Psychological stress and its impact on fertility

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Outline

- Background
  - Menstrual cycle review
  - The fertile window
  - Fertility – what is typical?
  - Stress – how do you measure it?
- Oxford Conception Study
- LIFE Study
- What does this mean for women?
- Next steps
The menstrual cycle

- Ovarian cycle: Growing follicle, Ovulation, Corpus luteum, Corpus albicans
- Body temperature: 37°C, 36°C
- Anterior pituitary hormones: Luteinizing hormone (LH), Follicle-stimulating hormone (FSH)
- Ovarian hormones: Estradiol, Progesterone
- Uterine cycle: Follicular phase, Luteal phase, Menses

Wexner Medical Center
Conception timing

Gamete survival:
- Egg: median ~ 12 hours
- Sperm: 1 - 6 days

Lynch CD et al., 2006, Paediatric and Perinatal Epidemiology
Methods of pinpointing ovulation

- U/S visualization (not practical)
- Basal body temperature chart (too late)
- Cervical mucus changes (low patient satisfaction)
- Ovulation prediction kits (better than temp charts)
- Clearblue® digital fertility monitor – best but expensive ($180 + test sticks)
How to maximize pregnancy probability?

- When to have intercourse?
  - Intercourse on day -1 (day prior to ovulation)
  - Best to have the sperm “waiting” when ovulation occurs

- More is better!
  - Ideally once daily around mid-cycle
  - At a minimum, twice/week NOT just on the weekends

- Misperception:
  - No empirical evidence supporting intercourse every other day unless male has low sperm count
What factors impact couples’ fertility?

- Age
- Female factors
  - Smoking
  - Alcohol
  - Caffeine
  - Egg quality
  - Tubal patency
  - Stress
- Male factors
  - Semen quality
  - Everything else is understudied

Dunson et al., 2002, Human Reproduction
So, how long does it take to get pregnant?

Lynch CD, 2011, Fertility & Sterility
What is stress?

*Environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease.*

-Cohen et al., Measuring Stress, 1997
How do you measure stress?

- Measure the environment
  - Life events scale
- Measure individuals’ appraisal of events
  - Cohen’s Perceived Stress Scale
  - Daily Life Events checklist
  - Hassles scale
- Biological measures
  - Stress biomarkers
  - Cardiovascular response
  - Immune response
Why study stress and fertility?

- The evidence:
  - Numerous case reports of successful pregnancy after adoption
  - Women in an infertility clinic setting report being more stressed on average than women in the general population
    - Directionality of the association remains unclear
  - Very few studies to date have examined the association between stress and fertility in a prospective fashion
Approach

- Build a stress assessment component into two planned time to pregnancy studies
  - Oxford Conception Study (U.K.)
  - The LIFE Study (U.S.)

Objectives

- Examine the association between stress biomarkers and time to pregnancy
- Examine the association between perceived stress and other psychosocial measures and time to pregnancy
Oxford Conception Study (2005-2006)

- Women enrolled in the UK
- Eligibility criteria:
  - Women ages 18-40 years
  - Having sexual intercourse with a regular partner
  - Average menstrual cycle length 21-39 days
  - Planning pregnancy or currently trying < 3 months
  - No hx of infertility
  - Not currently breastfeeding
  - Absence of hormonal contraception in past 3 cycles
  - No injectable contraceptives in the last year
- Followed for up to 6 months or until pregnancy occurred
Oxford Conception Study Methods

- **Biological measures**
  - Collected saliva specimen upon awakening for measurement of cortisol and alpha-amylase

- **Questionnaire measures**
  - Battery of psychosocial questionnaires in the first cycle
  - Cohen’s Perceived Stress and Hospital Anxiety and Depression Scale repeated in subsequent cycles
Biological measures of stress

Stressful Stimulus
- Hypothalamus
  - Chronic stress
    - Hypothalamic pituitary adrenal axis (HPA) activation
      - Increase in blood cortisol
      - Increase in salivary cortisol
  - Acute stress
    - Sympathetic adrenal medullary axis (SAM) activation
      - Increase in blood norepinephrine
      - Increase in salivary alpha-amylase
Results – descriptive statistics

- 370 women participated in the study
- 339 (92%) had complete data available for analysis

Characteristic of participants:
- 94.7% of participants were white
- 21.8% smoked
- 90.9% drank alcohol

Study outcomes:
- 61% achieved pregnancy
- 20% followed for six months but did not achieve pregnancy
- 19% withdrew
Results – biological measures

- No association between biomarkers and time to pregnancy
- No association between cortisol and day-specific probabilities of pregnancy
- For alpha-amylase, women in the highest tertile had pregnancy probabilities that were 12% lower on average compared to women in the lowest tertile

Buck Louis GM et al., 2010, Fertility & Sterility
Results – biological versus questionnaire measures

- Little to no correlation between physiologic and psychosocial measures in cycle one

<table>
<thead>
<tr>
<th></th>
<th>STAI-S</th>
<th>STAI-T</th>
<th>MOS</th>
<th>Pearlin</th>
<th>Rosenberg</th>
<th>HADS-A</th>
<th>HADS-D</th>
<th>PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>-0.01</td>
<td>-0.02</td>
<td>0.04</td>
<td>0.02</td>
<td>0.00</td>
<td>-0.02</td>
<td>0.10</td>
<td>-0.02</td>
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<tr>
<td>Alpha-amylase</td>
<td>0.09</td>
<td>0.02</td>
<td>-0.05</td>
<td>0.01</td>
<td>0.00</td>
<td>0.08</td>
<td>0.11</td>
<td>0.06</td>
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Results – questionnaire measures

- No association between the cycle one questionnaire measures and time to pregnancy or day-specific probabilities of pregnancy

Lynch CD et al., 2013, Fertility & Sterility
LIFE Study (2005-2009)

- Couples enrolled in MI and TX

- Eligibility:
  - Planning a pregnancy
  - Married or committed relationship
  - Female 18-40 and males 18+
  - Able to communicate in English or Spanish
  - Menstrual cycles 21-42 days in length
  - No hormonal birth control injections in the past 12 months

- Followed for up to 12 months or until pregnancy occurred
Sample characteristics

- Of the 501 couples enrolled:
  - 20% withdrew or were exited due to noncompliance
- Of the 401 couples who completed the protocol:
  - 87% achieved pregnancy
  - 13% did not get pregnant
- 373 (93%) had complete data available for this analysis
Female baseline characteristics

- **Race**
  - 78% non-Hispanic white
  - 5% non-Hispanic black
  - 10% Hispanic
- **Mean age** = 30 ± 4 years
- **Educational attainment**
  - 75% college graduates
- **Current smokers** = 27%
- **Nulliparous** = 53%
- **Overweight or obese** = 55%
### Adjusted odds of pregnancy by alpha-amylase level

<table>
<thead>
<tr>
<th>Tertiles of salivary alpha-amylase</th>
<th>Adjusted FOR (95% CI)</th>
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<tbody>
<tr>
<td>Lowest</td>
<td>1.0 (-)</td>
</tr>
<tr>
<td>Middle</td>
<td>0.89 (0.64, 1.24)</td>
</tr>
<tr>
<td>Highest</td>
<td>0.69 (0.49, 0.98)</td>
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*Adjusted for female age, difference between partners’ ages, income, race, smoking, caffeine intake, alcohol use.*
Time to pregnancy by alpha-amylase level

N = 373

= censored data

Probability of Remaining Non-Pregnant

Cycle

Amylase
  - Lowest
  - Middle
  - Highest
Potential limitations

- Confounding?
  - Alpha-amylase shown to be affected by smoking, eating, drinking and exercise
  - First morning sample with clear instructions should have minimized this issue

- Salivary alpha-amylase is a newer biomarker
  - Disagreement with regard to how to collect saliva
  - Does it change over the menstrual cycle?

- Lack of correlation between biological and questionnaire measures
  - This has been found in many other studies
Conclusions

- Stress as measured by salivary alpha-amylase is negatively associated with fertility and is associated with an increased odds of infertility

- Is the association causal?
  - Perhaps, but too soon to know for sure

- Biologic plausibility?
  - More intercourse
  - Delayed ovulation
  - Gamete transport
  - Hormonal milieu
What should we tell women?

- The jury is out but reducing stress is unlikely to cause harm
- What stress reduction modalities are likely to be the most helpful?
  - Unknown
  - Consider the yoga, mindfulness-based practice, etc.
- Must be careful to avoid victim-blaming
  - Stress is not the most important factor affecting one’s fertility
Future directions

- Association between stress and early pregnancy loss
- Association between mood disorders and time to pregnancy and early pregnancy loss
- More work on alpha-amylase
  - Does it change over the menstrual cycle?
  - Correlation with life events and more chronic stress?
Collaborators and funding

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