecimen</th>
<th>First Sample % Obtained</th>
<th>Second Sample % Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>Urine (6 mo. &amp; pregnancy)</td>
<td>100</td>
<td>94 (77 &amp; 95)</td>
</tr>
<tr>
<td>Saliva</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>Semen</td>
<td>94</td>
<td>77</td>
</tr>
</tbody>
</table>
Question 4:
Can a dependable web-based data management system be built to handle the hierarchical data structure & multiple remote users?

Challenges
- Web-based data management
  - Dependable server (24/7)
  - Multiple remote users

Emerging environmental chemical results...
Chemical Class | Females FOR (95% CI) | Males FOR (95% CI) 
--- | --- | --- 
PCB #118 | 0.82 (0.68, 0.98) | -- 
PCB #167 | 0.79 (0.64, 0.97) | 0.82 (0.70, 0.96) 
PCB #209 | 0.82 (0.68, 0.99) | 0.78 (0.65, 0.94) 
PFOSA | 0.82 (0.71, 0.95) | -- 

*Adjusted for age, BMI, cotinine, δ remaining chemicals in class & lipids (except for PFCs). Chemicals log transformed & rescaled by their standard deviations. 

4/5 chemicals remained significant for females (HCB fell out)
POP & Time-to-Pregnancy*

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Females FOR (95% CI)</th>
<th>Males FOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p,p'-DDE</td>
<td>--</td>
<td>0.83 (0.70, 0.97)</td>
</tr>
<tr>
<td>PCB #101</td>
<td>--</td>
<td>1.28 (1.09, 1.51)</td>
</tr>
<tr>
<td>PCB #138</td>
<td>--</td>
<td>0.71 (0.52, 0.98)</td>
</tr>
<tr>
<td>PCB #156</td>
<td>--</td>
<td>0.77 (0.62, 0.96)</td>
</tr>
<tr>
<td>PCB #157</td>
<td>--</td>
<td>0.81 (0.70, 0.97)</td>
</tr>
<tr>
<td>PCB #170</td>
<td>--</td>
<td>0.74 (0.56, 0.98)</td>
</tr>
<tr>
<td>PCB #172</td>
<td>--</td>
<td>0.82 (0.68, 0.99)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, cotinine, Σ remaining chemicals in class & lipids (except for PFCs).

9/12 chemicals remained significant for males (PBDE 183, PCBs 153 & 180 fell out).

Summary

- Challenging identifying eligible couples planning pregnancy in next 2 months
  - <1% couples planning pregnancy >2 months
- Couple based recruitment possible
  - No known iatrogenic harm
- Select environmental chemicals associated with diminished couple fecundity
  - Males matter!

Eliminating Misconceptions – LIFE Study Experience

- Prospective cohort designs with preconception enrollment not feasible
  - Feasible with a large N
- Selection bias
  - No known fecundity-related biases
- Men will not participate
  - Great male participation
Remaining Challenges

- Understanding individual contributions of age, lifestyle & chemicals --- mixtures
- Delineating mechanisms for reductions in fecundity
  - Alterations in menses & ovulation
  - Alterations in sexual libido
  - Alterations in semen quality
- Population impact & translation

Why Fathers Really Matter
By Judith Shulevitz
New York Times (Opinion Section), September 9, 2012

Thank you....