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BSc in Reproductive & Developmental Sciences

Ageing and Reproduction

Kate Hardy
Institute of Reproductive and Developmental Biology

Demographic analysis of ageing and fertility

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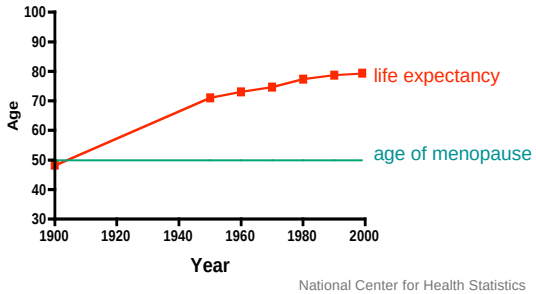
Life expectancy is increasing



National Center for Health Statistics
www.cdc.gov/nchs/

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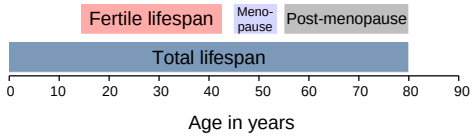
Female lifespan 2002



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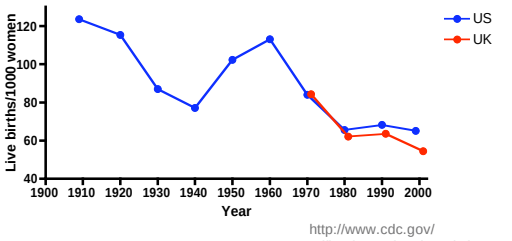
Declining birth rates



http://www.cdc.gov/
Office for National Statistics UK

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Impact of declining birth rates

- 1964: 2.95 children/woman
- 2001: 1.63 children/woman

Consequences

- ↓ working age population (productivity)
- ↑ pension burden
- ↓ ability to care for elderly
- ↑ costs to care for elderly

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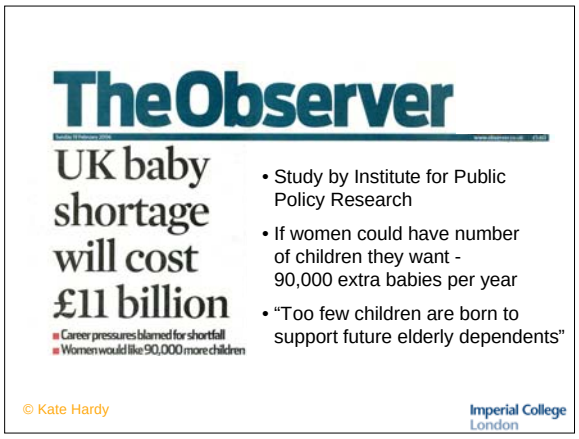

- Study by Institute for Public Policy Research
- If women could have number of children they want - 90,000 extra babies per year
- "Too few children are born to support future elderly dependents"

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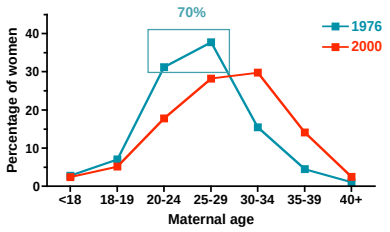
Women are delaying childbearing



Office for National Statistics UK

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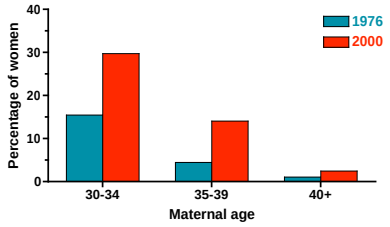
The number of women in their 30s having babies has doubled



Office for National Statistics UK

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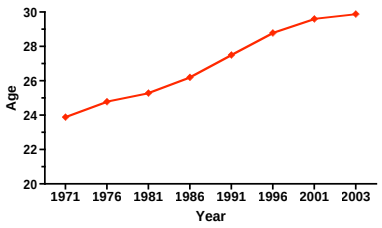
Maternal age at first birth is increasing



Office for National Statistics UK
data for married women

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Contraception and choice

- Introduction of reliable and well-tolerated forms of contraception - change in reproductive behaviour
- Having children is no longer the biological imperative of most women
  - planned postponement of children
  - decision to have no children
  - spacing birth order

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Why are women delaying childbearing?

- "Female emancipation"
  - equality in education
  - equality in workplace
- Changing expectations/aspirations
  - family planning
  - individualistic behaviour
  - children expensive/hard work
- Different life-path
  - education
  - establishment of career/home

Delaying childbearing profoundly affects birth rates

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Is delaying child-bearing a problem?

- Greatest cause of declining birth rate
- ↓ fertility
- ↑ miscarriage
- ↑ chromosomally abnormal pregnancies
- ↑ health risks to mother and baby
- ↑ need for assisted reproduction

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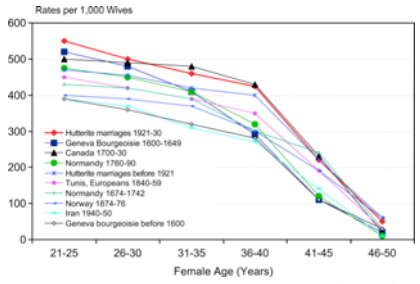
Fertility declines after mid-30s



Menken et al, 1986

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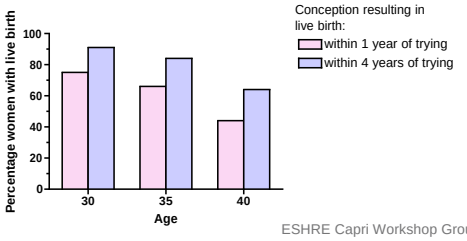
Conception rates for women trying to conceive



ESHRE Capri Workshop Group

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Infertility precedes menopause

- Natural fertility population
  - mean age at last birth = 41
  - mean age of menopause = 51
- 10 years of sterility before menopause

Te Veldt, 2002

- Sufficient follicles, but too high a frequency of early pregnancy loss from chromosomal anomalies

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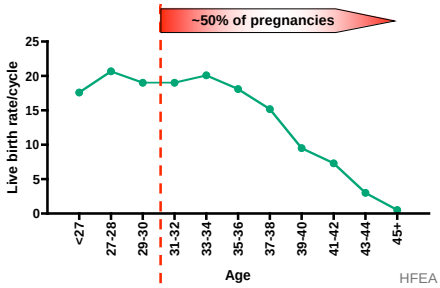
Fertility declines after mid-30s



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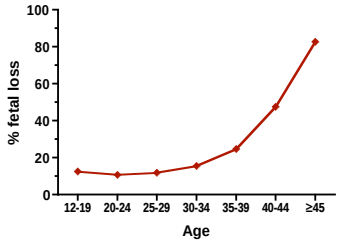
Fetal loss increases with age



% of intended pregnancies that result in spontaneous miscarriage, ectopic pregnancy or stillbirth

Nybo Andersen (2000) BMJ 320, 1708

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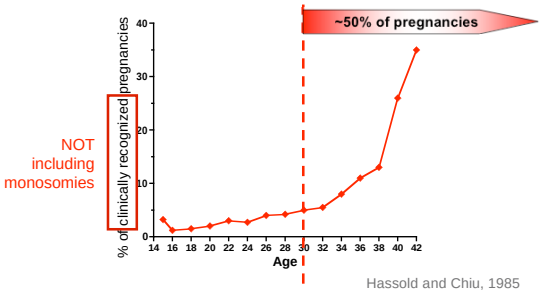
Aneuploidy increases with age



Hassold and Chiu, 1985

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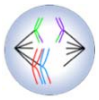
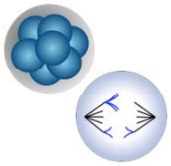
Origins of aneuploidy

- meiotic non-disjunction



- mitotic non-disjunction



*see "Genesis of aneuploidy" lecture

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Why does aneuploidy increase?

'Two hit' hypothesis:

- First hit - some oocytes at the outset have reduced recombination between homologues - predisposition to non-disjunction*
- Second hit - non disjunction, which increases with age
  - oxidative stress
  - reduced microcirculation round dominant follicle
  - defective granulosa cells

*see "Genesis of aneuploidy" lecture

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Why does aneuploidy increase?

- Limited pool hypothesis
  - number of antral follicles declines with age
  - fewer antral follicles at optimal stage for selection at start of follicular phase
- abnormal meiotic spindles seen in older women

Battaglia, 1996; Volarcik, 1998

- decreased cohesion between chromatids*
- increasing FSH levels causing aneuploidy?

*see "Genesis of aneuploidy" lecture

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Declining fertility

- reduced uterine selection against trisomies?
- post-ovulatory ageing of oocytes before fertilization
  - decreased coital frequency with age

Results

- decreased monthly probability of conception
- increased probability that pregnancy will terminate

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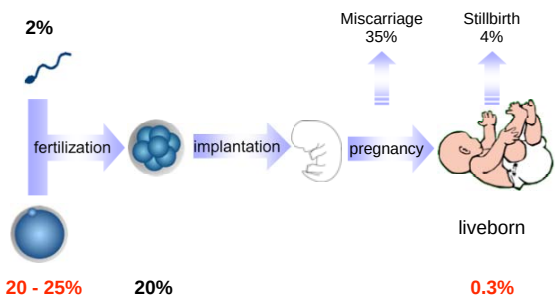
Incidence of aneuploidy



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Is ageing due to the ovary/oocytes?

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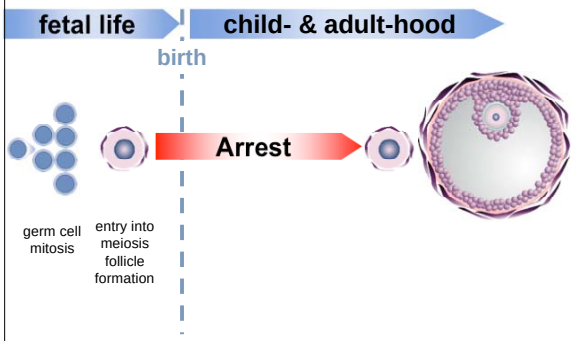

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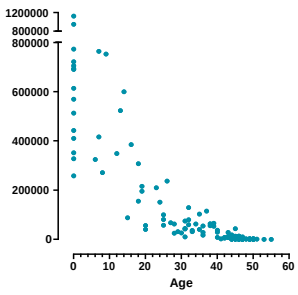
Finite oocyte pool declines with age



Block 1952
Block 1953
Richardson 1987
Forabosco 1991
Gougeon 1994

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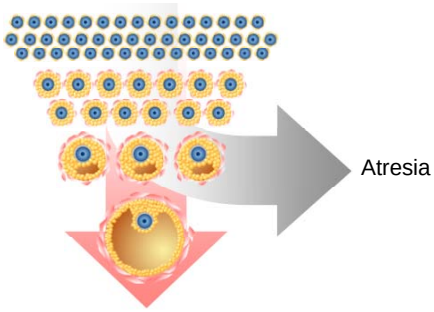

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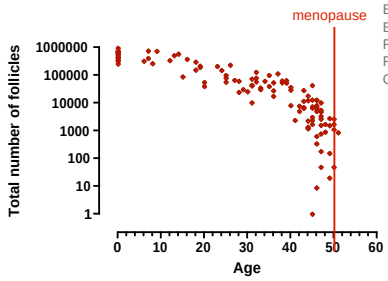
Declining number of oocytes



Block 1952
Block 1953
Richardson 1987
Forabosco 1991
Gougeon 1994

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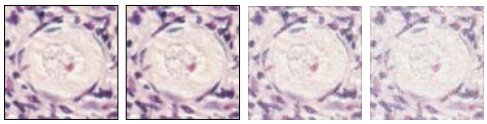
Deterioration of oocyte quality with age



Birth 20 years 30 years 40 years

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Fertility Decline

- female germ cells not replenished
- number of oocytes declines
  - attrition
  - utilization
- decline in oocyte 'quality'
- frequency of intercourse declines with age
- male factors only significant after age 40-45

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Does the uterus age?

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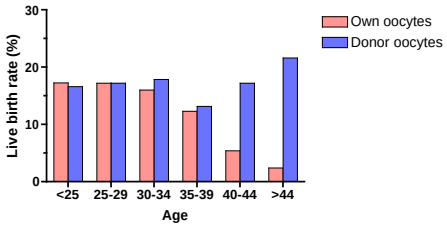
The oocyte ages



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Does the HPO axis age?

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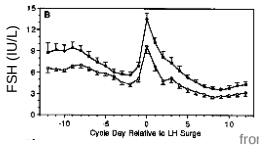
Reproductive ageing

- Normal LH, slight increase in oestradiol
- Increased FSH levels in early follicular phase from 35-40 years onwards - possibly due to…
- Decreased inhibin B secretion from antral follicles
- Increased FSH may explain increase in dizygotic twins



older (mean 43 yr)
younger (mean 23 yr)

from Klein et al (1996) JCEM 81, 1038

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Reproductive ageing

- Shorter cycle length due to shorter follicular phase
- Decreased number of antral follicles
- Variable cycles (reduced availability of small antral follicles for selection?)

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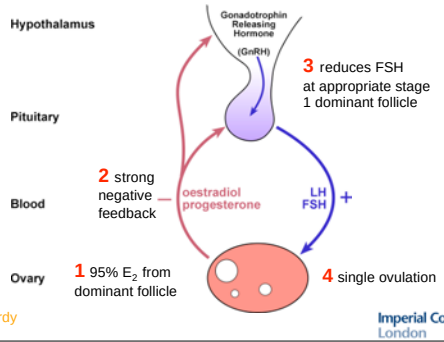
The hypothalamic-pituitary-ovarian axis



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The peri-menopause often means endocrine chaos!

- As ovarian reserve of follicles declines, oestradiol levels fall and FSH increases
- High FSH may "hyperstimulate" the next "crop" of follicles
- Multiple antral follicles and/or follicular cysts may develop
- Oestradiol levels may transiently become supraphysiological and FSH is suppressed
- Abnormal menstrual patterns are common

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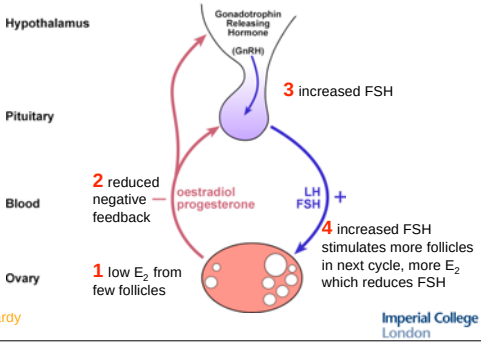
The hypothalamic-pituitary-ovarian axis in the perimenopause



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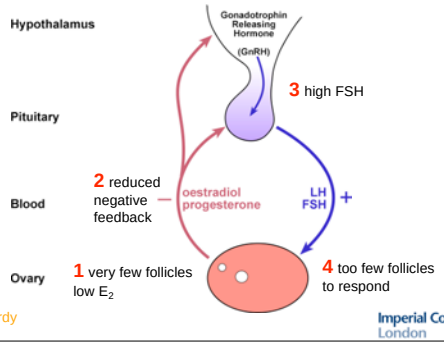
The hypothalamic-pituitary-ovarian axis in the post-menopause



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Post menopausal reproductive hormones

- Androgen production decreases but still produced by adrenal and, in small amounts, by ovary
- Low levels of oestrogen in circulation produced mainly by peripheral conversion of androgen
- Gonadotrophins remain high

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Effects of oestrogen deficiency

- Mucosal
  - Vaginal dryness and dyspareunia
- Vasomotor
  - Hot flushes
- Neurological/ Psychological
  - Forgetfulness, irritability, lack of concentration, depression
- Skeletal
  - Osteoporosis
- Cardiovascular
  - Increased risk of CHD and stroke?

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Endocrinology and physiology of ovarian ageing

- Ovarian ageing
  - depletion of stock of follicles (ovulation and attrition)
  - subfertility 10 years before menopause
  - increased chromosomal abnormalities
  - increased embryonic and fetal loss
- Peri-menopausal hormones
  - erratic ovarian activity
- Post-menopausal hormones
  - oestrogen deficiency

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Increased maternal and perinatal mortality

- As women get older, they suffer increasingly from cardiovascular disease and type 2 diabetes, giving rise to age-related increase in
  - pregnancy-induced hypertension
  - pre-eclampsia
  - placental abruption
  - gestational diabetes
- Also increase in dysfunctional labour → caesarian section
  - longer labour
  - fetal distress
  - multiple pregnancy
- Increased maternal death with age

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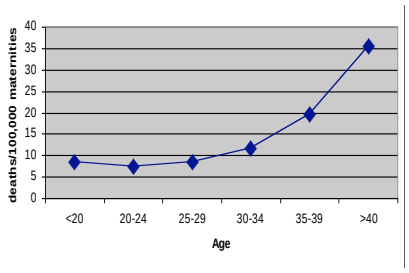
Maternal deaths by age, UK 1985-02



Why Mothers Die 2002 CEMACH RCOG press 2004

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‘Prediction’ of ovarian reserve

- Ovarian volume (reflects antral follicle number excluding CL)
- Inhibin B secreted by antral and preovulatory follicles
- Anti-müllerian hormone (AMH) secreted by preantral and antral (but not preovulatory) follicles
- FSH

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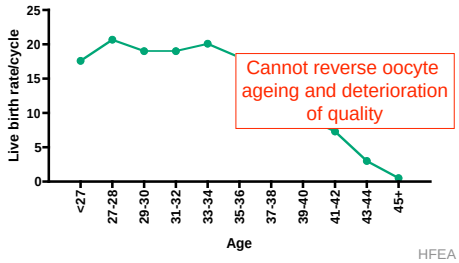
IVF does not solve the problem



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