Biology of the Perimenopause: Impact on Health and Aging Workshop
National Institute on Aging

Rodent Models

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Rodent Models of Perimenopause/Postmenopause

- Perimenopause:
  - Bax -/-
  - Bcl-x -/-
  - FSHR-haploinsufficient
  - VCD
- Postmenopause:
  - Ovariectomized
  - FSHR-haploinsufficient
  - VCD

Bax -/- Model

Perez et al., 1999 Nat. Gen. 21:200

- Pnd 4 – primordial follicles (no diff., WT)
- Pnd 7 – primordial follicles (↑-/- vs WT)
  - (Greenfeld et al., 2003BOR, Suppl1 68:1)
- Pnd 42 – atretic primordial follicles (↓ -/-)
- 20-22 months
  - WT, follicle deplete
  - -/-, ↑ # all follicles, uterine weight, retreived follicles fertilized, fail to become pregnant

Bax -/- Model

- Benefits:
  - Ovarian function in aged animals
  - Fertility in aged animals
- Drawbacks:
  - Fertility is compromised
  - May never become follicle deplete

Bcl-x -/- Model

Rucker et al., 2000 Mol. Endo. 14:1038

- Relative to WT:
- Ed 13.5 - ↓ gonocytes (42%)
- Pnd 1 - ↓ primordial follicles (3X)
- Pnd 19 - ↓ primordial follicles (15X)
- 3 months - ↓ primordial, 1°, 2° follicles (>15X)
- 25% females fertile (<4 pups)
- Bax deletion restored WT phenotype

Bcl-x -/- Model

- Benefits:
  - Compromised follicle pool (birth-3 months)
  - Extended period of ovarian failure
    - » Perimenopausal studies
- Drawbacks:
  - May not become follicle deplete

FSHR-haploinsufficient

Danilovich et al. 2002
BOR 67:370; Endocrinol. 143:3618

- Relative to WT:
- 3 months – ↓ ovulation, ↓CL,
  - ↓ ovarian wt., ↓ P_4, ↓ # eggs ovulated
- 7 months - ↓ ovulation, ↓ CL, ↓ E_2, ↓ P_4
  - ↑ FSH, ↑ LH, ↑ T
- 12 months – follicle deplete, no CL, ↓ P_4
  - ↑ FSH, ↑ LH, ↑ T, ↑ # resorbed fetuses
  - ↑ uterine weight*
- * ↑ uterine/ uterine horn pathologies

FSHR-haploinsufficient Model

- Benefits:
  - Ovarian failure within 1 year
    - » Post menopause studies
  - Fertility compromised (3 mos.-1 year)
    - » Perimenopause studies
- Drawbacks:
  - Lifetime compromised ovarian function
  - Uterine pathologies

Ovariectomized Model

- Numerous studies
- Benefits:
  - Removes endogenous E2 and P4
  - Abrupt and timed ablation
- Drawbacks:
  - Mimics surgical oophorectomy
  - No period analgous to perimenopause

VCD Model

Mayer et al. 3/3 2004 BOR Epub

4-Vinylcyclohexene Diepoxide

VCD-induced Ovarian Failure
Female mice or rats
15d daily dosing (i.p.)
Selectively destroys
primordial/primary follicles
Continue to cycle
Complete ovarian failure
d43-d88

TOXICITY
No effects at 15d
Weights:
adrenal, kidney, ovary,
uterus, spleen
Morphology/enzymes:
liver (AST, ALT)

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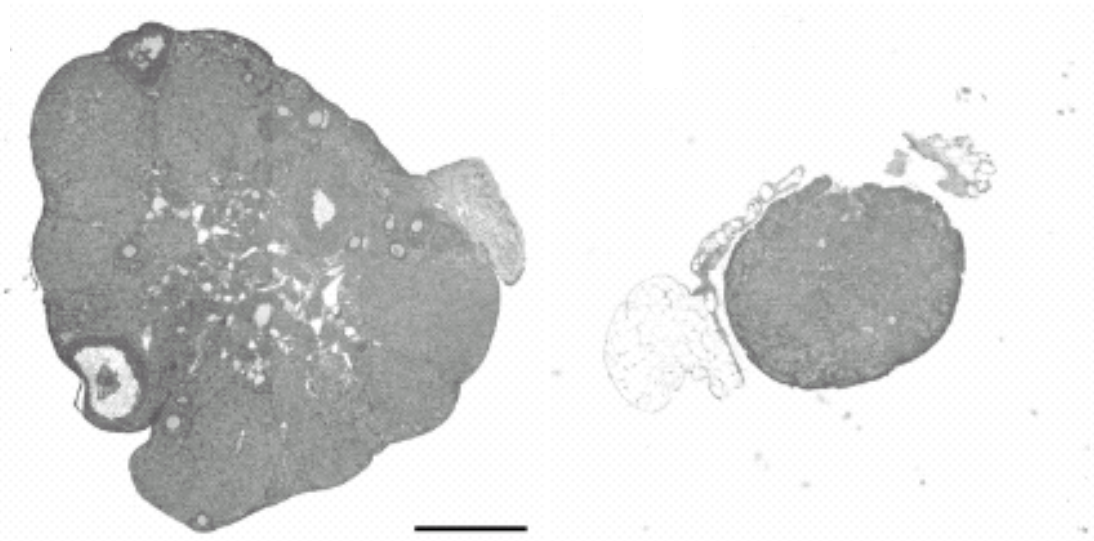
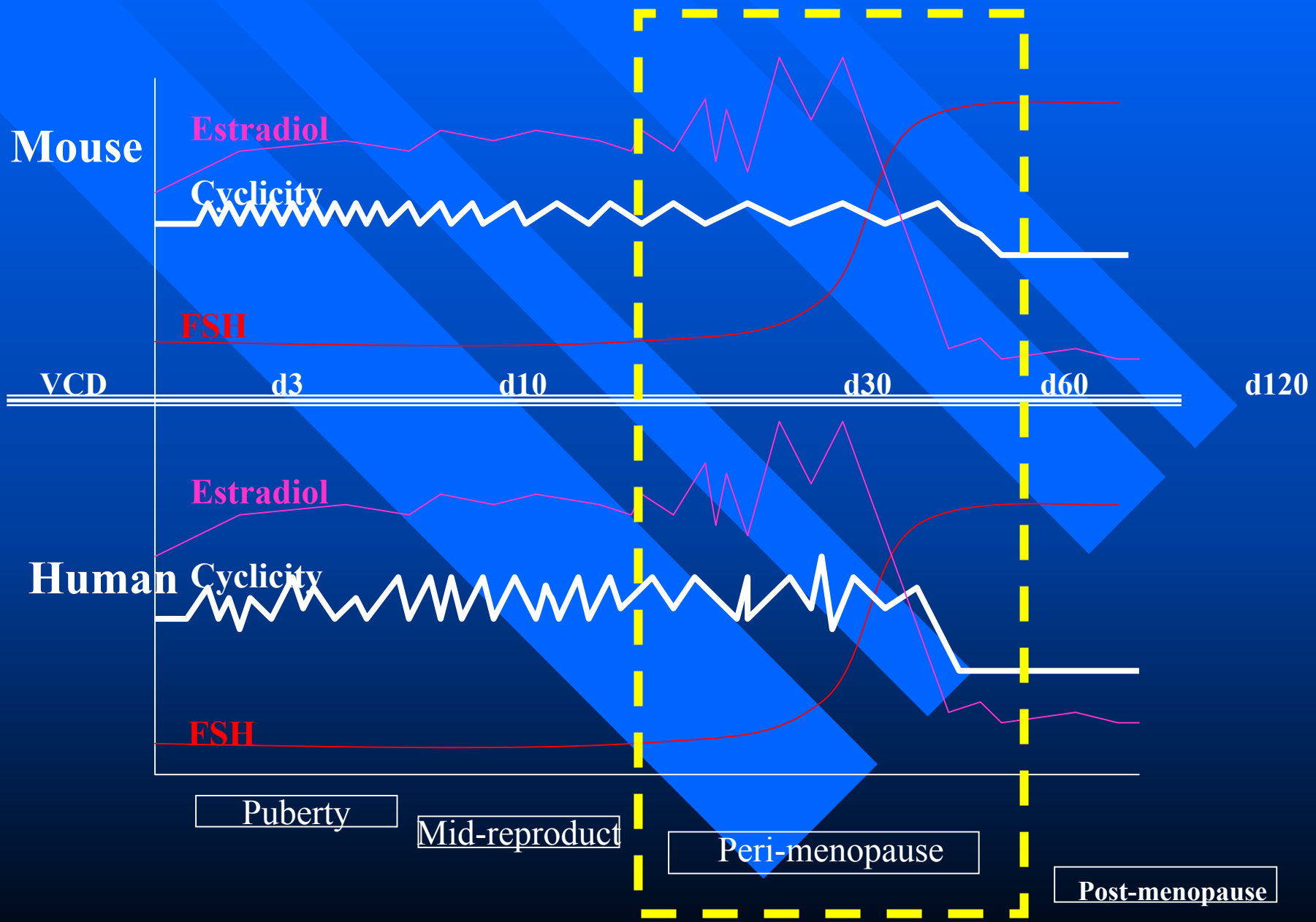
B6C3F1 Ovaries – d120

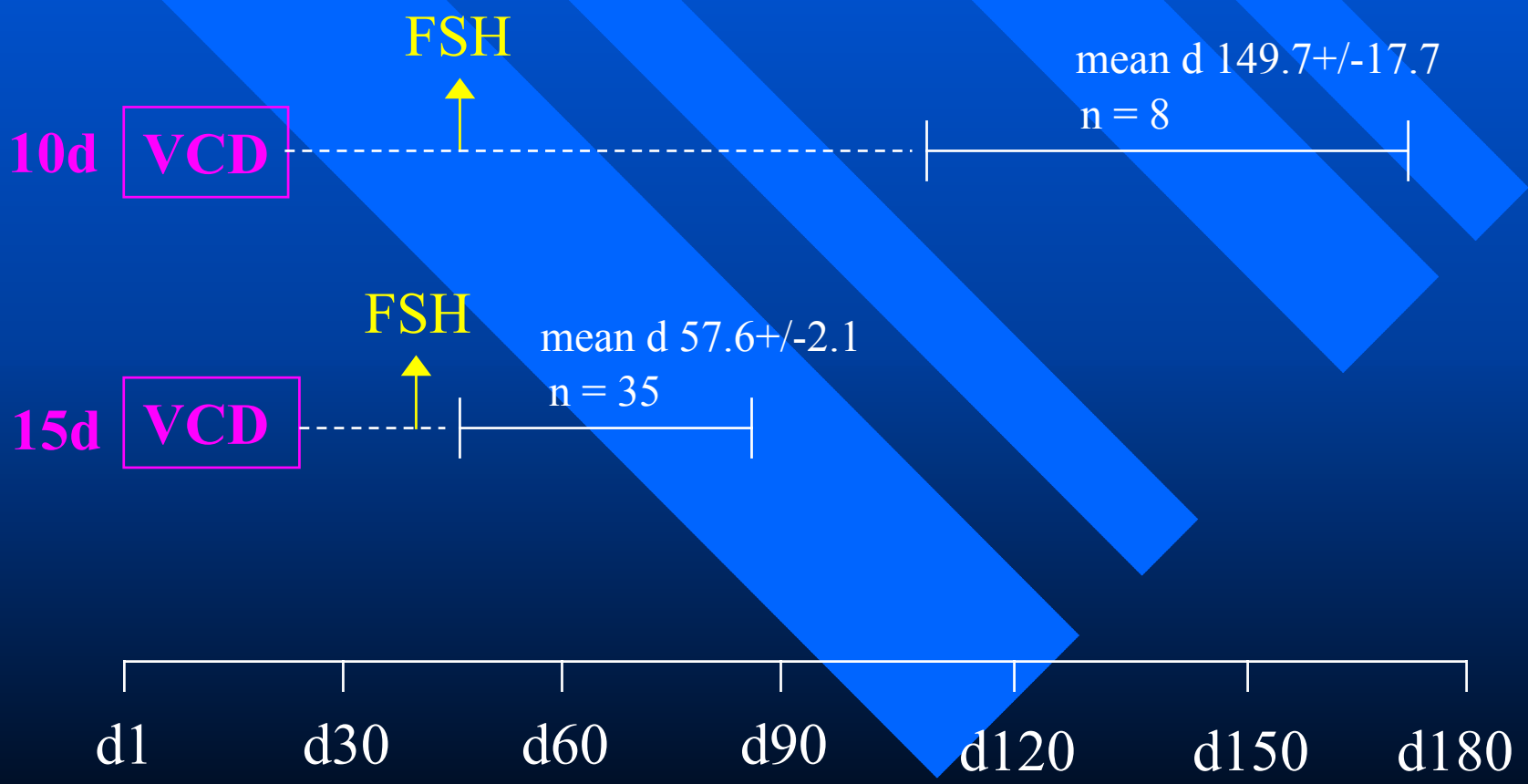


Control

VCD


Mouse
Estradiol
Cyclicity
FSH
VCD
d3
d10
d30
d60
d120
Human
Estradiol
Cyclicity
FSH
Puberty
Mid-reproduct
Peri-menopause
Post-menopause

Varying Time to Ovarian Failure
(Perimenopause Model)



VCD Model - Benefits

- Lends itself to:
  - Mice or Rats (other species?)
  - Induced in any age animal
  - Prior normal cyclicity established
  - Retains residual ovarian tissue (androgenic)
  - Adjusted times of impending ovarian failure (perimenopause) and complete failure (postmenopause)
  - Animals with normal or altered genotype

VCD Model - Drawbacks

- Individual animal variation for ovarian failure
- Longer to ovarian failure than ovex
- Possible chemical effects (none ever observed)

VCD Collaborations

- Cardiovascular Disease –
  - C. Banka, La Jolla Inst. Mol. Med.
- Osteoporosis –
  - J. Funk, Univ. of AZ
- Alzheimer's Disease –
  - C. Dyer, N. AZ. Univ.
  - M. Golub, Univ. Cal. – Davis
- Ovarian Cancer –
  - B. Vanderhyden, Univ. Ottowa
  - P. Devine, Quebec Univ.
  - J. Barton, Univ. AZ

References

- Danilovich N., Javeshghani, D., Xing, W., Sairam, M. 2002 Endocrine alterations and signaling changes associated with declining ovarian function and advanced biologicla aging in follicle-stimulating hormone receptor haploinsufficient mice. Biol. Reprod. 67:370-378.
- Danilovich, N., Roy, I., Sairam, M. 2002 Emergence of uterine pathology during accelerated biological aging in FSH receptor-haploinsufficient mice. Endocrinol. 143:3618-3627.
- Greenfeld, C., Tilli, M., Babus, J., Marion, S., Hoyer, P., Furth, P., Flaws, J. Deletion of bax results in increased follicular endowment in the mouse. Biol. Reprod. Suppl. 1 68:#1.
- Mayer, L., Devine, P., Dyer, C., Hoyer, P.B. 2004 The follicle-depleted mouse ovary produces androgen. Biol. Reprod. March 3, Epub ahead of print.
- Perez, G., Robles, R., Knudson, C., Flaws, J., Korsmeyer, J., Tilly, J. 1999 Prolongation of ovarian lifespan into advanced chronological age by Bax-deficiency. Nat. Genet. 21:200.
- Rucker, E., Dierisseau, P., Wagner, K., Garrett, L., Wynshaw-Boris, A., Flaws, J., Hennighausen, L. Bcl-x and Bax regulate mouse primordial germ cell survivial and apoptosis during embryogenesis. Mol. Endo. 14:1038-1052.