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

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Dean Donna Petersen, ranked 21st on the "100 Awesome Deans of Public Health" (MPHProgramsList.com)

Happiness gene for women (Henian Chen, MD, PhD, Department of Epidemiology & Biostatistics, USF College of Public Health)

Researcher extraordinaire!

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…

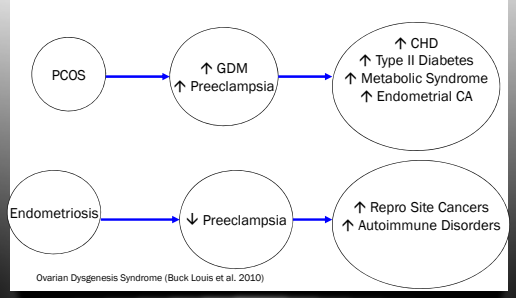
- Basic lack of understanding of human reproduction & development
  - Folklore, myths & urban legends
- Under-appreciated endpoint
  - Reproductive health ≥ pregnancy

Data Gaps - Reproduction

- Inefficiency of human reproduction
  - Monthly probability of conception ≈20% (Robert & Lowe 1975)
  - Post-implantation pregnancy loss rate ≈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?

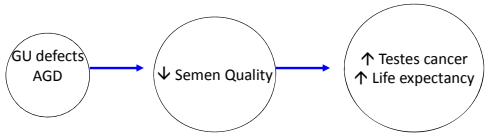
Fecundity & fertility may be informative for health & disease across the lifespan…

Female Fecundity & Health



Ovarian Dysgenesis Syndrome (Buck Louis et al. 2010)

Male Fecundity & Health



Testicular Dysgenesis Syndrome (Skakkebaek et al. 2001)

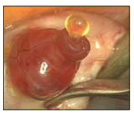
Persistent Misconceptions

- 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

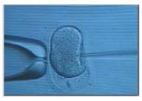
- Conceptual
  - Series of highly timed, interrelated & conditional outcomes, some of which are "hidden"
  - Couple dependent
- Methodologic
  - Hierarchical data structure
  - Correlated outcomes (& exposures)
  - Conditioning on intermediates
  - Missingness & censoring

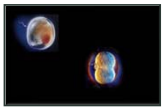
Hidden Reproductive Endpoints



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

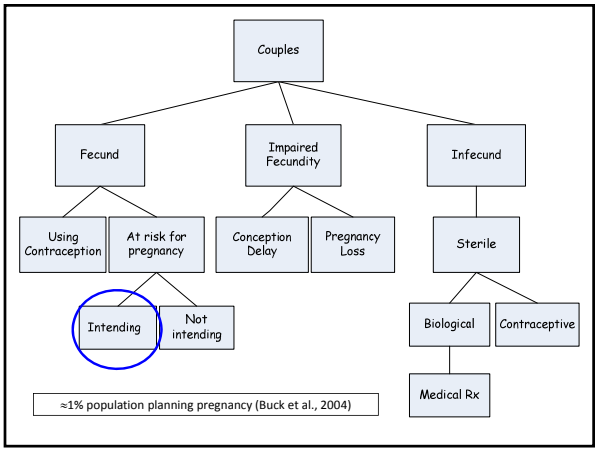
- Prospective cohort comprising 501 couples recruited upon stopping contraception in two targeted geographic areas
  - Committed relationship; females 18-44 years; English or Spanish; 21-42 day menstrual cycles; no infertility
- Longitudinal data & biospecimen collection
  - Baseline interview & anthropometric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

LIFE Study

- Environmental chemicals
  - Persistent compounds: OCPs, PBBs, PBDEs, PCBs, PFCs, metals
  - Short-lived compounds: BPA, phthalates, UV filters
- Lifestyle
  - Alcohol, caffeine, exercise, fish, smoking, stress, vitamins
- Outcomes
  - 1° TTP, infertility, pregnancy loss, gestation, birth size
  - 2° 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 (EPL)
- Whittaker et al., 1983 (EPL)
- France et al., 1984
- de Mouzon et al., 1988
- Wilcox et al., 1988
- Vartiainen et al., 1994
- Zinaman et al., 1996
- Columbo et al., 2000

Population Based

- Sweeney et al., 1989 - MVA
- Hakin et al., 1995 - occupational
- Ellish et al., 1996 - MVA
- Brown et al., 1997 - HMO
- Bonde et al., 1998 - occupational
- Buck et al., 2002 - fish license registry

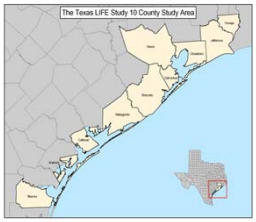
Couples: Bonde, Buck Louis, Colombo, de Mouzon, & Zinaman

Recruitment yield 0.1% - 4.0% for studies with denominator

Recruitment Strategy – LIFE Study

Michigan	Texas
4 counties	12 counties
InfoUSA®	Texas Parks & Wildlife Registry
Mailing with telephone follow up	Mailing with telephone follow up

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

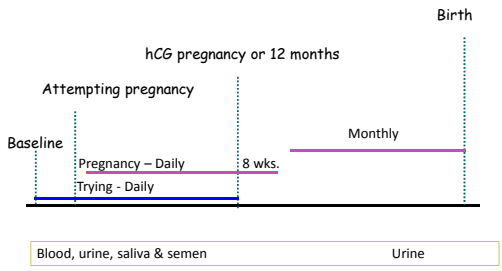
	Letters Mailed (N)	Recruited n (%)	Enrolled n (%)
Texas	355,087	981 (3%)	397 (40%)
Michigan	69,336	203 (1%)	104 (51%)

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



Data Completion

Card	Male %	Female %
Michigan		
•Journal	82	84
•Early pregnancy (daily)	--	80
•Pregnancy (monthly)	--	76
Texas		
•Journal	85	88
•Early pregnancy	--	82
•Pregnancy	--	81

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

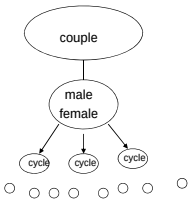
Biospecimen	First Sample % Obtained	Second Sample % Obtained
Blood	100	--
Urine (6 mo. & pregnancy)	100	94 (77 & 95)
Saliva	98	87
Semen	94	77

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…

Metals & Fecundability

Adjusted Model	Female FOR (95% CI)	Male FOR (95% CI)
Cadmium (ug/L)	0.77 (0.62, 0.97)	0.85 (0.71, 1.01)
Lead (ug/dL)	0.97 (0.85, 1.11)	0.85 (0.73, 0.99)
Mercury (ug/L)	0.99 (0.87, 1.12)	0.98 (0.86, 1.11)
Cotinine (ng/ml)	0.98 (0.81, 1.18)	0.96 (0.83, 1.10)
Serum lipids (ng/g)	0.93 (0.82, 1.06)	0.98 (0.87, 1.10)
Age (years)	0.80 (0.70, 0.91)	0.85 (0.75, 0.97)
BMI (kg/m^2)	0.91 (0.79, 1.04)	0.99 (0.88, 1.12)
Site (Michigan/Texas)	1.23 (0.91, 1.66)	1.30 (0.96, 1.76)
Parity (null/parous)	1.72 (1.34, 2.21)	1.66 (1.31, 2.11)

Couples' Metals & Fecundability

Adjusted Model	FOR (95% CI)
Female cadmium (µg/L)	0.81 (0.64, 1.02)
Female lead (ug/dL)	1.05 (0.91, 1.23)
Female mercury (µg/L)	1.00 (0.86, 1.16)
Male cadmium (µg/L)	0.93 (0.78, 1.12)
Male lead (µg/dL)	0.83 (0.70, 0.98)
Male mercury (µg/L)	0.98 (0.84, 1.14)
Female age (years)	0.81 (0.70, 0.94)

*Adjusted for couples' cotinine, lipids, BMIs, female age (years) & delta of ages.

POPs & Fecundability*

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, Σ 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)

POPs & Time-to-Pregnancy*

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

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….