Monitoring Personal Hormonal Measurements in Relation to Environmental Exposures

Rajeshwari Sundaram, Ph.D.
Division of Epidemiology, Statistics and Prevention Research,
Eunice Kennedy Shriver National Institute of Child Health & Human Development
Background

- Growing evidence that endocrine disrupting chemicals affect human reproduction & development, possibly by modulating hormones or their function
- Challenging to study at population level
  - Need longitudinal measurement of time varying exposures & outcomes
  - Many outcomes not readily observable (e.g., ovulation, conception)
Unobserved Reproductive Endpoints?

- Menses & ovulation
- Semen quality & fertilization
Challenges in Measuring Time-Varying Hormonal Profiles

- Intra- and inter-woman variability
  - Inherent variability during menstrual cycles
- Methods vary in intensity (as do costs)
  - Daily collection
  - Abbreviated collection (on fixed days in cycle)
- Research implications
  - Potential for mistimed data & biospecimen collection
  - Considerable costs & logistical issues (e.g., storage urine in home freezers)
  - Burden with no immediate feedback for women, particularly those wishing to become pregnant
Home as the Lab!

- Commercially available personal fertility monitors that measure & track urinary estrone–3–glucuronide (E₃G) & luteinizing hormone (LH)
  - Time biospecimen collection relative to the cycle
  - Capture hormonal profiles without requiring daily biospecimens & laboratory analyses
  - Distinguishes missing data if no test done
  - Direct uploading data to data systems
  - Prompts for timing intercourse relative to the fertile window (participant incentive)
Home Fertility Monitors

ON-OFF BUTTON
FERTILITY STATUS
DISPLAY SCREEN
DAY NUMBER
M BUTTON
'M' SYMBOL
TEST STICK SLOT
TEST STICK
INITIAL DISPLAY

PRESS M BUTTON AND HOLD FOR 5 SECONDS UNTIL "I" APPEARS

DISPLAY AFTER "M" BUTTON IS PRESSED

FERTILITY STATUS BAR

DISPLAY INDICATES THAT THE MONITOR REQUIRES A TEST

LOW FERTILITY:
very small chance of conception

HIGH FERTILITY:
increased chance of conception

PEAK FERTILITY:
highest chance of conception
Monitor Output

User Name: Hello Kitty
User Reference: 1000819520
Card Use
Time: 1:38 PM
Date: March 25, 2004

Cycle: 1, Start: February 03, 2004, Length: 25 days

Cycle: 2, Start: February 28, 2004, Length: 24 days

Fertility Monitors & Gold Standard

- Ovarian ultrasonology affirms that LH surge occurs 24–36 hours before follicular rupture

- WHO recognizes that urinary $E_3G$ correlated with plasma estradiol

- Increased pregnancy rate associated with use of fertility monitor (Robinson et al., 2007)
Serum Hormone versus Monitor Data

Howards et al., 2009
% Women whose LH Peak Is Within Conventional LMP Windows

![Graph showing percentage of women whose LH peak is within conventional LMP windows for Cycle 1 and Cycle 2. The graph includes bars for Days 12-14, from end 13-15, and midpoint +/-1.](image-url)
Monitor provides software that can be adapted to collect relevant information (e.g., E3G, LH, date/time stamp, various test diagnostics)

Continuous monitoring of data to identify irregularities or malfunctions

- Each upload typically creates duplicate records of previous tests not yet overwritten by the monitor
- Repeat records also created due to multiple testing attempts within the same time frame

Program developed to efficiently handle duplications in the LIFE Study
Relevancy of Fertility Monitor for the Exposome – LIFE Study
Do persistent environmental chemicals affect human reproduction & development in the context of couples’ lifestyles?

- **Study outcomes**
  - 1° Time-to-pregnancy; infertility; pregnancy loss, gestation & birth size
  - 2° Menses; ovulation; reproductive profiles; semen quality; sex ratios

- **Chemicals**
  - PCBs, PBDEs, PFCs, pesticides, metals, cotinine, phytoestrogens, BPA, phthalates, & UV filters

- **Lifestyle**
  - Smoking, alcohol, caffeine, exercise, fish consumption, stress, vitamins
Time-Based Data Collection

Baseline

Attempting pregnancy

Blood, urine, saliva & semen

Daily

hCG pregnancy or 12 months

Monthly

Birth
Home-Based Data Collection

Daily Journals
How Did the Monitor Work?

- Number of tests uploaded (n=30,975)
- Number of failed tests uploaded (n=1,827; 5.9%)

<table>
<thead>
<tr>
<th>Cycle Characteristic (in days)</th>
<th>Monitor Based</th>
<th>Diary Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,567</td>
<td>2,673</td>
</tr>
<tr>
<td>Range in cycle lengths</td>
<td>11–150</td>
<td>3–135</td>
</tr>
<tr>
<td>Mean (±SD) cycle length</td>
<td>29.7 (±10.7)</td>
<td>28.6 (±10.9)</td>
</tr>
<tr>
<td>Mean (±SD) day of LH peak</td>
<td>15.9 (±3.8)</td>
<td>14.3 (±5.8)</td>
</tr>
</tbody>
</table>
A woman’s hormonal profile—E3G & LH

Days within Cycle

LH

Days within Cycle

E3G
A woman’s hormonal profile—E₃G & LH

Days within Cycle

LH

Days within Cycle

E₃G
Unanticipated field issues...
The Texas LIFE Study Proposed County Area, October 2008

Hurricanes ... Katrina, Rita & Ike
...the dog ate it!
Summary

- Fertility monitors have utility & are feasible for collecting time varying hormonal data (also for timing data & biospecimen collection)
- Minimal learning curve for participants, despite diverse cohort with varying educational & economic backgrounds
- Web–based data management essential for such data collection
- Quantitative assessment of mixtures in relation to sensitive interrelated reproductive outcomes possible!

Buck Louis et al., 2011
Acknowledgements

- LIFE Study – Research Team

**NICHD**
- Dr. Germaine Buck Louis (Study PI)
- Dr. Zhen Chen
- Dr. Enrique Schisterman
- Dr. Rajeshwari Sundaram

**Texas A&M University**
- Dr. Anne Sweeney

**RTI International**
- Dr. Tim Wilcosky

**The EMMES Corporation**
- Dr. Rob Gore-Langton
- Dr. Seth Sherman

**Ohio State University**
- Dr. Courtney Lynch

**Emory University**
- Dr. Dana Boyd Barr

**CDC**
- Dr. Steven Schrader
Thank you!
sundaramr2@mail.nih.gov
Identification of LH Peak
Serum LH & Estradiol Levels
Woman with Monitor Peak

LH (ng/mL)

Estradiol (pg/mL)

Cycle Day

Monitor Peak

End Cycle

BioCycle