Human genomic insights into reproductive ageing and fertility
Stasa Stankovic | PhD student | stasa.stankovic@mrc-epid.cam.ac.uk

INTRODUCTION
- Menopause age varies considerably in population
- It impacts infertility and women’s health status
  - Early menopause (<45 years): 10% of women
  - Premature menopause (<40 years): 1%
- Fertility deteriorates 10 years before menopause
- No long-term clinical predictors of infertility
- UK Gov: First Women’s Health Strategy (2021)

What determines the timing of menopause?
How does menopause impact infertility and other health outcomes?

USING GENOMICS TO UNDERSTAND AND PREDICT VARIATION IN FERTILITY LIFESPAN

**AIM:** Understand how genes influence the fertility lifespan

**STEP 1:** Collect genomics and reproductive data from 500,000 women in UK Biobank and other studies --> test their association using big data analytics and statistical models.

**STEP 2:** Discover genetic variants and genes responsible for differences in fertility lifespan using genome-wide association and whole exome sequencing.

**RESULT TO DATE**
Identification of ~300 regions in DNA that influence fertility lifespan.

**AIM:** Predict women’s fertility lifespan to enable more informed reproductive choices

**GENOMICS**

- Sum of the individual genetic variants associated with menopause will impact where you are in the distribution
- Women with a mutation that stops BRCA1 gene from working have menopause 2.6 years earlier
- Prediction test using human genomics data and other blood based biomarkers has the potential to identify women with early menopause

**IMPACT:** testing for reproductive expectations could allow family planning, treatment of early menopause and timely management of later life diseases

USING GENOMICS TO IMPROVE FERTILITY AND HEALTH OUTCOMES IN WOMEN

- Human genomic findings tested in developed eggs to understand how identified genes impact fertility
- Drug discovery: novel target identification

**Egg in a dish:** mimic egg development from stem cells

**Genomics**

- INCREASED FERTILITY
  - 25% LONGER REPRODUCTIVE LIFESPAN
  - ↑ IVF EFFICIENCY ➔ potential treatment for improving IVF

- Early menopause and disease risk
  - DNA damage
  - Cell death
    - Extra copy of CHEK1
    - Lacking CHEK2

- Breast cancer
- Reproductive cancers
- Bone health
- Diabetes
- Cardio
- Obesity
- Alzheimer’s
- Longevity

**Chek1 and Chek2**

- N eggs at birth: CHEK1
- Rate of eggs death: CHEK2

Genomics helps us understand why women with early menopause have increased risk of later life diseases like type 2 diabetes ➔ design intervention strategies