Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS) and Women’s Reproductive Aging

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Reproductive Aging and Menopause

Defined as one year without a menstrual period
Age at menopause and women’s health risks

Most women reach menopause between 45 and 55, with a median age between 50 and 52.

**Earlier onset**
- Increased overall mortality
- Higher risks of cardiovascular disease
- Lower bone density
- Higher risks of osteoporosis
- Higher risks of neurological disease

**Later onset**
- Increased risks of breast, endometrial, and ovarian cancer
Factors related to age at menopause

- Race/ethnicity
- Family history
- Socioeconomic status
- Obesity
- Physical inactivity
- Smoking
- Surgery
- Pesticides
- Solvents
- Metals
- Pharmaceuticals
- Industrial ingredients

Source: https://www.healthandenvironment.org
PFAS are potential EDCs and ‘forever chemicals’

- **Anthropogenic chemicals**

- **Two main groups**
  - **Carboxylates**: perfluorooctanoic acid (PFOA)
  - **Sulfonates**: perfluorooctane sulfonate (PFOS)

- **Sources**

(Domingo and Nadal, 2017, Domingo and Nadal, 2019, Hu et al., 2016; Post et al., 2009, Trudel et al., 2008, Boronow et al., 2019)
200,000,000+

Americans consume drinking water contaminated by PFAS

Andrews and Naidenko 2020
PFAS and their effects on the ovary

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary

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- Higher PFAS were associated with:
  - Later menarche
  - Irregular menstrual cycles
  - Reduced levels of estrogen

- Folliculogenesis and steroidogenesis
PFAS may deplete the ovarian reserve.

Activate PPAR-α and PPAR-γ

Oxidative stress

Genes in the meiosis of oocytes

Nutrient supply between granulosa cells and oocytes

(Ding et al. 2020)
PFAS and their effects on the ovary

- **Research Gaps:**
  - Lack of prospective cohort
  - PFAS mixture

**Question about reverse causality**

![Diagram showing the relationship between PFAS in Serum and Menopause with question marks indicating uncertainty]

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Study of Women’s Health Across the Nation (SWAN)

- Initiated in 1996-97
- N=3302 women aged 42-52 y
- White from all 7 sites
- Black from Chicago, SE Michigan, Pittsburgh, Boston
- Asians from Oakland (Chinese) and Los Angeles (Japanese)
- Hispanic from Newark
- Approximately annual or biannual follow-up
**SWAN Multi-Pollutant Substudy (SWAN-MPS)**

PI: Dr. Sung Kyun Park

- Serum/urine samples collected at third SWAN visit, which is the baseline for SWAN-MPS (1999-2000).
- N=1,400
- 5 study sites: Boston, SE Michigan, Oakland, Los Angeles, Pittsburgh.
- White, Black, Chinese, and Japanese.
Determinants of per- and polyfluoroalkyl substances (PFAS) in midlife women: Evidence of racial/ethnic and geographic differences in PFAS exposure

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Longitudinal trends in perfluoroalkyl and polyfluoroalkyl substances among multiethnic midlife women from 1999 to 2011: The Study of Women’s Health Across the Nation

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 Detection > 95%
- Linear PFOS
- Branched PFOS
- Linear PFOA
- PFNA
- PFHxS
- EtFOSAA
- MeFOSAA

 Detection < 40%
- Branched PFOA
- PFDA
- PFUnDA
- PFDaDA

 Determinants
- Race/ethnicity
- Menstrual bleeding
- Parity
- Consumption of salty snacks (e.g. popcorn, chips)
- Age
Decline in PFOA and PFOS

PFHxS unchanged

PFNA increased

Concentrations of selected PFAS by study visits between 1999 and 2011 (N=75).
PFAS and Incident Natural Menopause in Midlife Women.
Study population and statistical methods

- **Incident natural menopause**: amenorrhea for at least 12 months not due to hormone therapy, oophorectomy and/or hysterectomy,

- **Cox proportional hazards model** adjusting for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status and prior hormone use at baseline.
Earlier natural menopause with PFOA and PFOS

1.1 years earlier

- PFOA: Hazard Ratio = 1.65, 95% CI: 1.40 to 1.91, P for trend = 0.01

0.9 years earlier

- PFOS: Hazard Ratio = 1.59, 95% CI: 1.27 to 1.97, P for trend = 0.03
PFAS Mixture

- Unsupervised learning method: K-means clustering
- Minimize within-cluster sum of squares.
- Number of cluster determined using cubic clustering criterion, pseudo F statistic (i.e. the ratio of between-cluster variance to within-cluster variance), and r-squared statistics.
High vs. low overall concentrations patterns: 2.0 years earlier natural menopause

HR (95% CI) comparing High vs. Low: 1.66 (1.17-2.36)

Predicted median age at menopause:
- Low: 52.7 (95% CI: 51.8-54.6) years
- Medium low: 51.9 (95% CI: 51.5-52.7) years
- Medium high: 52.6 (95% CI: 51.8-53.3) years
- High: 50.7 (95% CI: 50.4-51.7) years
Summary: PFAS were associated with earlier natural menopause, a risk factor for overall health.

- PFAS are potential EDCs and ovarian toxicants (Ding et al. 2020).

- Determinants and temporal trends of PFAS

- 2.0 years earlier natural menopause was associated with shorter life expectancy (HR=1.04, 95% CI: 1.02-1.07) in a cohort of 12,134 postmenopausal women followed for an average of 17 years (Ossewaarde et al. 2005).
Future directions

- Linking natural menopause to health conditions.

- Other EDCs and mixture analysis;

(Grindler et al. 2015)
On-going projects

SWAN-MPS (PI: Sung Kyun Park):

- Chemicals: PFAS, metals, PCBs, flame retardants, pesticides, phthalates, phenols, and parabens in serum or urine
- Evaluation of chemicals and their relationships to reproductive traits:
  - Age at natural menopause
  - Hormone profiles
  - Menstrual cycle characteristics
  - …

- Evaluation of metal exposures and their relationship to metabolic traits:
  - Body composition
  - Diabetes
  - Metabolic syndrome and its components
  - …
Thank you!

Questions / Comments

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Participants in SWAN.

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