

How do Environmental Chemicals Impact the Female Cycle?

A Pilot Project to Integrate Exposure Assessment and Cycle Tracking

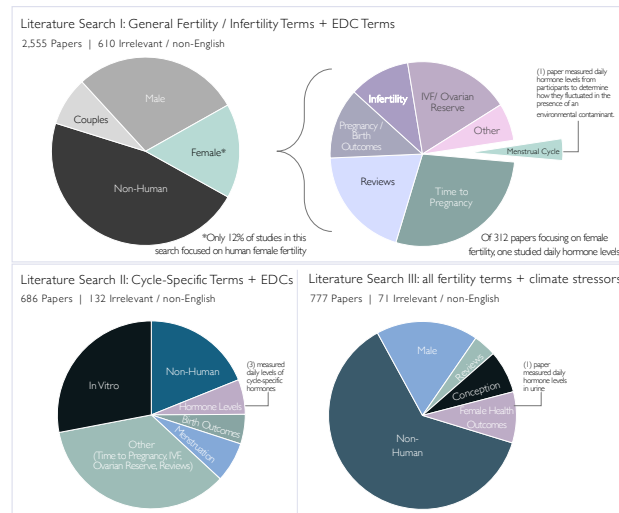
Background

Environmental Exposures and Female Fertility

The impacts of endocrine disrupting chemicals (EDCs), and other environmental exposures, on female fertility are understudied. EDCs are prevalent in the environment, and exposure to these contaminants is cited as a likely reason for growing rates of human infertility. In addition, heat stress and atmospheric pollution are suspected to impact the menstrual cycle.

However, little is known about the day-to-day influences that EDCs, air pollutants, or extreme heat may have on the female cycle. Three literature searches were conducted to explore this topic.

In over 5,000 papers published about environmental impacts on human fertility, only five (5) examined how they impacted daily hormone levels during the female cycle.



Fertility Awareness Methods (FAMs)

To fill this knowledge gap, this project will harness the growing interest in cycle tracking and fertility awareness methods. The American College of Obstetrics and Gynecologists cites three biomarkers that can be monitored daily to track the female cycle:

- **Cervical fluid**, which changes before, during, and after ovulation
- **Basal body temperature**, which rises following ovulation
- **Urinary hormones**, in which estrogen and luteinizing hormone (LH) can be tested to predict the beginning of the fertile window.

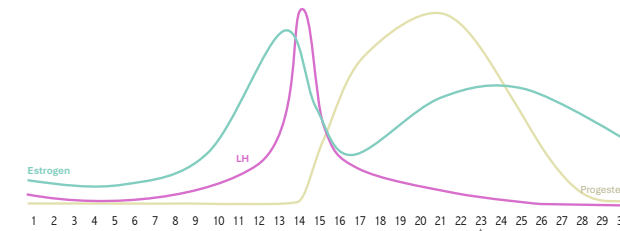
Methods

Data Collection

Recruitment: participants will be recruited via outreach with physicians / nurses who incorporate FAM charting into their clinical practices, as well as via FAM educators.

Eligibility Criteria: women who use an evidence-based FAM, reside in the US, who have neither been pregnant nor breastfeeding in the last 6 months, have not been told by a doctor that they may be menopausal, and are using an FAM to achieve or avoid pregnancy.

Cycle and Environmental Data: participants will be asked to provide 3-6 cycle charts, fill out a questionnaire about their health history, and give four urine samples. The samples will be collected at set points during the cycle.



- Urine Sample 1: Collected on the first day of menstruation
- Urine Sample 2: Collected at approximate midpoint of the follicular phase
- Urine Sample 3: Collected on peak day
- Urine Sample 4: Collected at approximate midpoint of the luteal phase

Analysis

Covariates: relevant health information will include age, weight, parity, education, ZIP code, smoking status, information on past breastfeeding, list of current/previous medications, and whether they have experienced any significant stress in previous 6 months.

Exposure variables: each participant's ZIP code will be used to determine urbanicity, as well as exposure to air pollutants (collected from the Air Quality Index) and frequency of exposure to extreme heat during the time frame in which cycle data was collected. Targeted analyses will be conducted on a subset of urine samples for common non-persistent EDCs (see list at right). Most urine samples will be banked for future analysis.

Chart Coding: this project will collaborate with FAM experts to code cycle charts for the following characteristics: menses length, follicular and luteal phase length, whether there is a clear indicator of likely ovulation, and any additional abnormalities.

Environmental Exposures

Endocrine Disrupting Chemicals (EDCs)

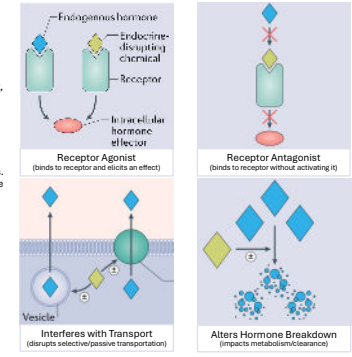
EDCs are prevalent in the environment and can include natural (heavy metals) as well as anthropomorphic contaminants (pesticides, phthalates, flame retardants, etc). This pilot study focuses on non-persistent EDCs that can be detected in urine. Exposure to EDCs occurs via ingestion, inhalation, and/or dermal absorption.

Common EDCs

- Triclosan**
an anti-bacterial agent, common in soaps and other personal care products. Can mimic thyroid hormones and estrogen.
- Phthalates**
lend flexibility to plastic food packaging, toys, and other products. Reduce testosterone and estrogen levels and interfere with thyroid function.
- Bisphenols**
provide the backbone to polycarbonate plastics and are present in epoxy resins. Can bind with ERα and ERβ and activate other estrogen receptors.
- Parabens**
commonly used to prevent mold and bacterial growth in personal care products and food. Capable of mimicking estrogen.
- Pesticides**
a wide group of compounds (including herbicides, fungicides, rodenticides). Can alter hypothalamic and pituitary function, impacting FSH and LH levels.

EDC Mechanisms of Action

Source of Images: Caption: La Merrill, M.A. et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 16, 45-57 (2020).



Above: four (4) of the ten (10) main mechanisms of action, summarized by Merrill, et al., as the ways EDCs impact the endocrine system.

Climate Related Exposures

Extreme heat and air pollution are also thought to impact the female cycle, but research is limited.

Air Pollution

Animal and in-vitro studies have shown that air pollutants are capable of causing oxidative stress. Particulate matter was observed to increase inflammation; these studies provide evidence of a biological mechanism for air pollution leading to menstrual cycle irregularities.

Extreme Heat

Many papers devoted to the subject of heat and ovulation/menstruation focus on the fluctuations in body temperature during those times. Some researchers posit that the increased discomfort and stress of excessive heat exposure may lead to cycle alterations.

Future Work

This project will lay the groundwork for future biomonitoring studies. Additional funding will be sought to:

- (1) analyze the banked urine samples from this pilot study;
- (2) recruit a wider cohort of participants; and
- (3) introduce blood sampling for persistent EDCs (such as perfluoroalkyl substances [PFAS] and polycyclic aromatic hydrocarbons [PAHs]).

The menstrual cycle is "a complex process orchestrated by interactions between many of the body's tissues, cells, and hormones [and] reflects a person's overall health status and can be thought of as a "fifth vital sign." "

– National Institute of Child Health and Human Development, 2021

Hypothesis: women with higher levels of adverse environmental exposures will be more likely to have abnormal cycle charts. Conversely, women with lower exposures will be more likely to have normal cycle charts.

Impact: the goal of this research is to elucidate the mechanisms by which the environment may impact the female cycle, to provide evidence-based suggestions for women interested in limiting or ameliorating their exposures to EDCs or climate-related stressors.