

The value of AMH in assessing ovarian function and damage in women with cancer

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Chemotherapy: immediate and late effects on the ovary

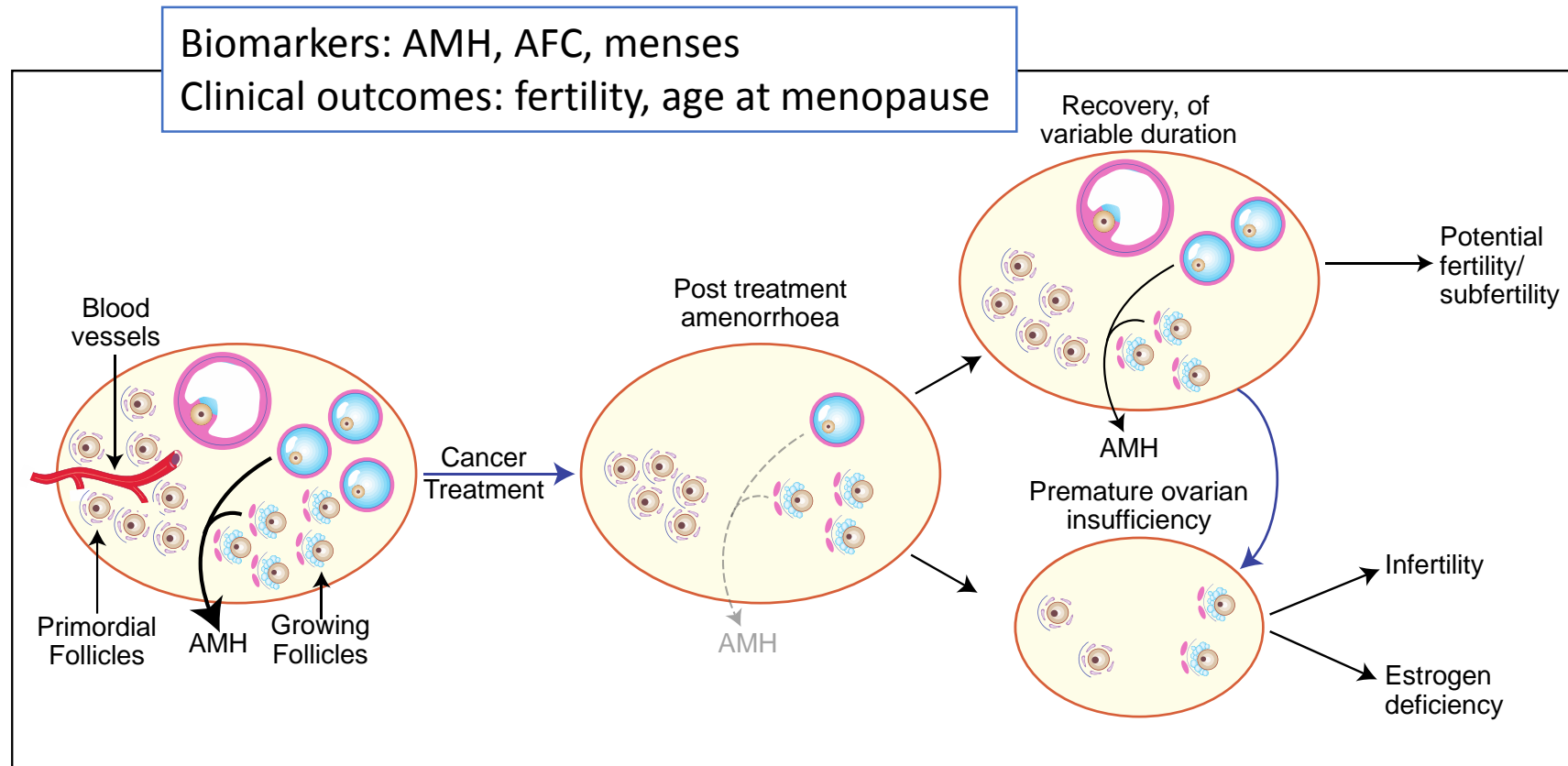
- Depletion of growing follicles

Himelstein-Braw R, Peters H and Faber M (1978)
Morphological study of the ovaries of leukaemic children.
Br J Cancer 38, 82-87

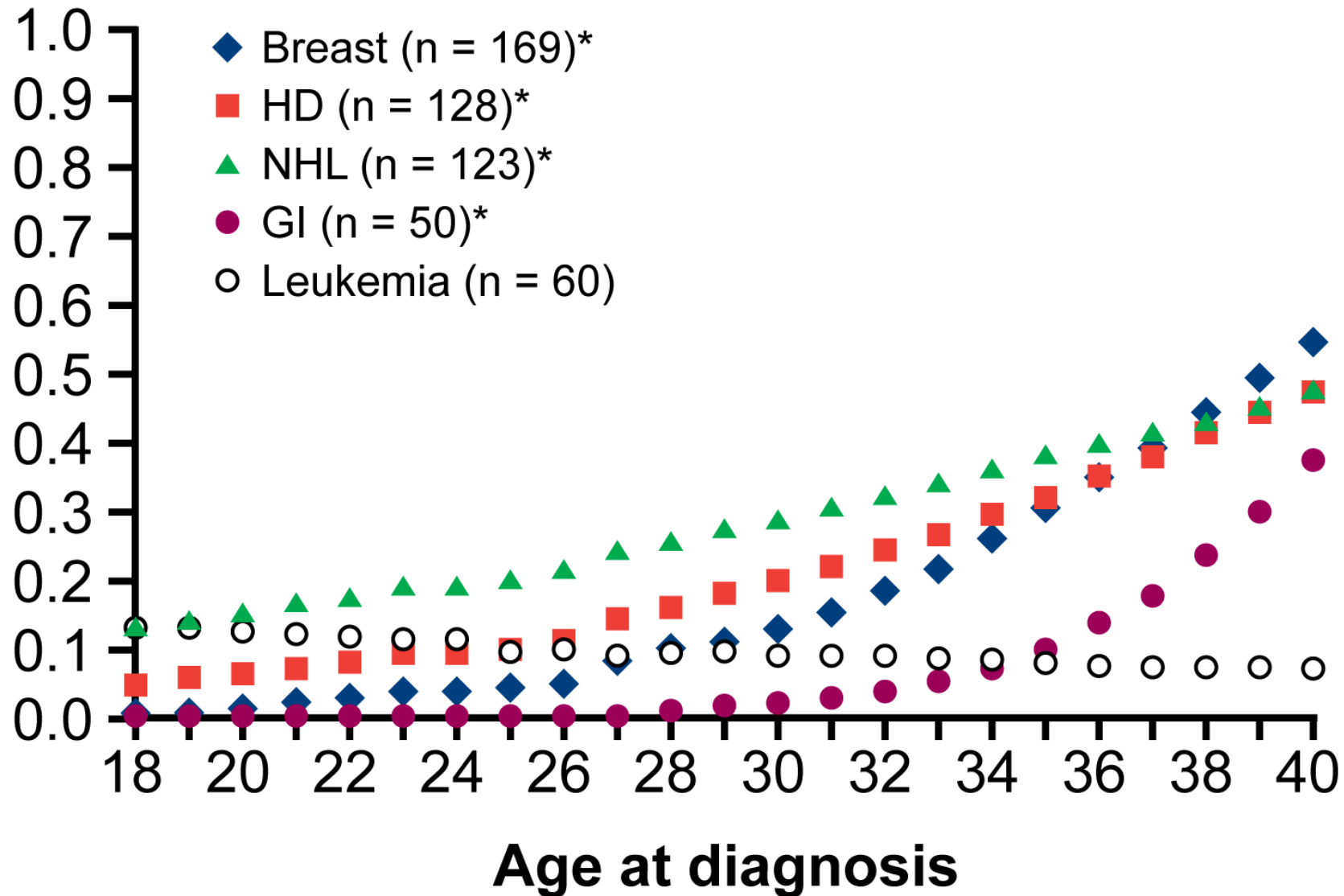
- Premature ovarian failure

Chapman RM, Sutcliffe SB and Malpas JS (1979)
Cytotoxic-induced ovarian failure in women with Hodgkin's disease.
I. Hormone function.
JAMA 242, 1877-1881

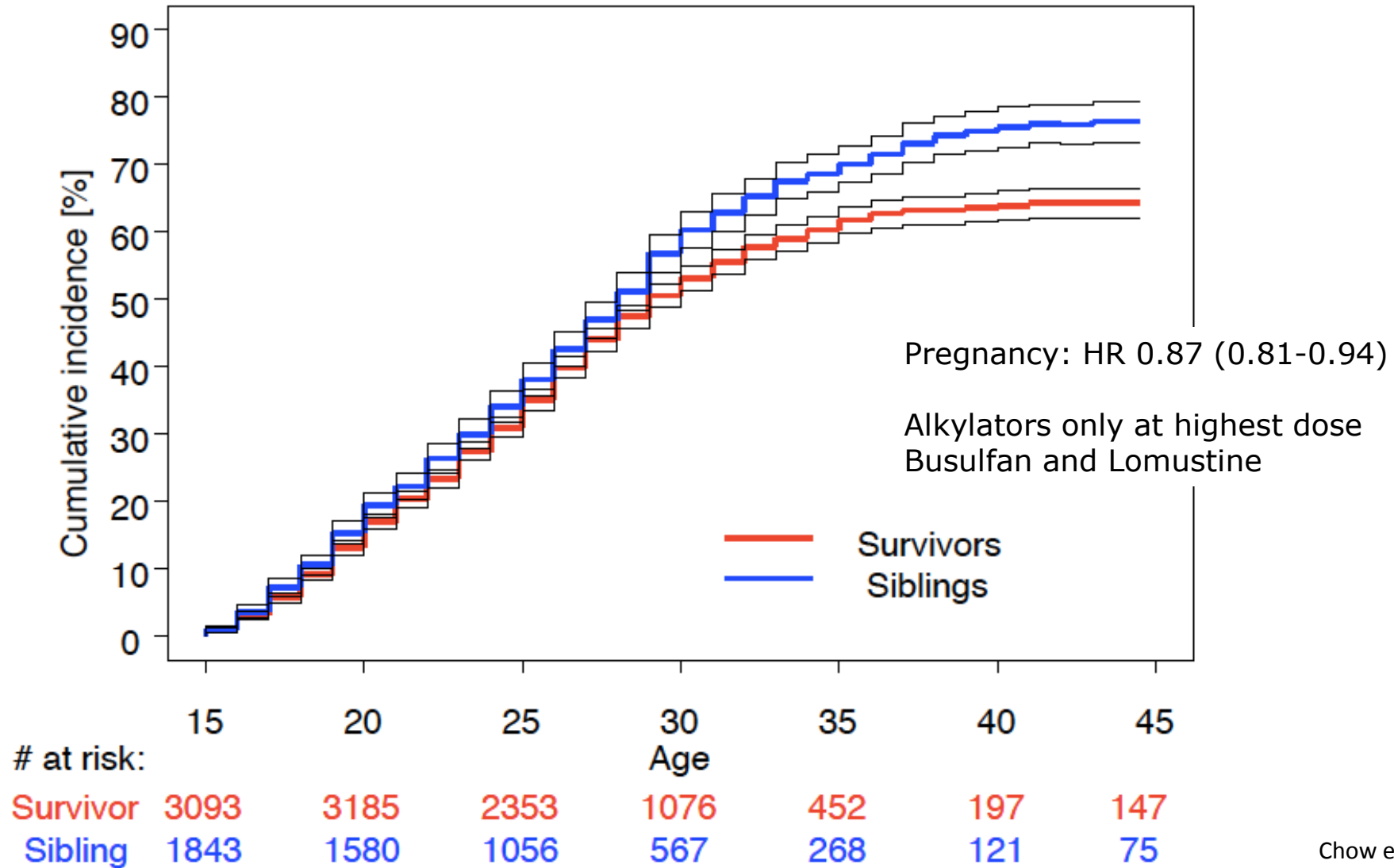
Effects of cancer therapy on the ovary



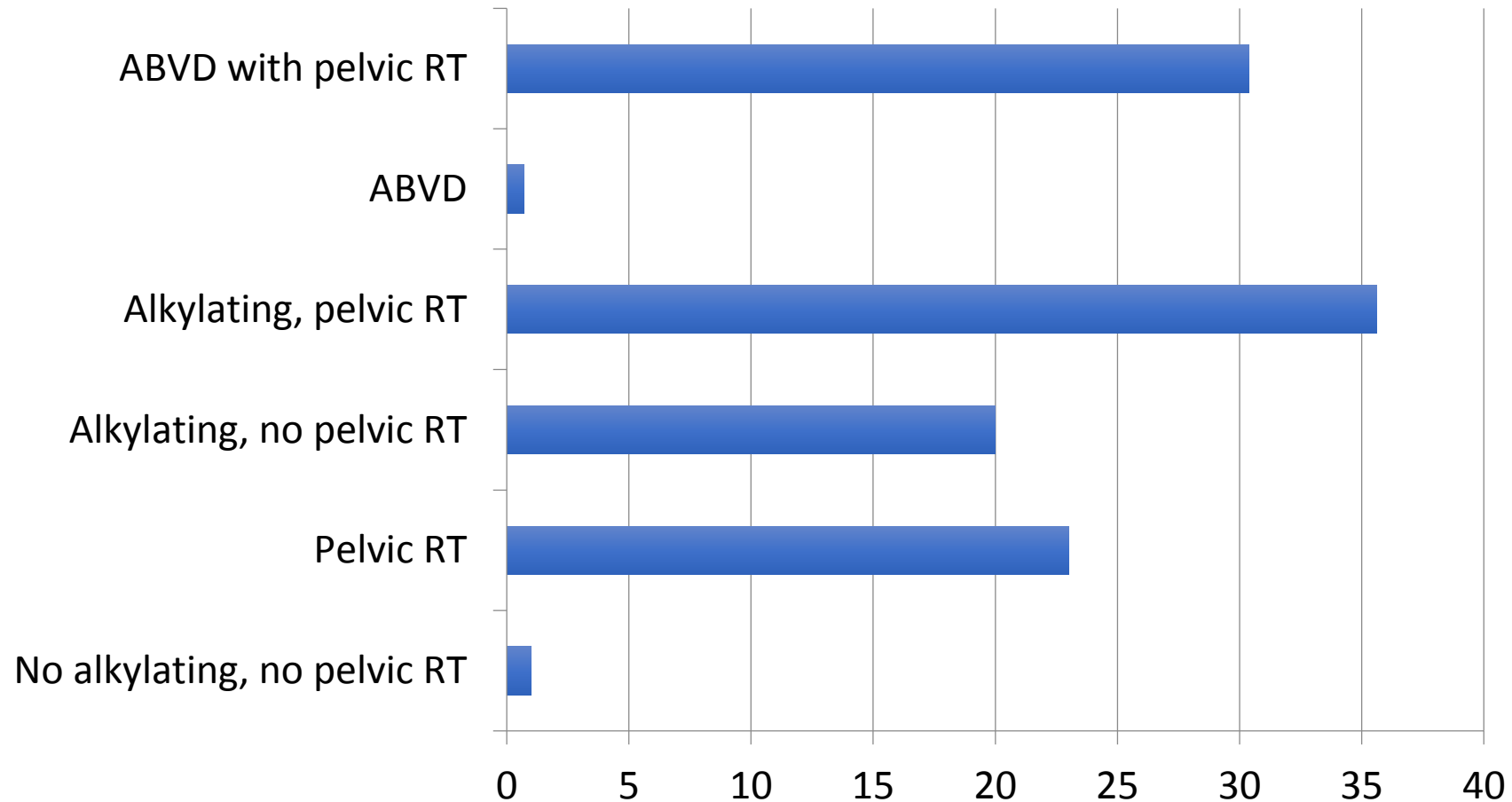
Acute ovarian failure after chemotherapy



Live birth to female childhood cancer survivors: chemo only

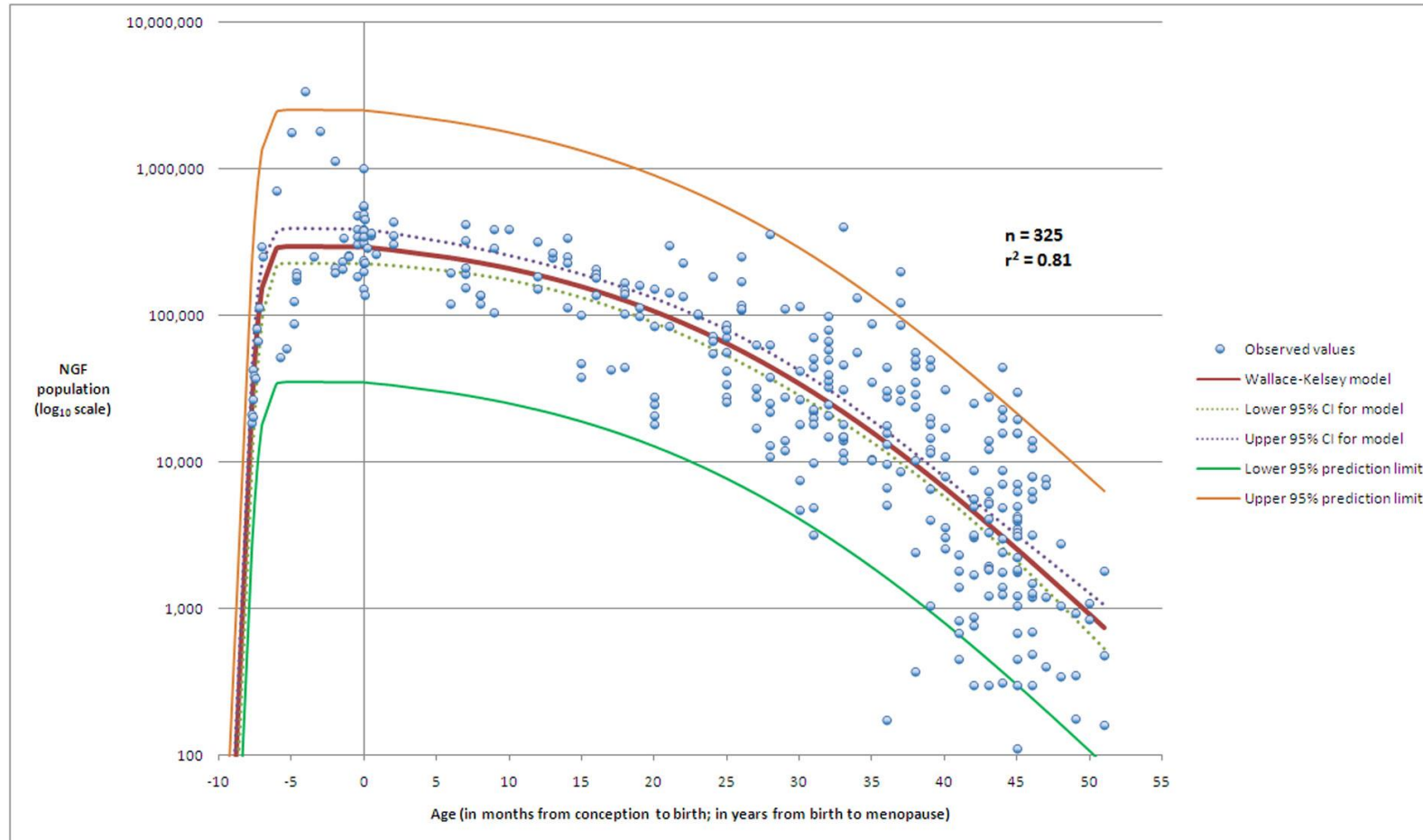


Hazard ratio for menopause <40 yrs in Hodgkin Lymphoma

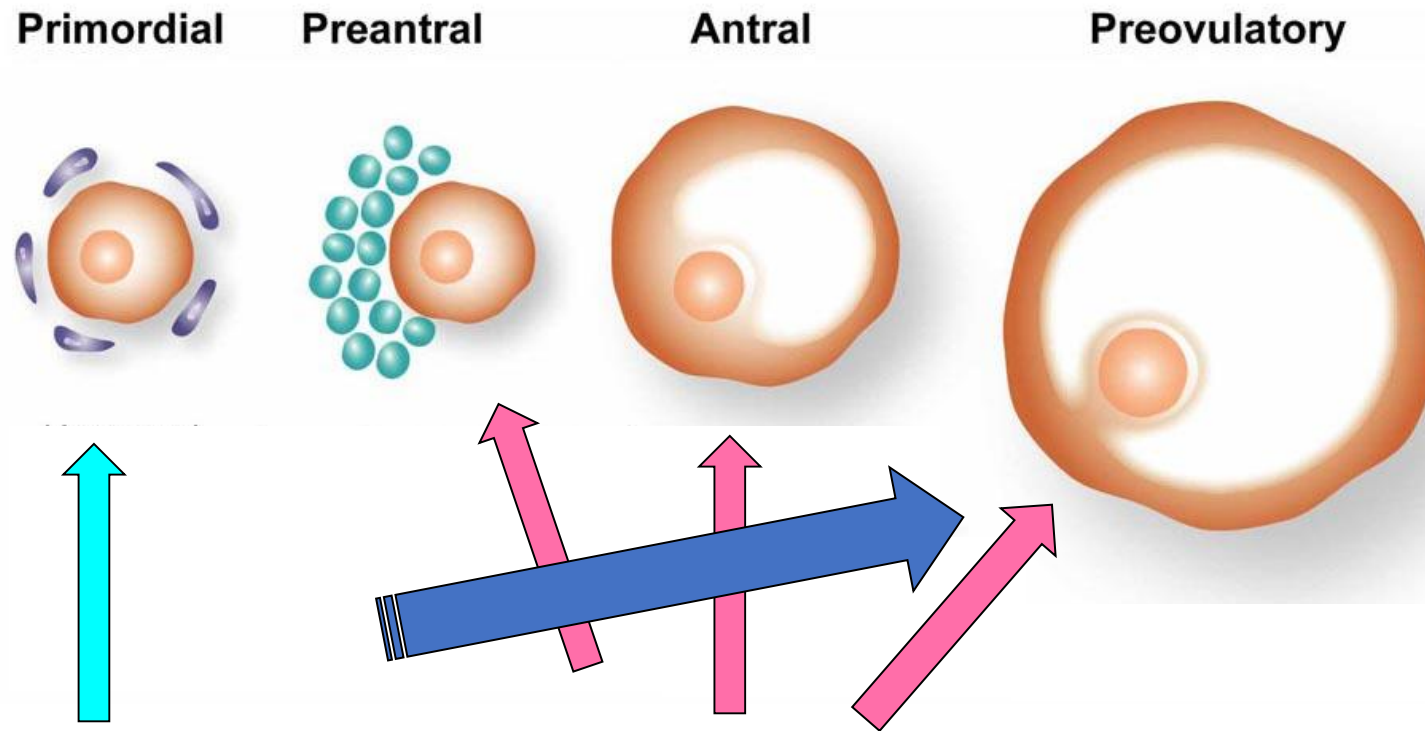


All adjusted for age, overall n=2127 (though data only from 50%)

Age-related changes in the ovarian reserve

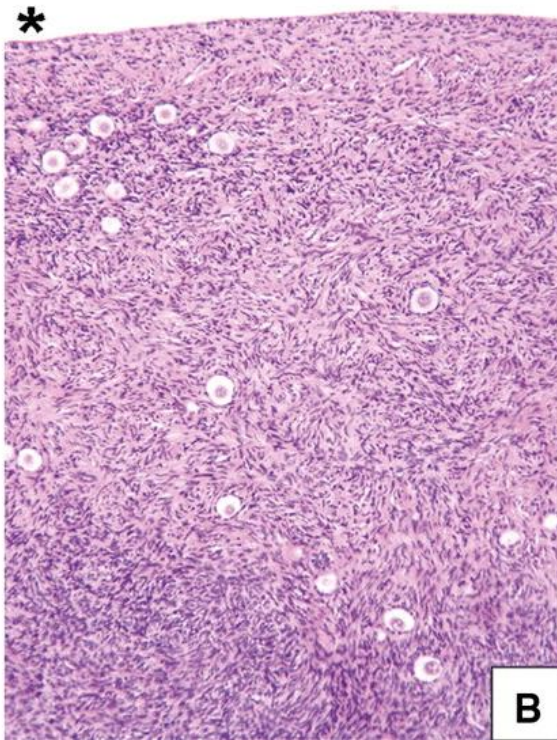


Which stages of follicle growth are key targets of cancer therapies?

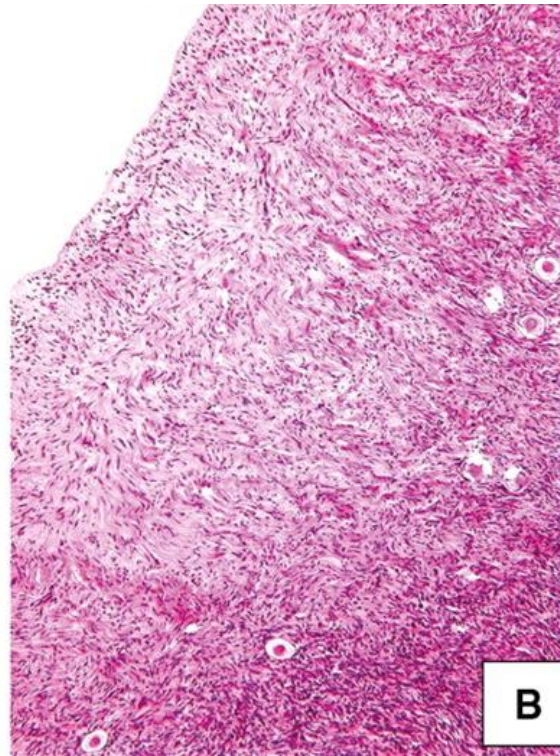


Loss of growing follicles may increase growth activation?

The ovarian stroma and vasculature are also targets

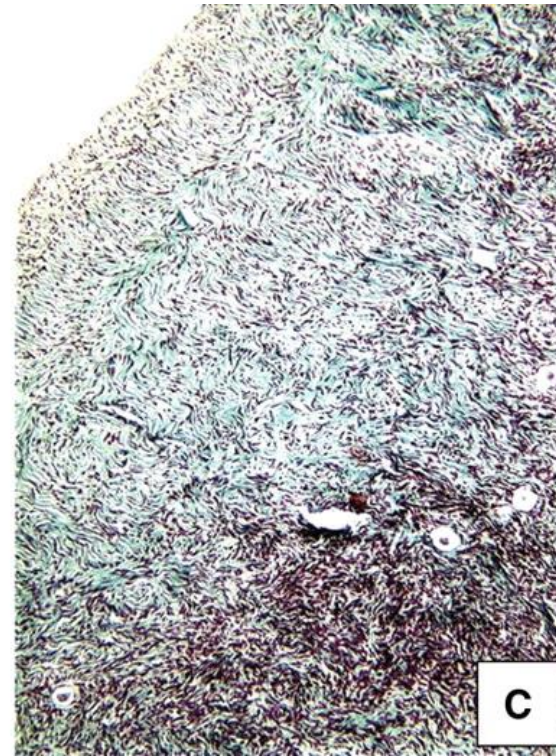


Normal control

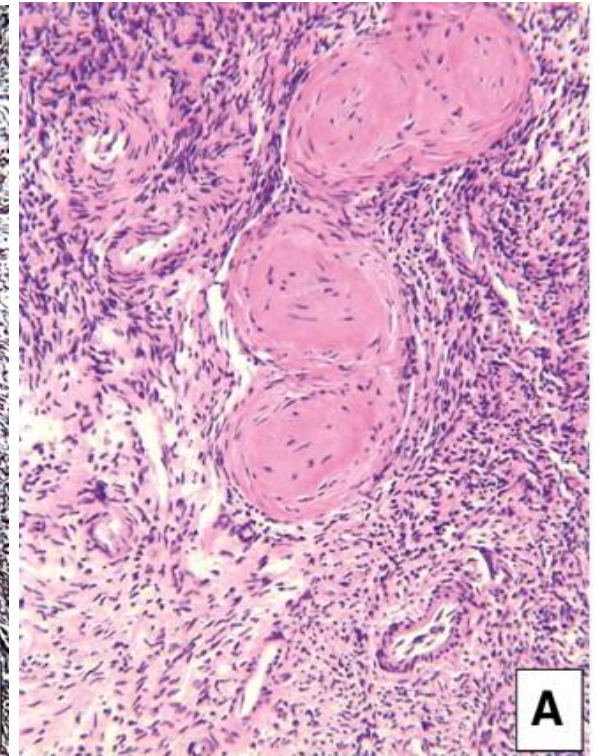


After chemotherapy

Focal cortical fibrosis in ovaries
exposed to chemotherapy

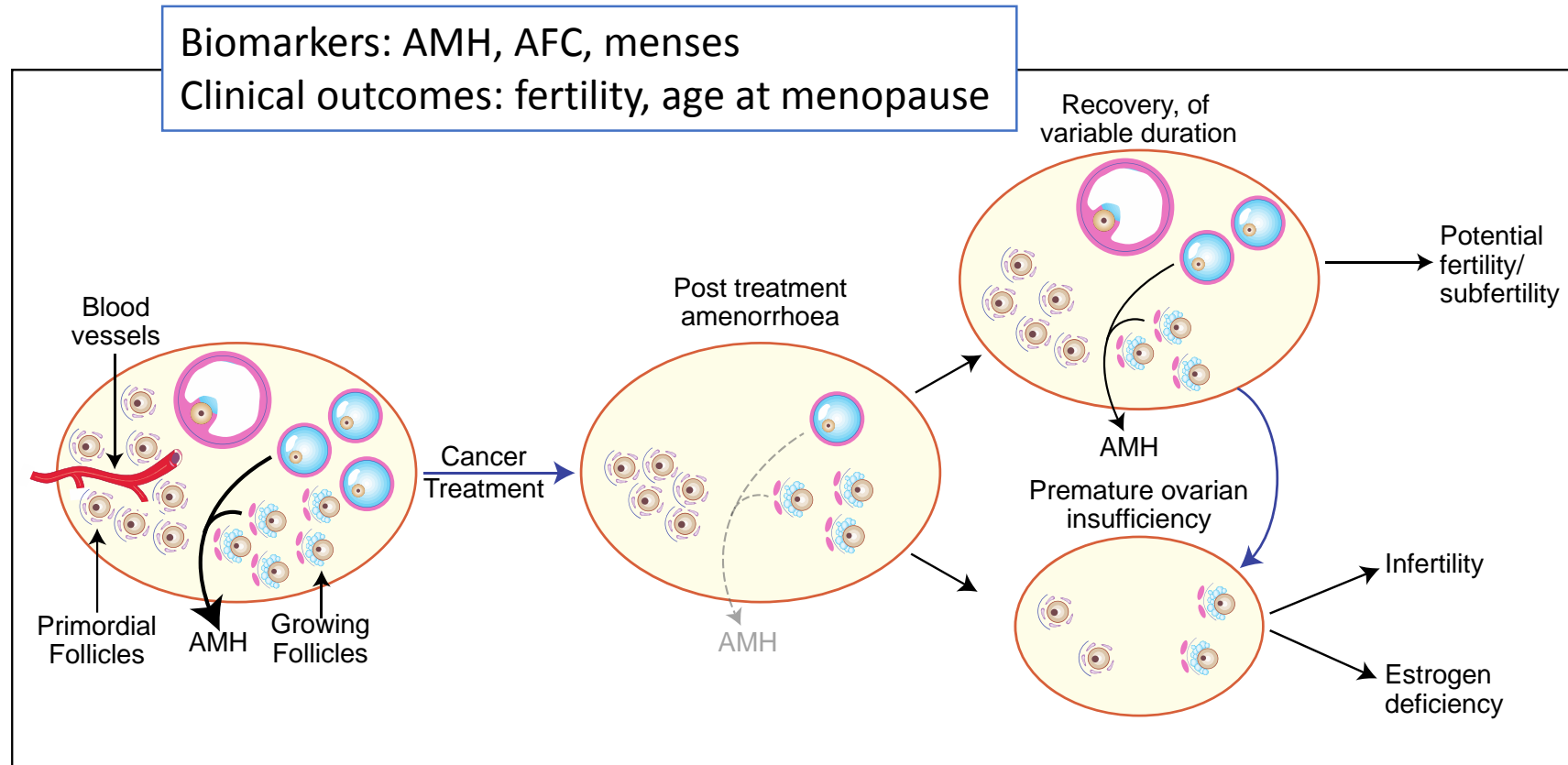


Green: Masson stain for collagen

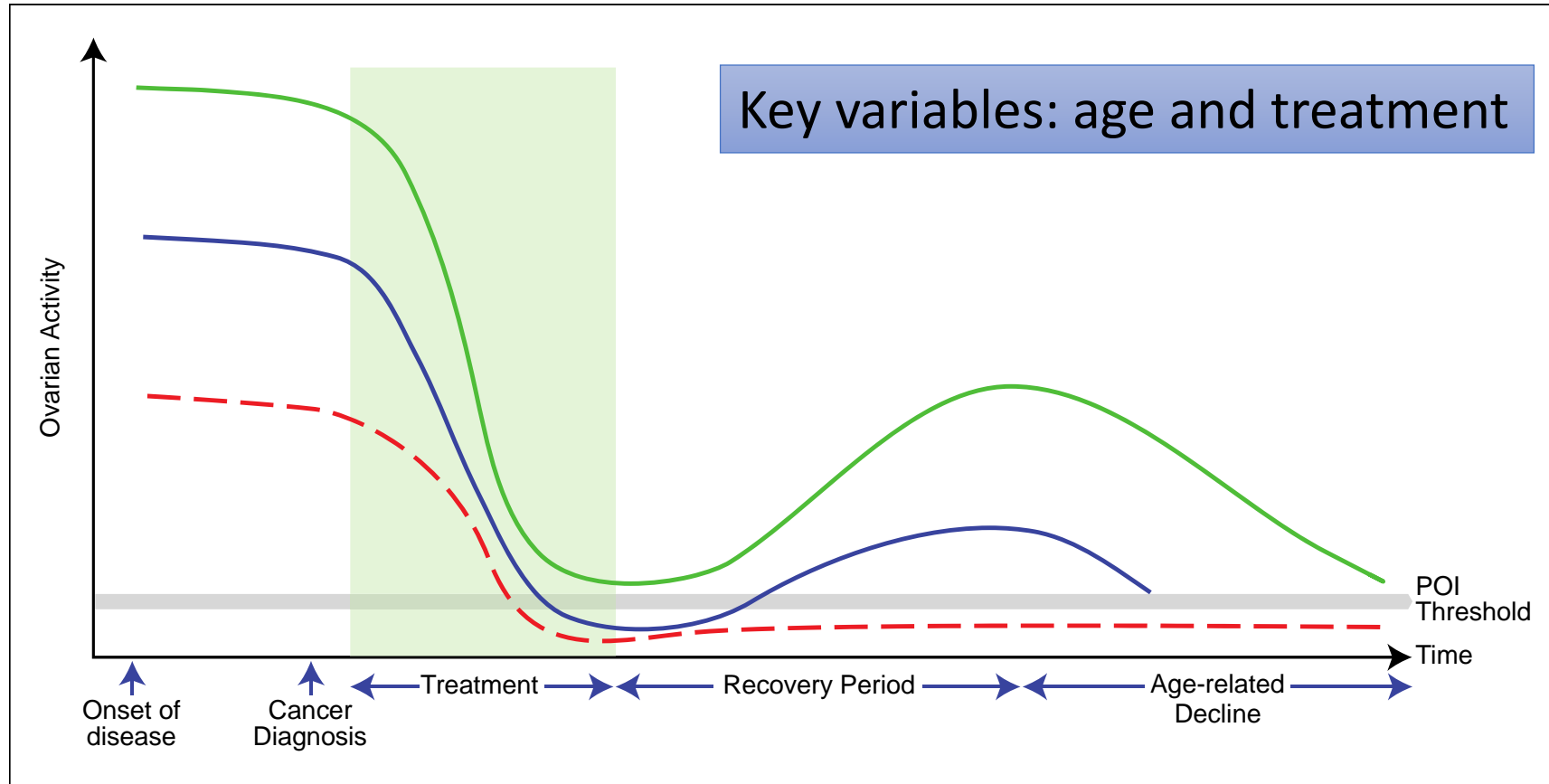


Prominent thickening and
hyalinization, with narrowing
/obliteration of the lumen

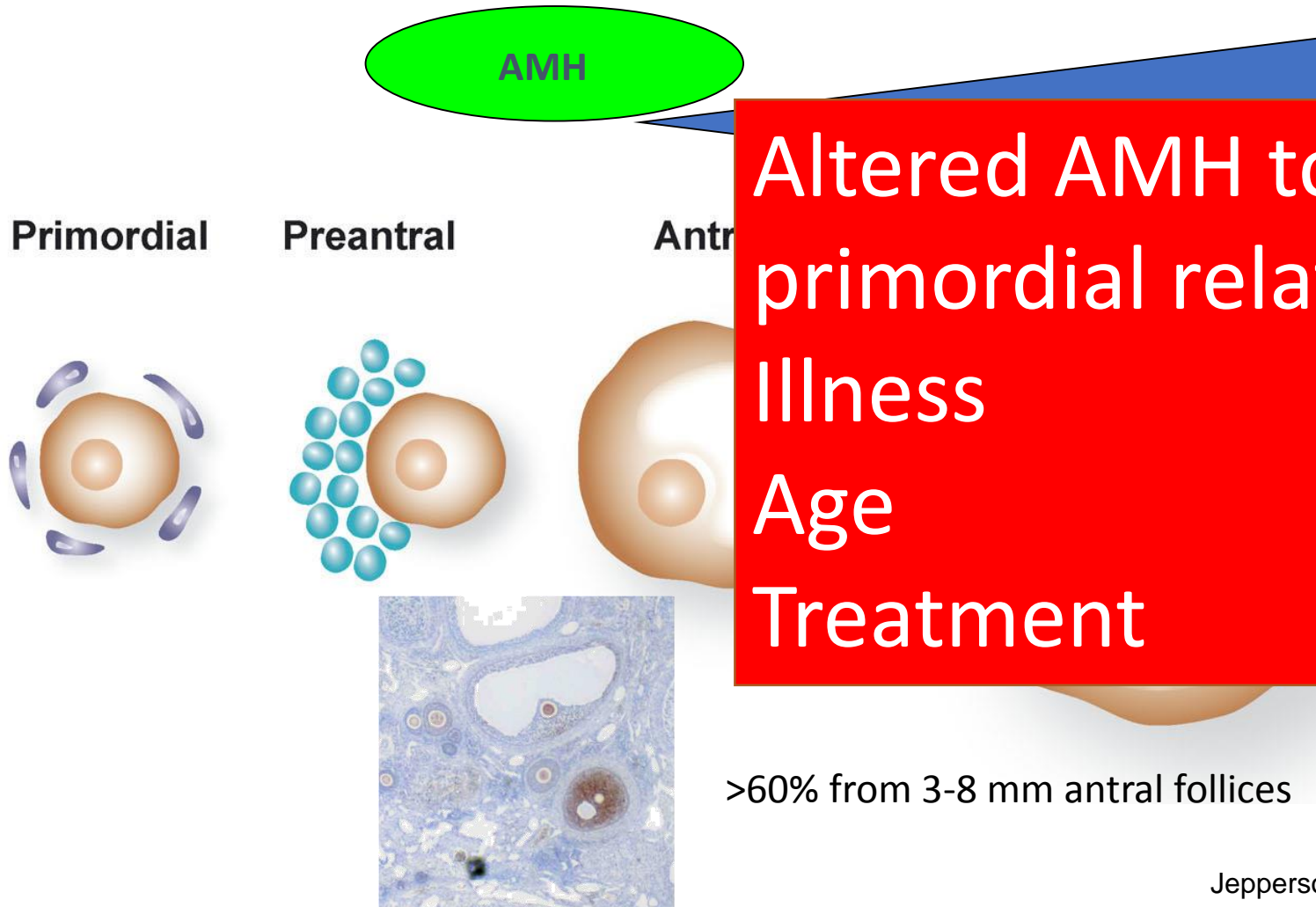
Effects of cancer therapy on the ovary



The variability in ovarian activity after cancer treatment

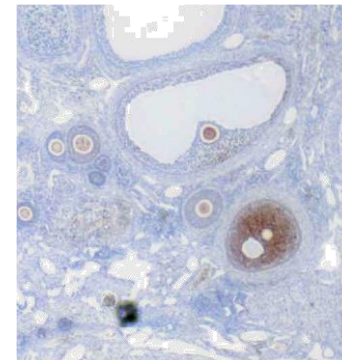
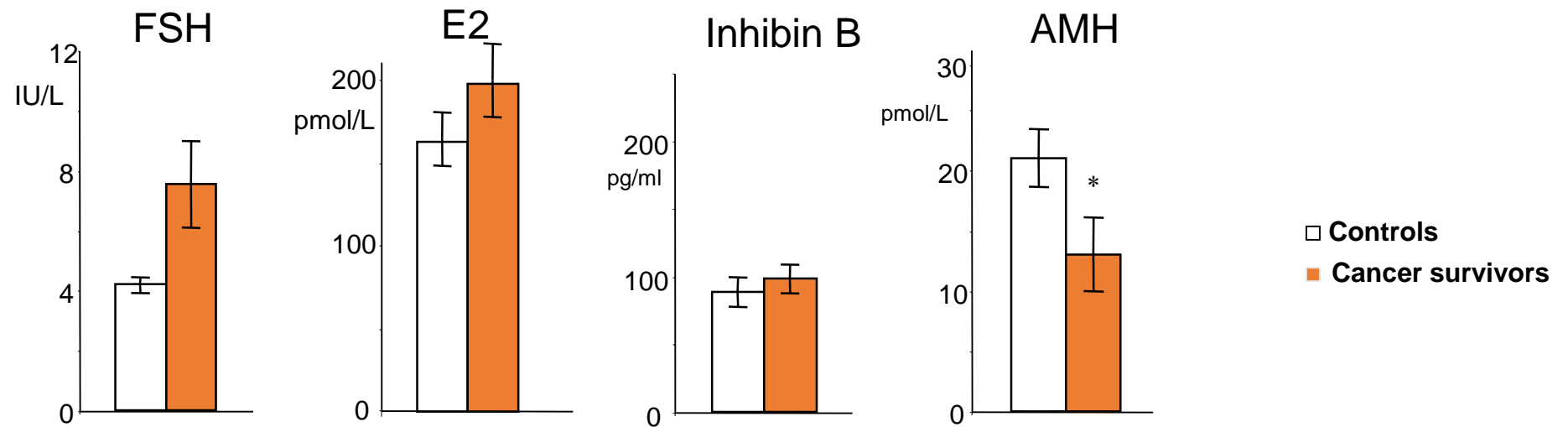


AMH reflects the number of small growing follicles

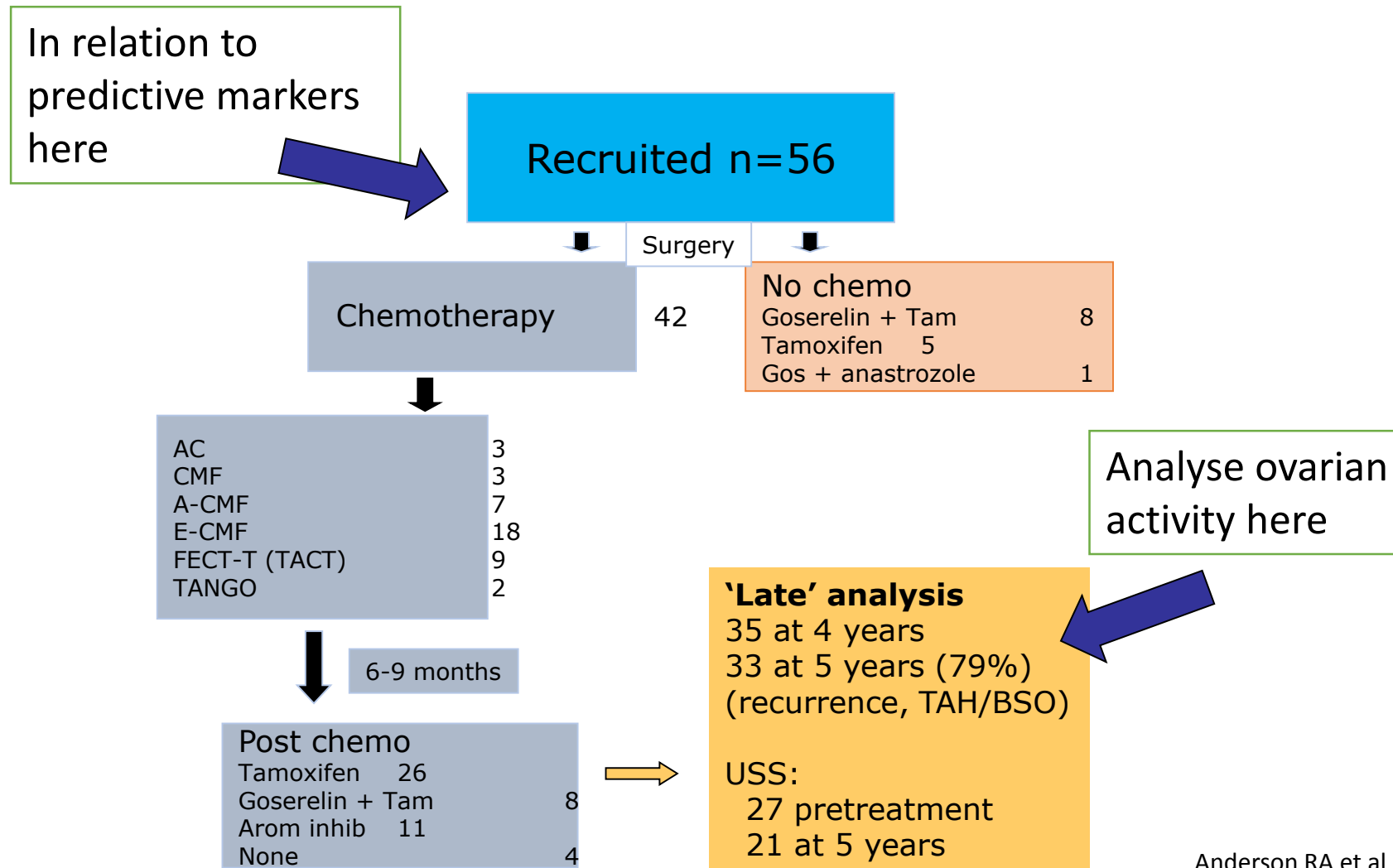


>60% from 3-8 mm antral follicles

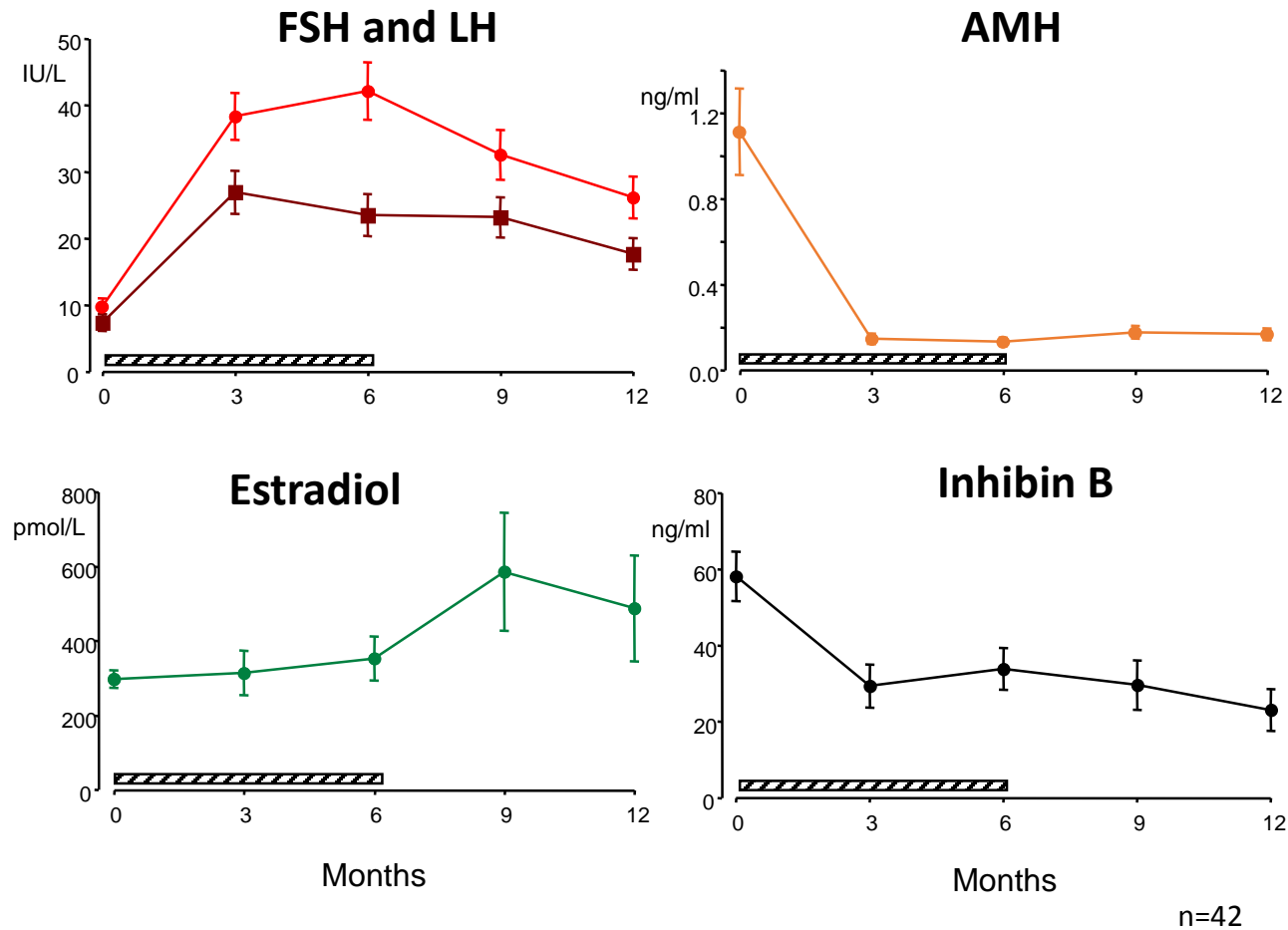
AMH reveals ovarian damage in childhood cancer survivors despite regular cycles



Effect of chemotherapy in eBC: acute toxicity and long-term prediction

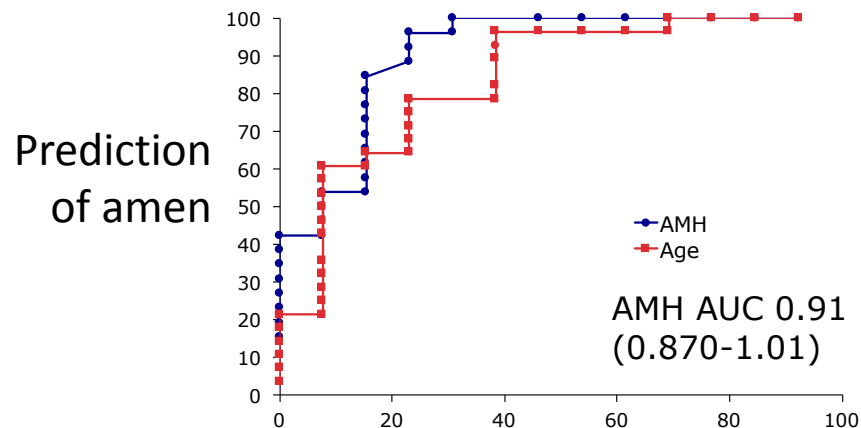
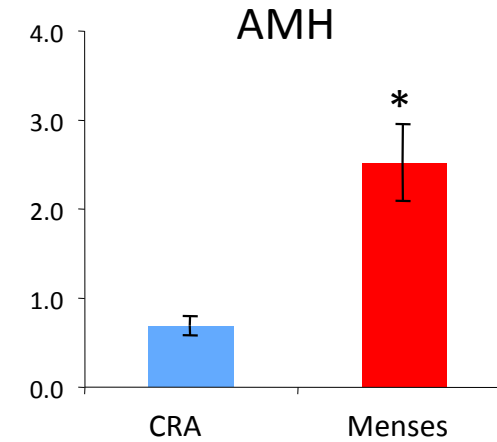
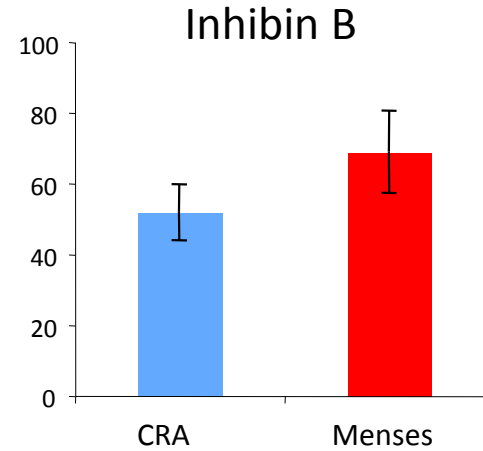
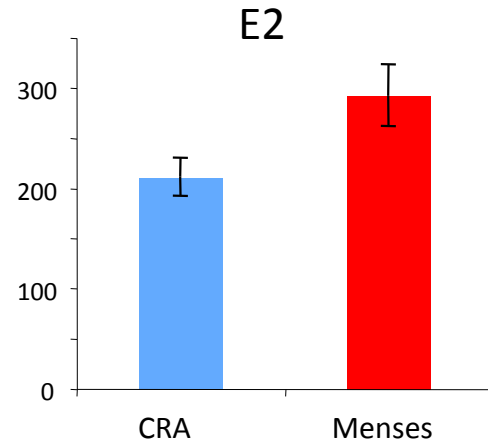


Effect of chemotherapy in eBC: acute toxicity



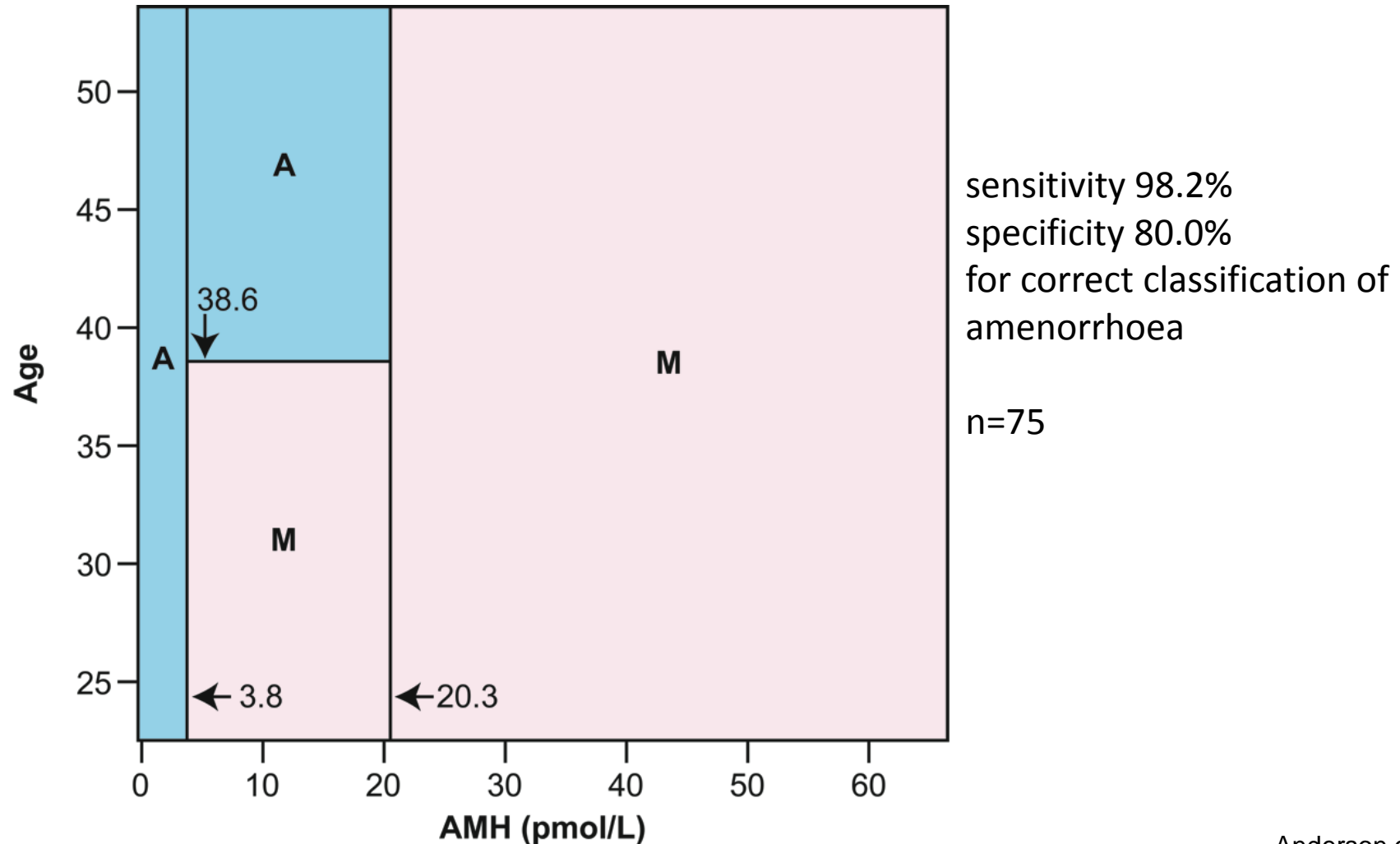
Effect of chemotherapy in eBC: long-term prediction

Pretreatment
hormones vs late
ovarian function

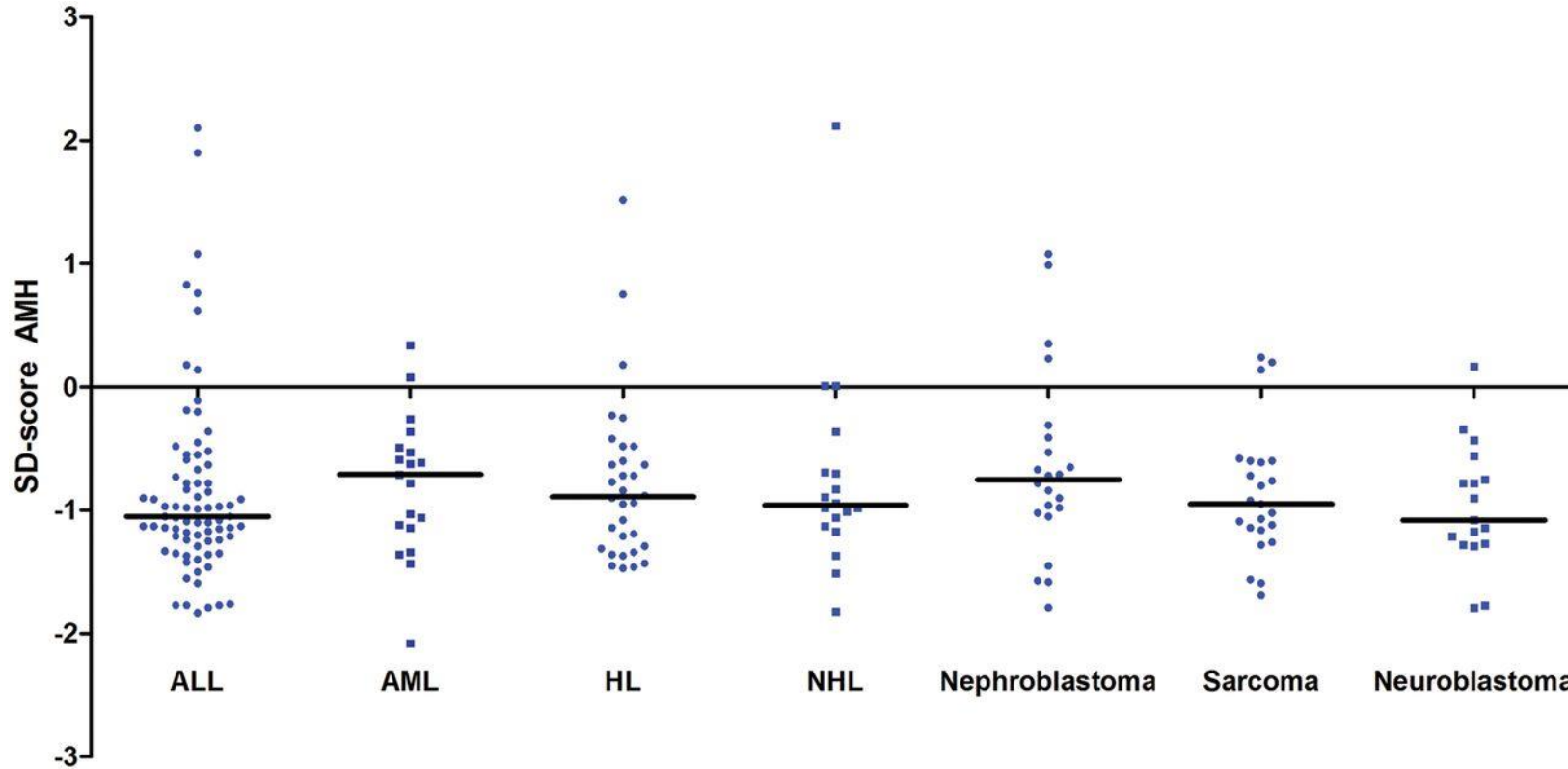


AMH at diagnosis of early breast cancer is higher in those women who will still be having menses 5 years later

Clinical application: predictive mosaic chart in eBC



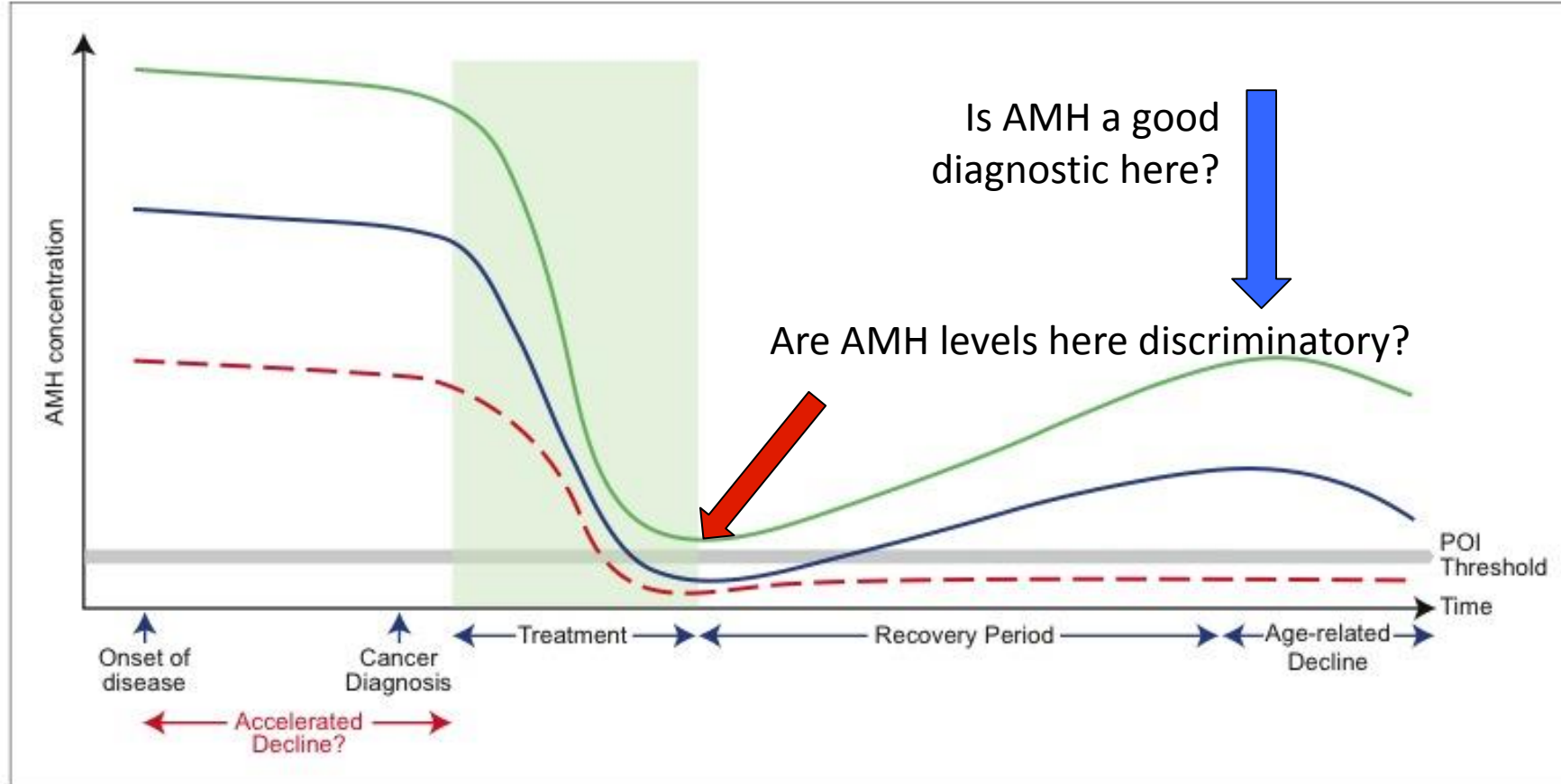
Pretreatment AMH is reduced in girls with childhood cancer



n=208

Temperature and CRP inversely correlated with AMH
Hb positively correlated

AMH profiles after chemotherapy



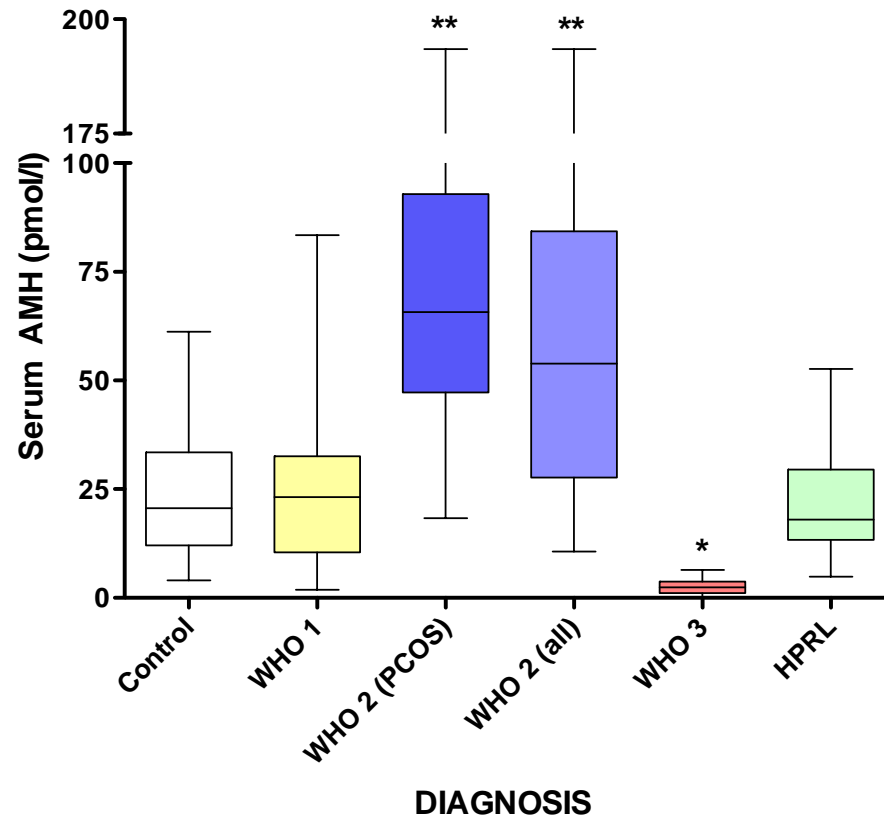
ORIGINAL ARTICLE

GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial

R. C. F. Leonard^{1*}, D. J. A. Adamson², G. Bertelli³, J. Mansi⁴, A. Yellowlees⁵, J. Dunlop⁶, G. A. Thomas¹, R. E. Coleman⁷ & R. A. Anderson⁸, for the Anglo Celtic Collaborative Oncology Group and National Cancer Research Institute Trialists

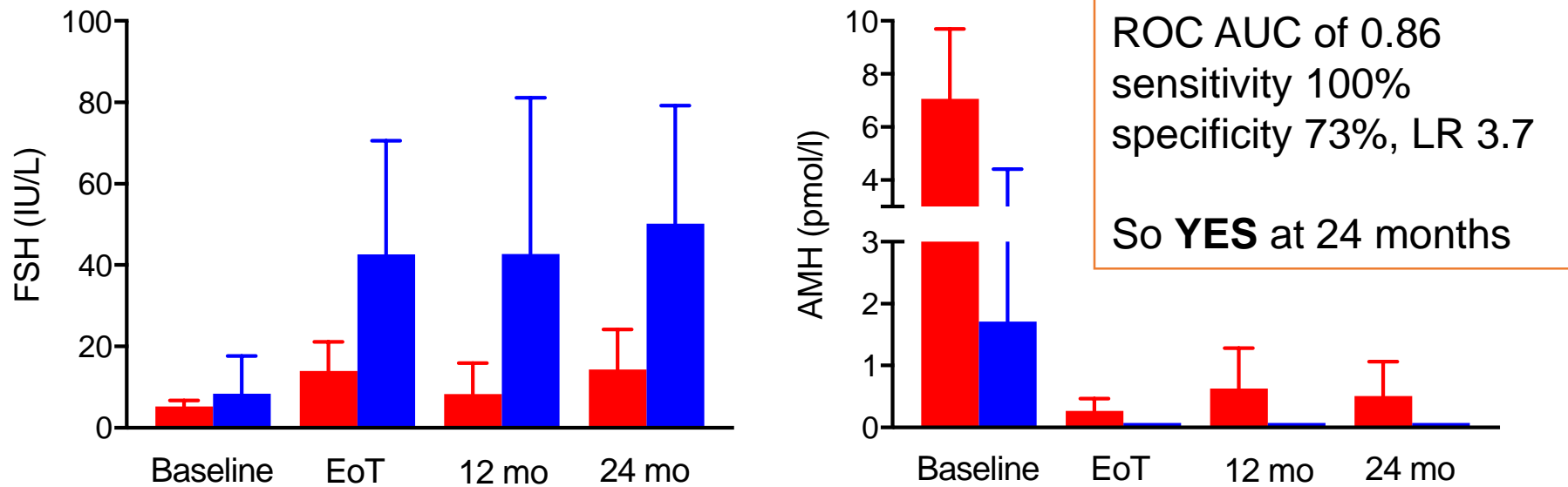
227 women with breast cancer, randomised to \pm goserelin during chemotherapy

AMH as a diagnostic test in POI?



- Not part of the diagnosis at present
- Will increased assay sensitivity help?
- Useful in 'fluctuant' stage of condition when E2 and FSH very variable?
- But value post chemo excluded in STRAW+10

Can AMH diagnose POI after chemo?



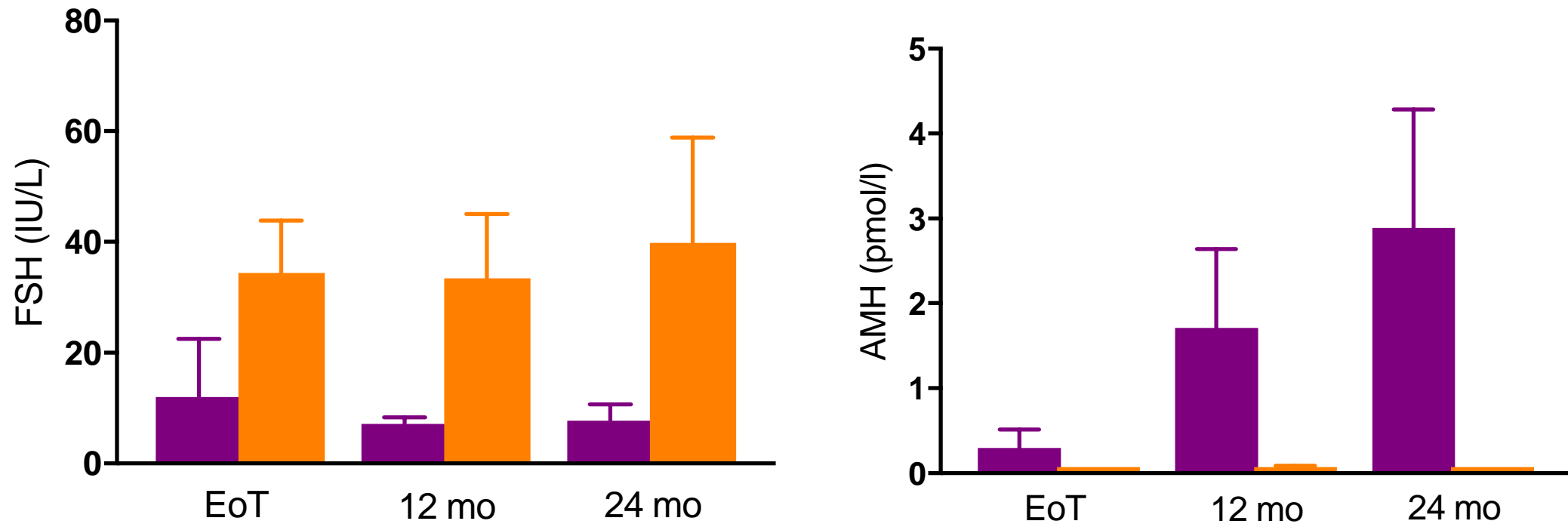
Serum FSH and AMH by POI at 24 months. Data from all women from OPTION
Roche automated AMH assay

Red, not POI

Blue: POI (amenorrhoea plus FSH >25IU/L).

N=96 and 28 respectively; median \pm 95% confidence intervals.

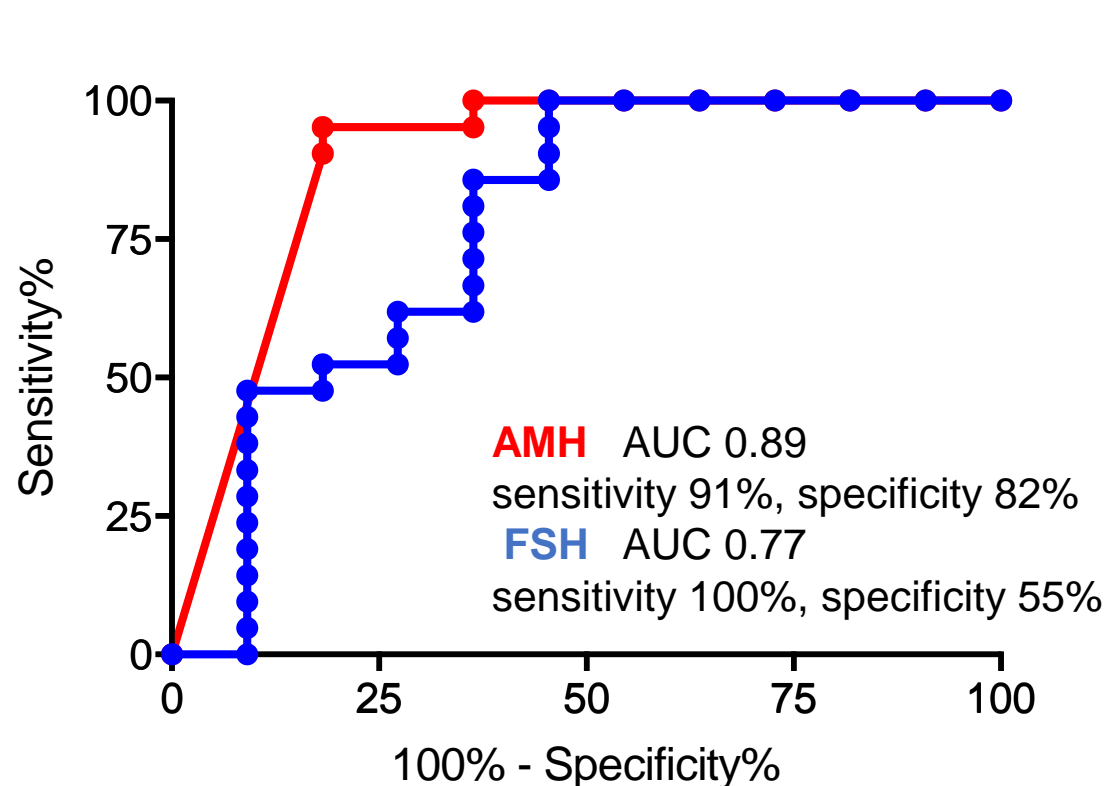
Importance of age for recovery of ovarian function after chemotherapy



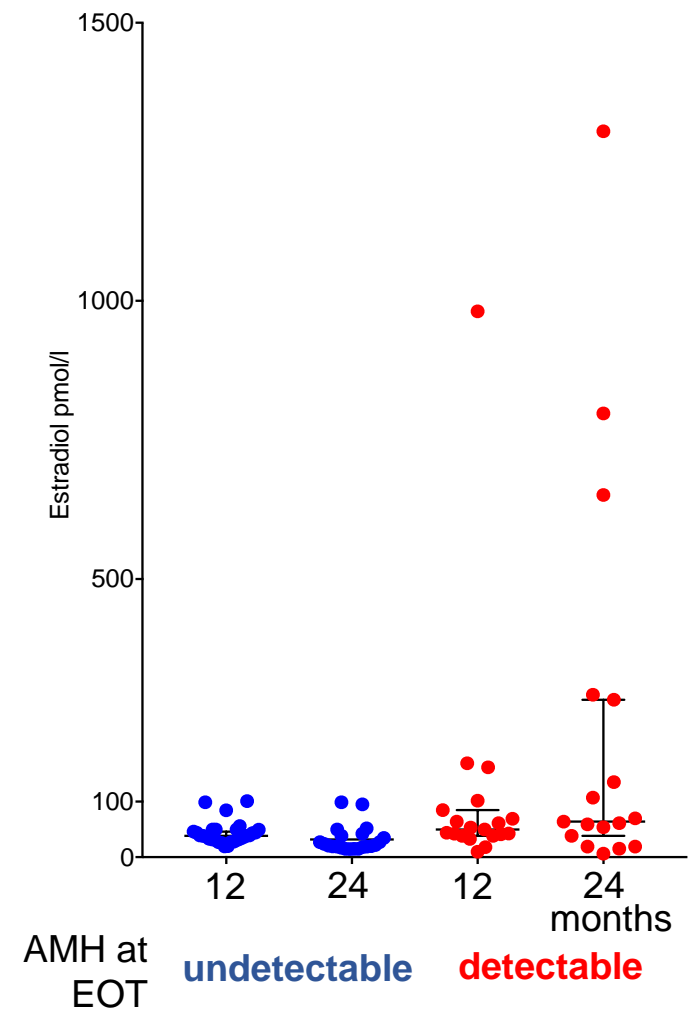
Data from
OPTION trial

Women aged ≤ 40 (purple) vs >40 years (orange)
 $n=62$ and 81 , median \pm 95% CI.

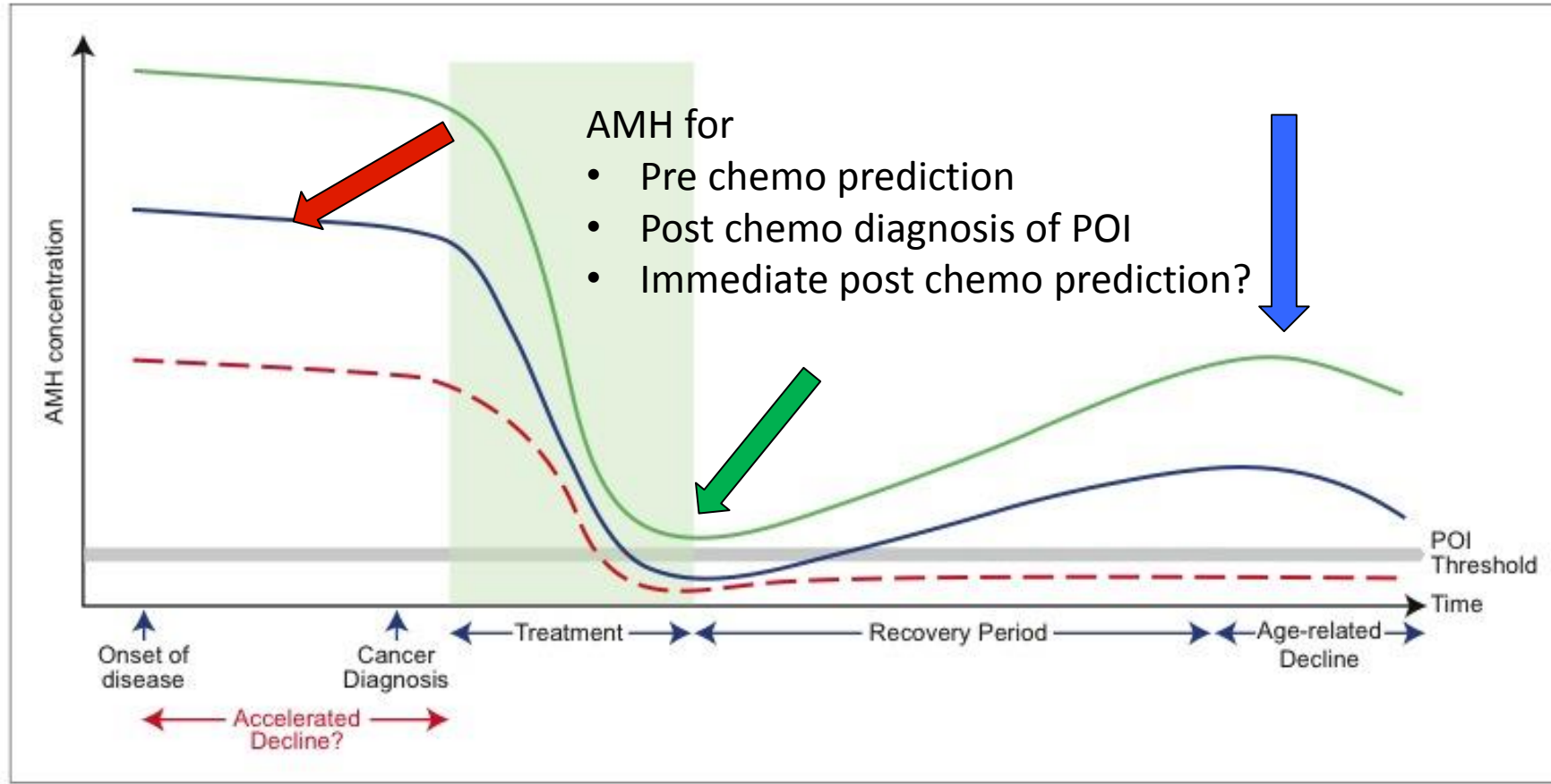
EOT predictive analysis in women >40 yrs



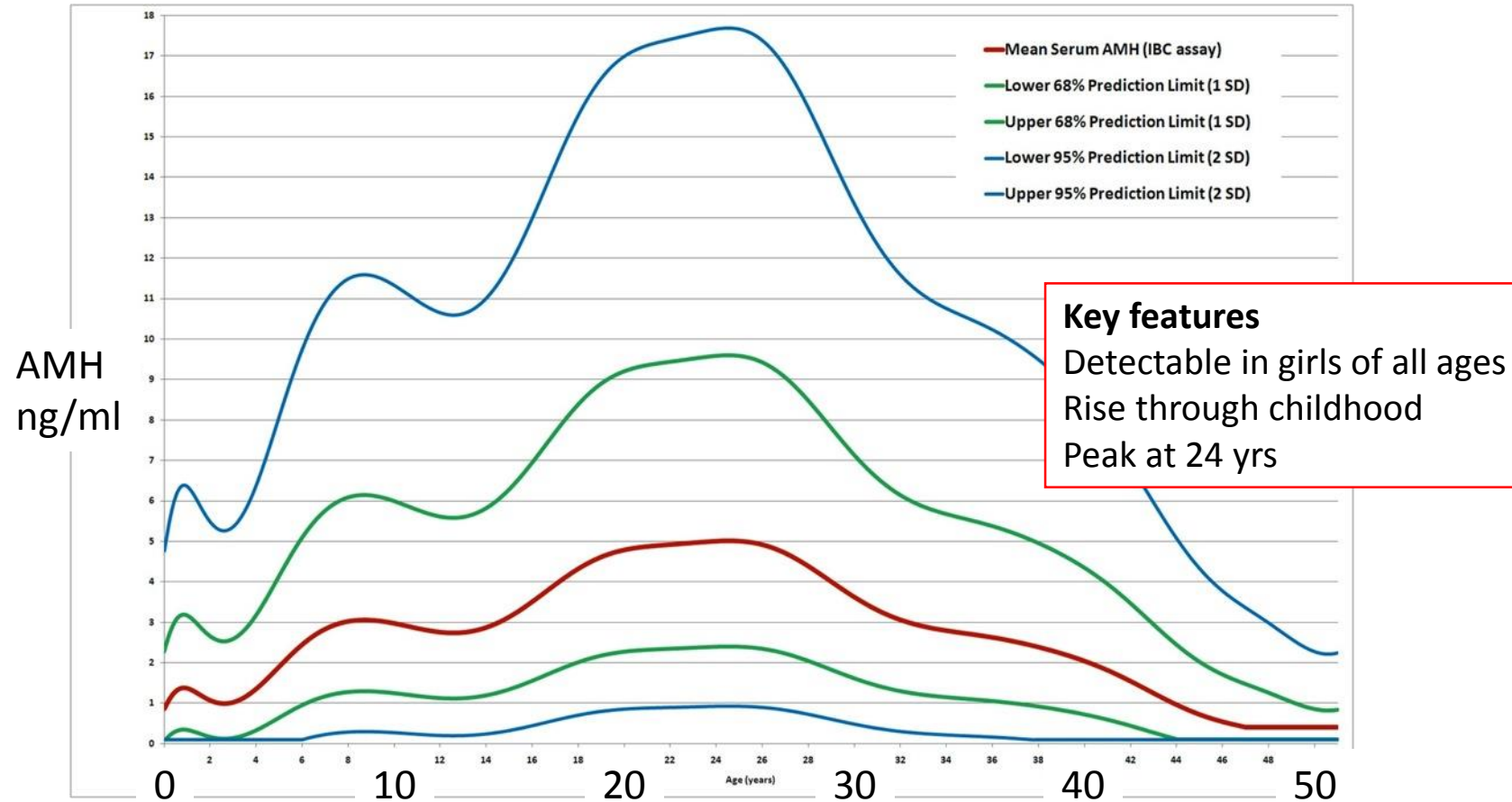
AMH and **FSH** at end of treatment for prediction of POI at 24 months
OPTION control group, n=32



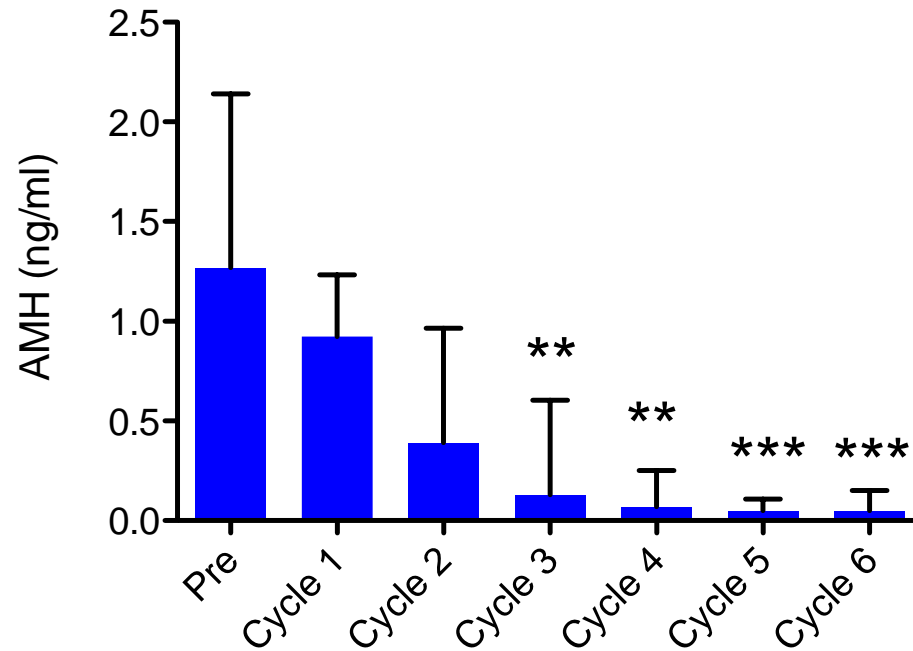
AMH and ovarian function after chemotherapy



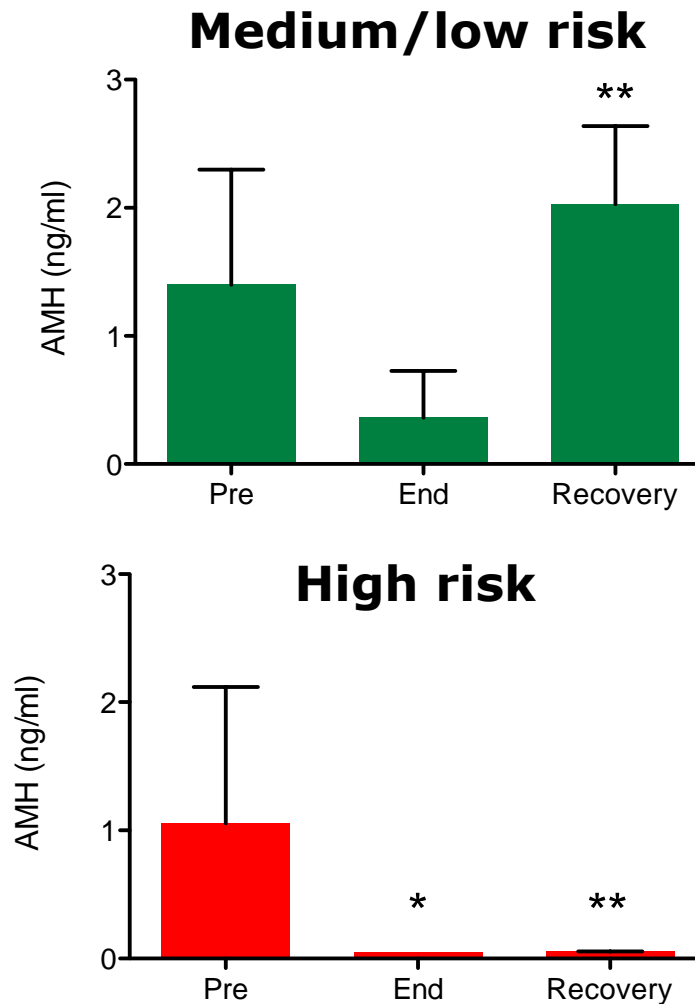
The AMH normal range from birth to menopause



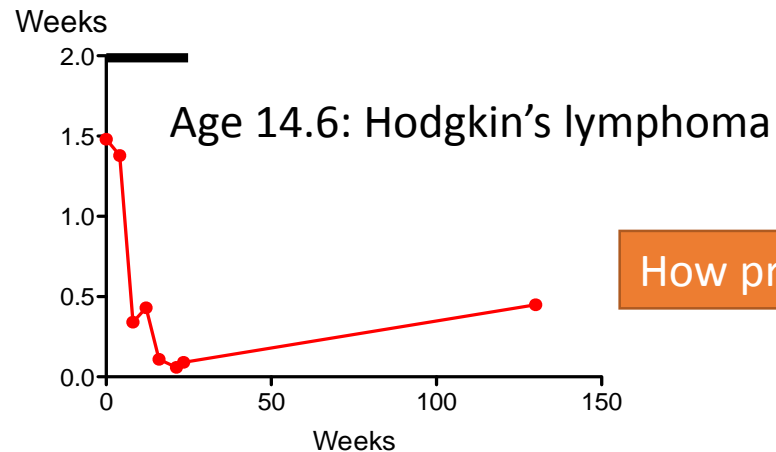
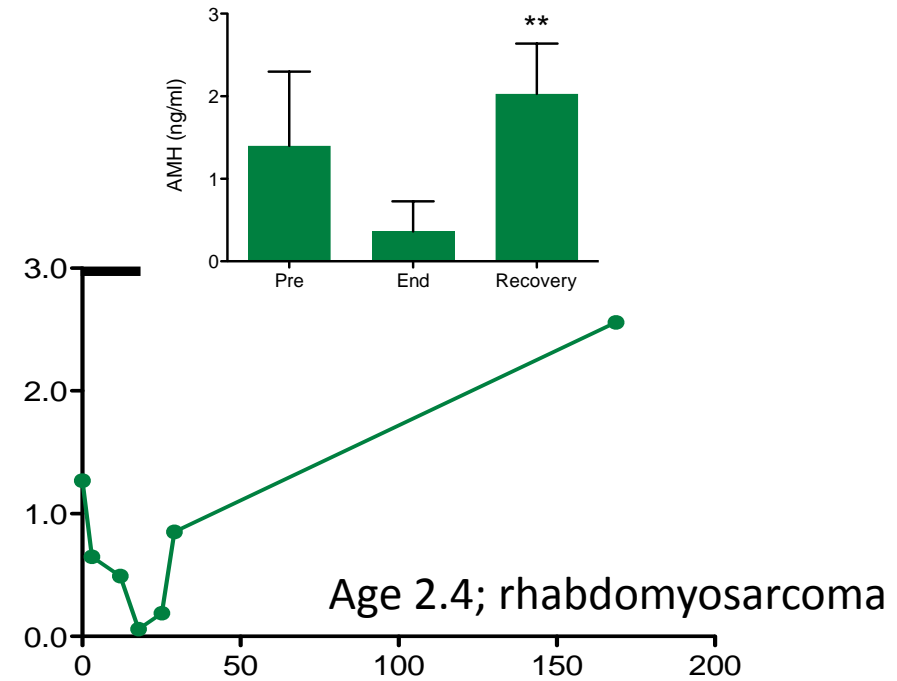
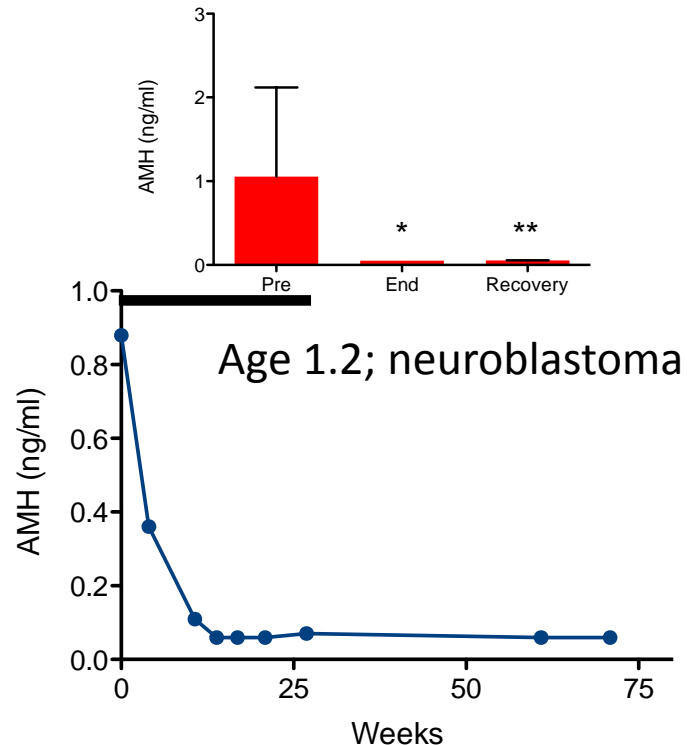
AMH: application in childhood cancer



22 girls age 0.3-15yr
17 prepubertal



AMH in 3 girls with cancer



How predictive is this?

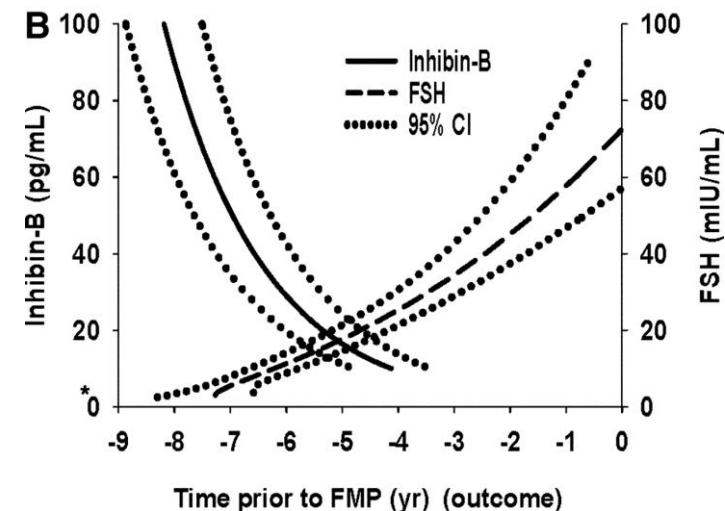
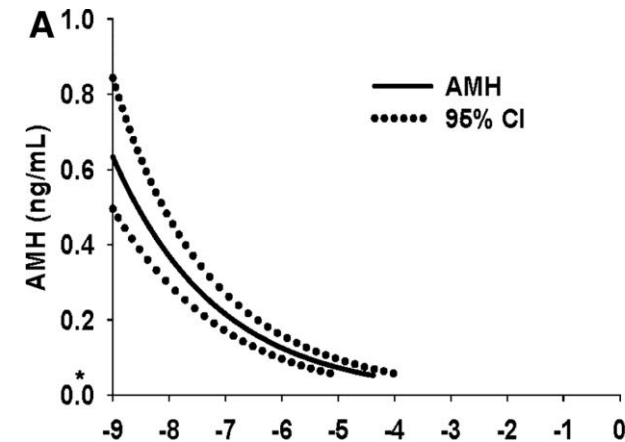
Does AMH predict natural menopause?

50 women followed prospectively
(Michigan Bone Health and Metabolism Study)
6 annual assessments

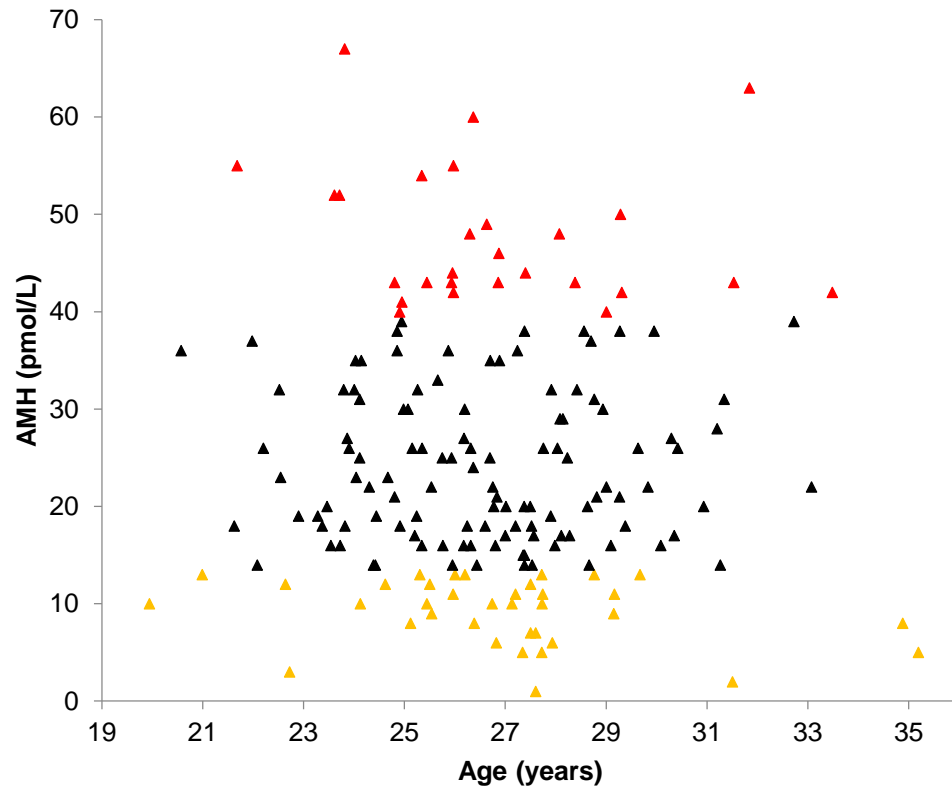
Mean initial age 42 yr

AMH related to both time to and age
at FMP

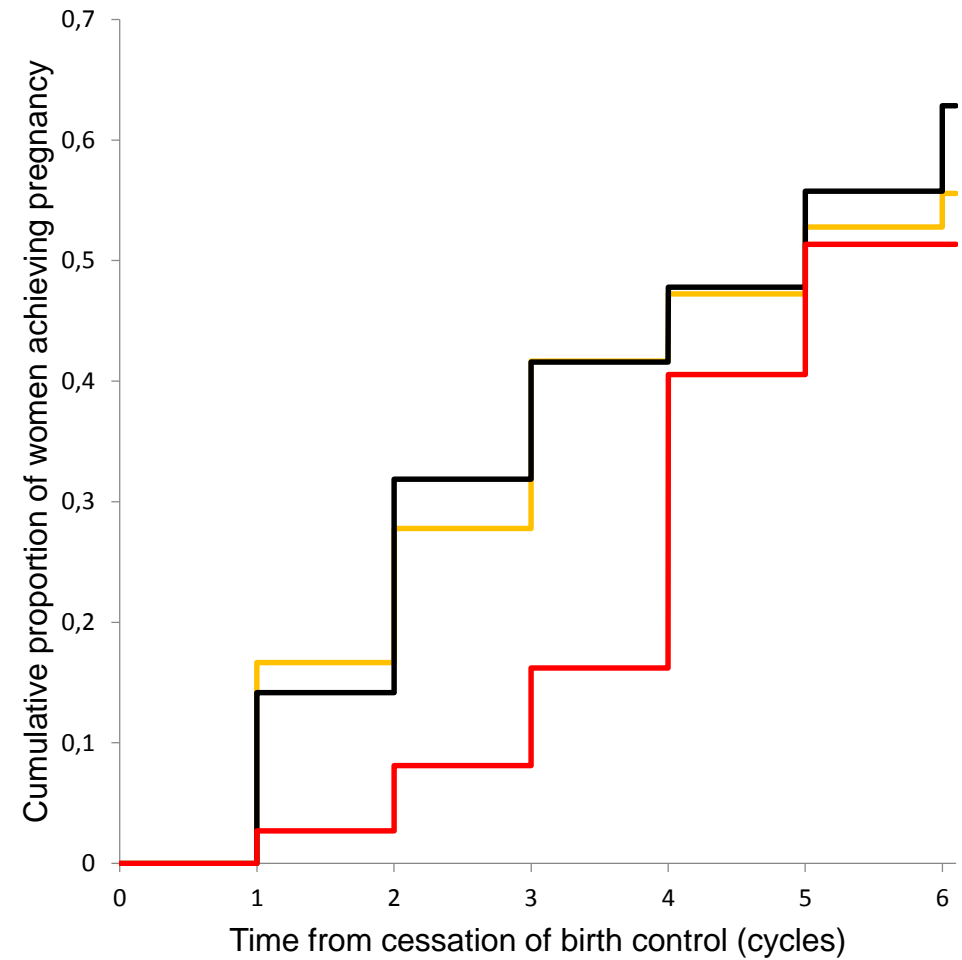
Inhibin B less predictive of both



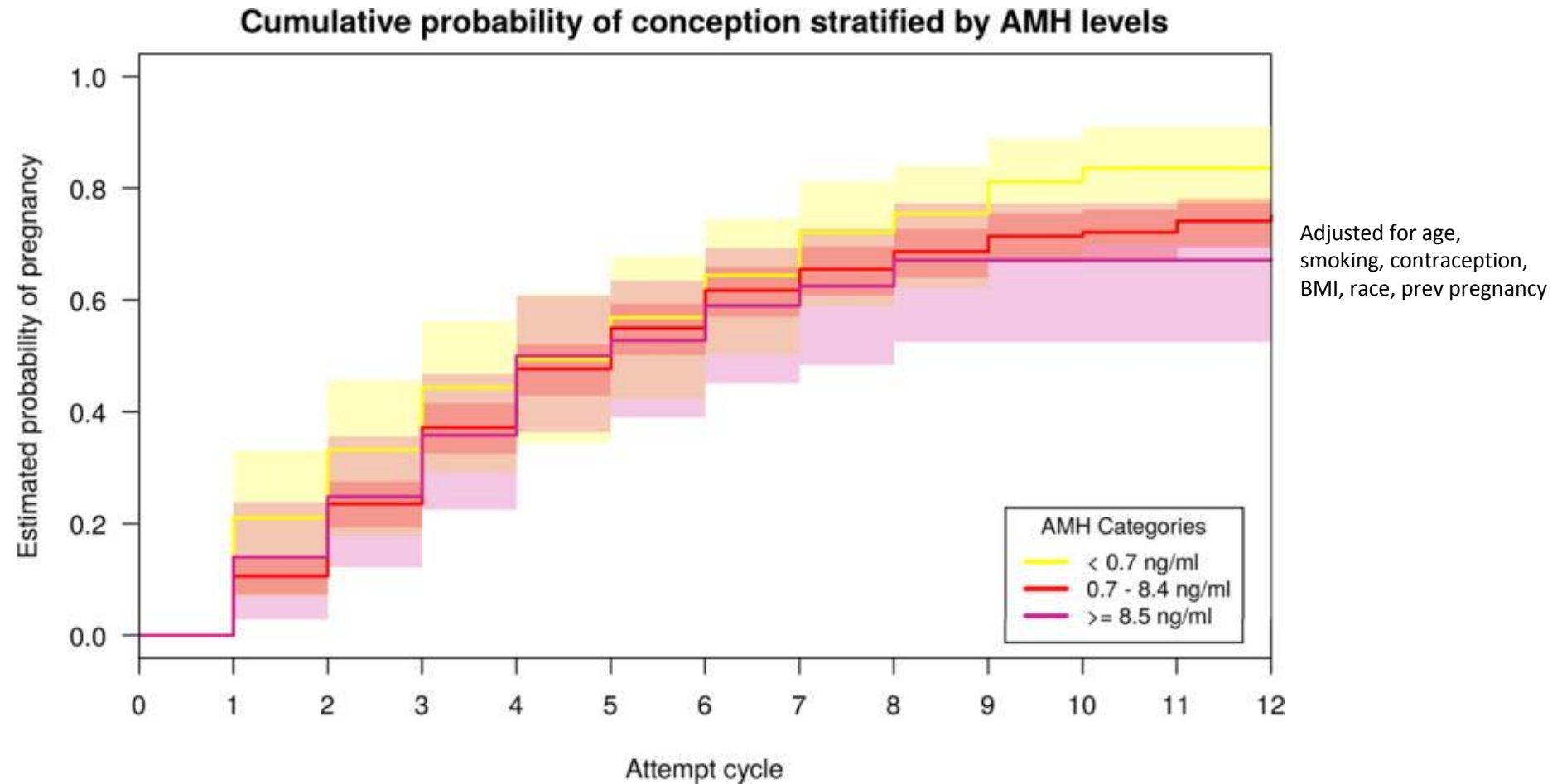
AMH and fecundability



AMH quintiles, middle 3 combined



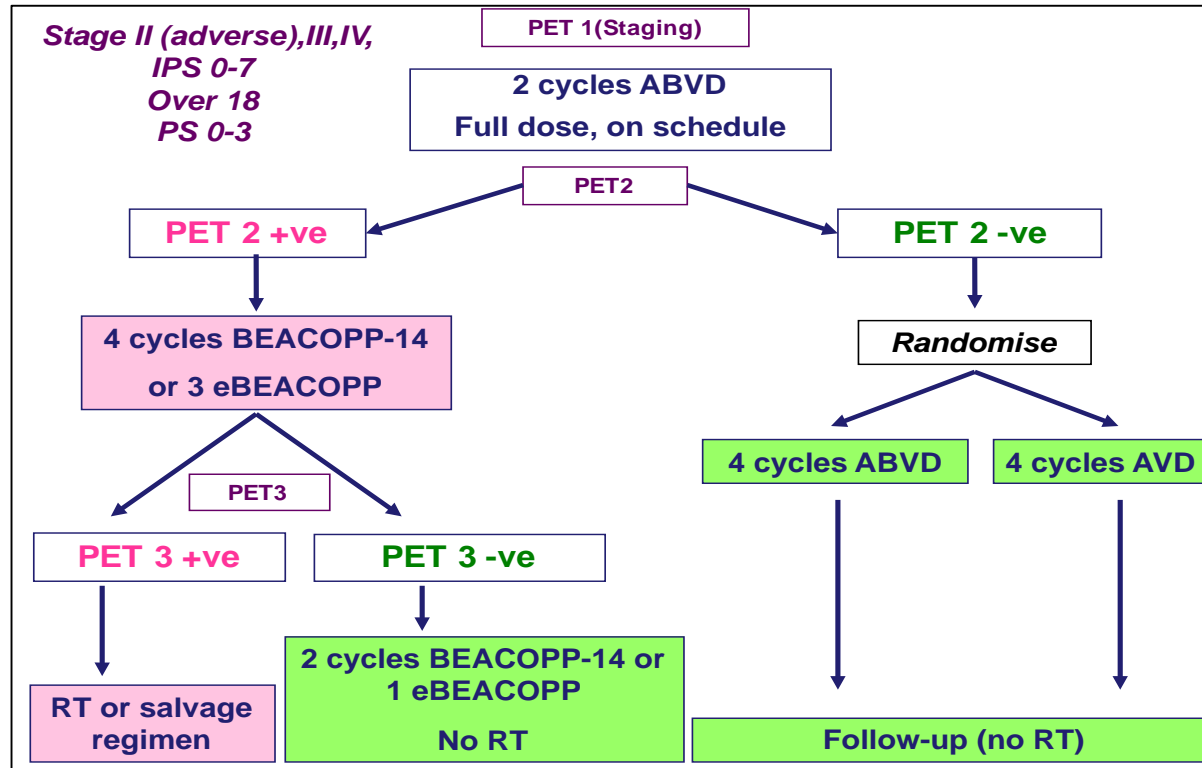
AMH and fertility in older women



981 women aged 30 to 44, trying to conceive max 3 months at study entry

What about low toxicity regimens?

RATHL trial in Hodgkin Lymphoma



Ovarian substudy method

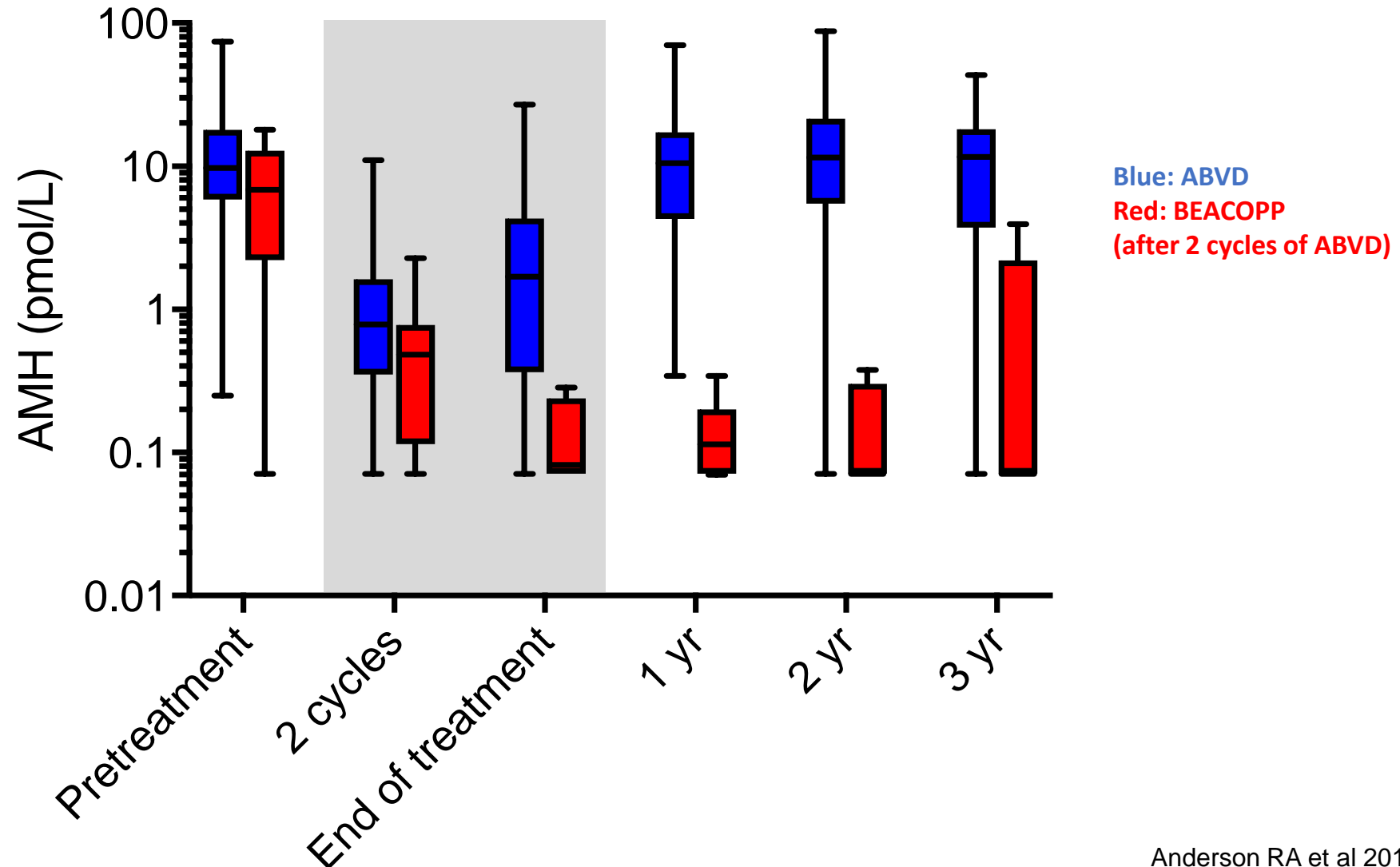
Women aged 18-45 were recruited (ethics approval/consent)

Blood samples:

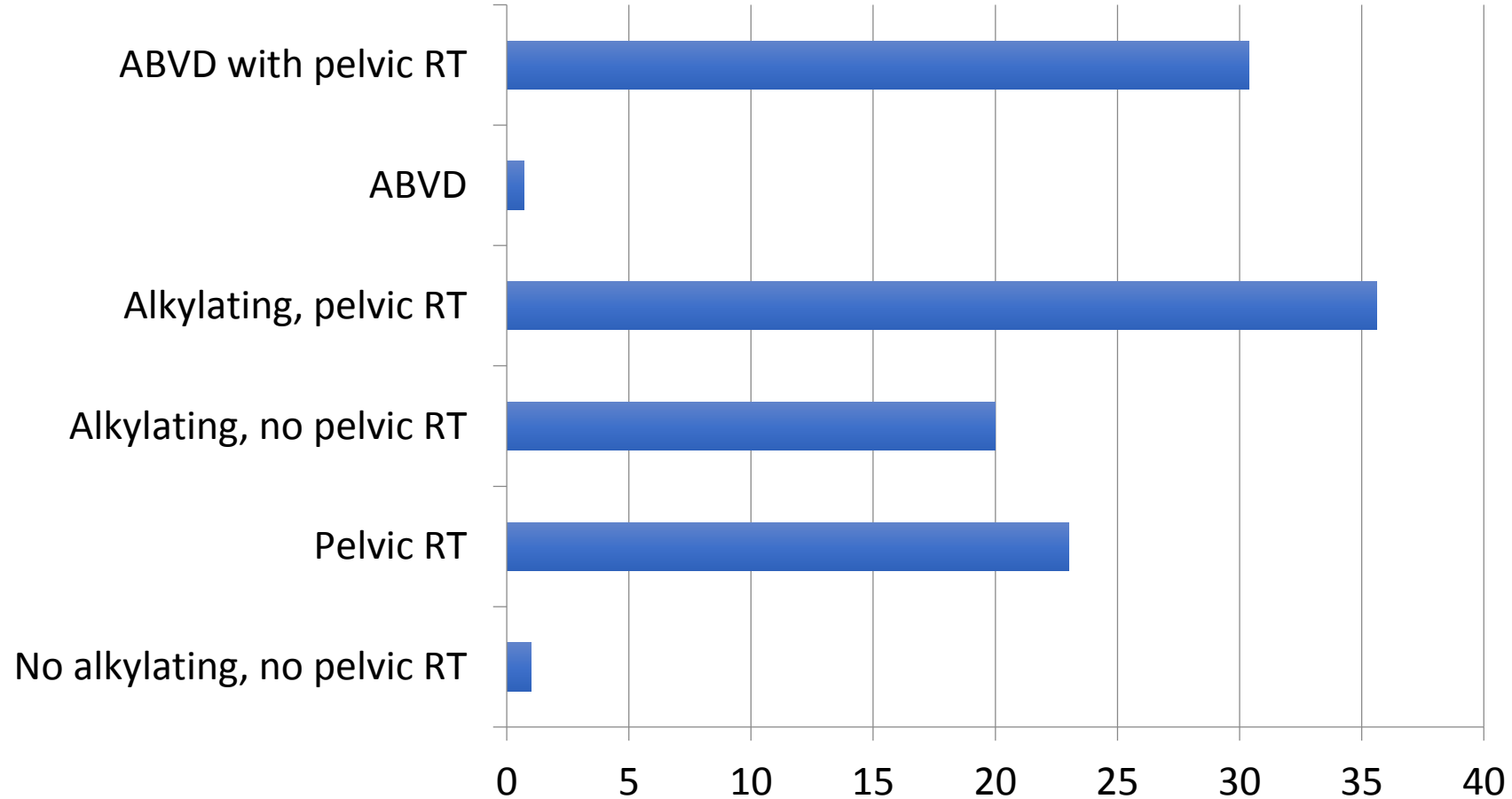
- Pre-treatment
- After 2 cycles ABVD
- End of chemo
- 1, 2, 3 years later
- Analysed for AMH, FSH (Roche)

Johnson P et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma.
N Engl J Med. 2016; **374**: 2419-29

Effects of A(B)VD and BEACOPP on ovarian function

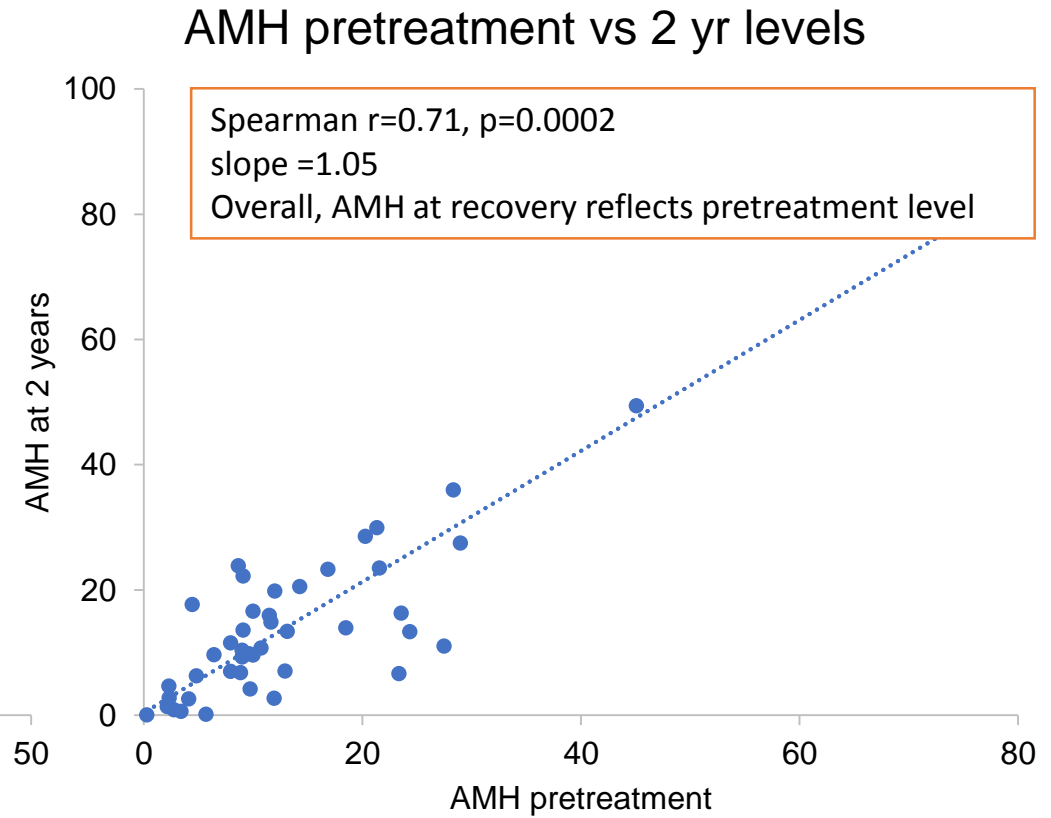
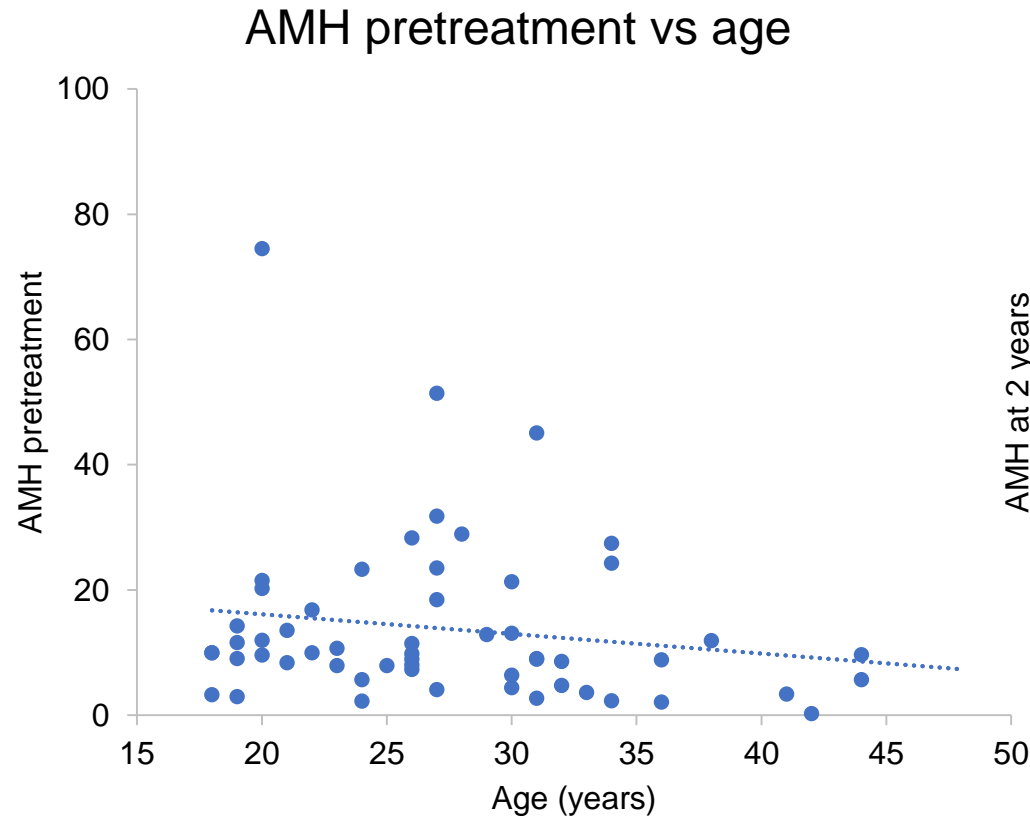


Hazard ratio for menopause <40 yrs in treatment of HL

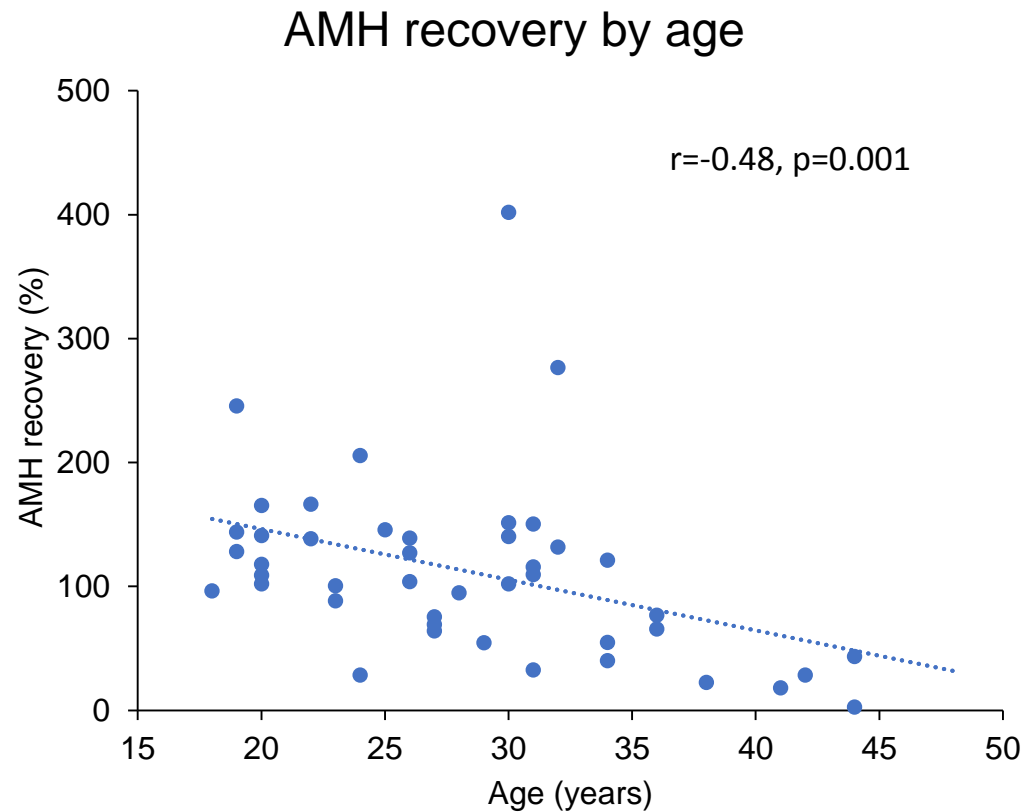


All adjusted for age, overall n=2127 (though data only from 50%)

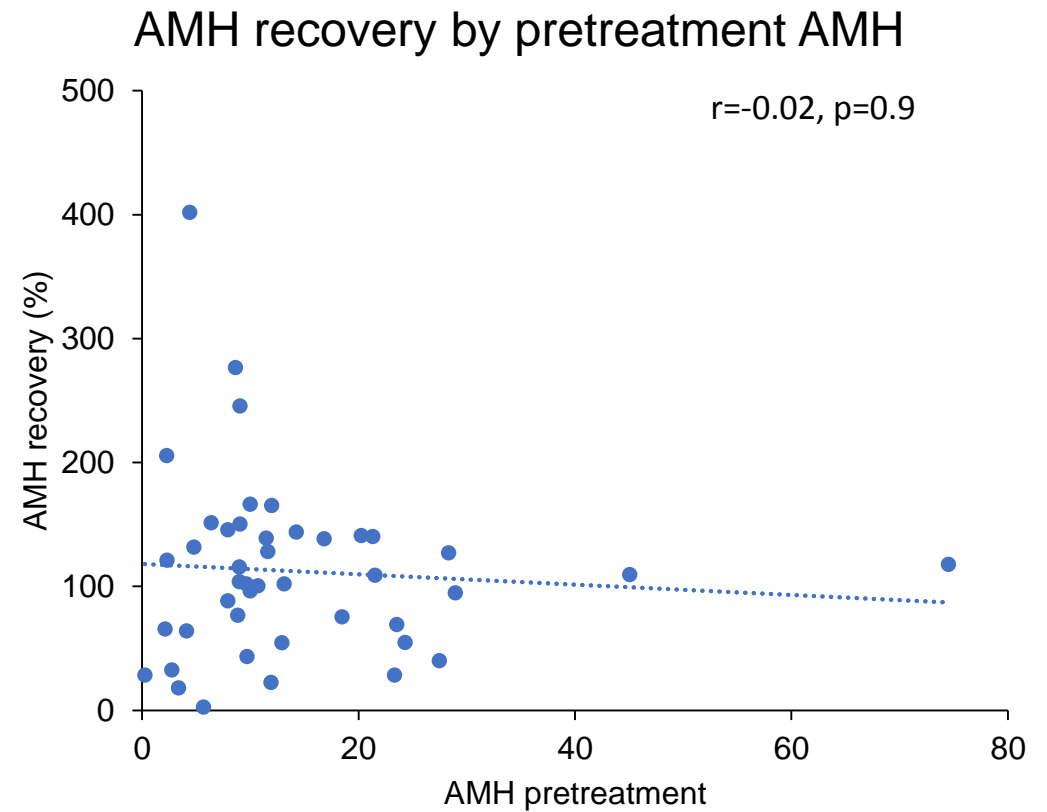
Main relationships: AMH, age, recovery



Is AMH recovery always good?

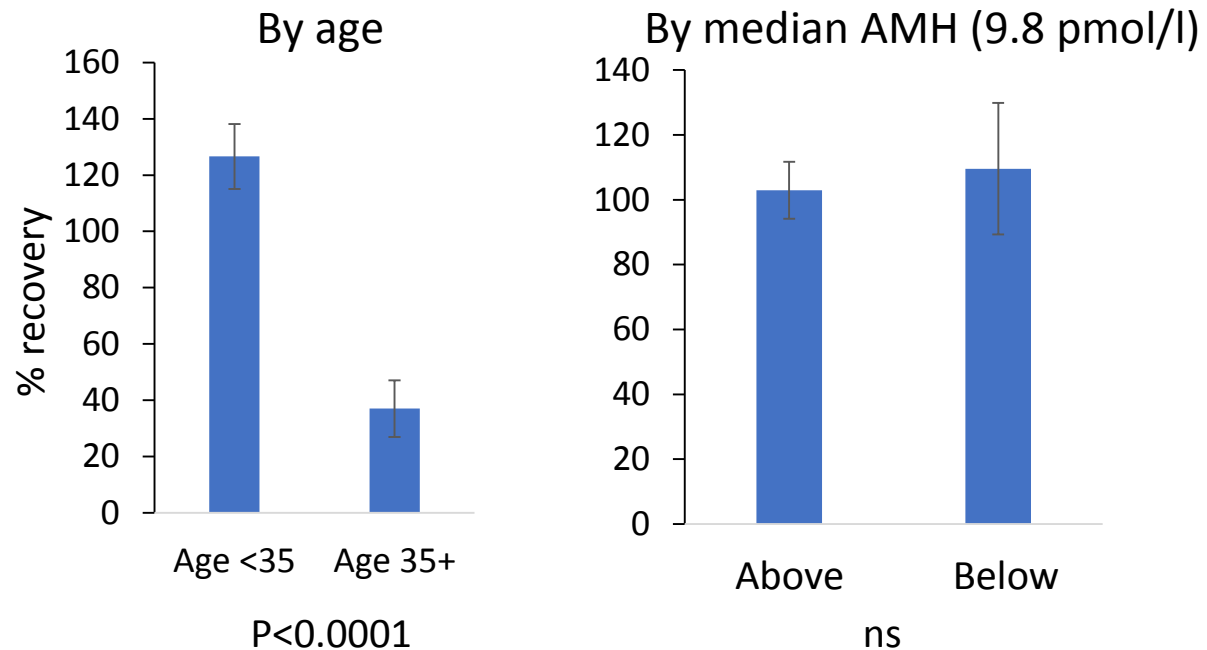


Older women show reduced recovery



Women with low AMH show full recovery

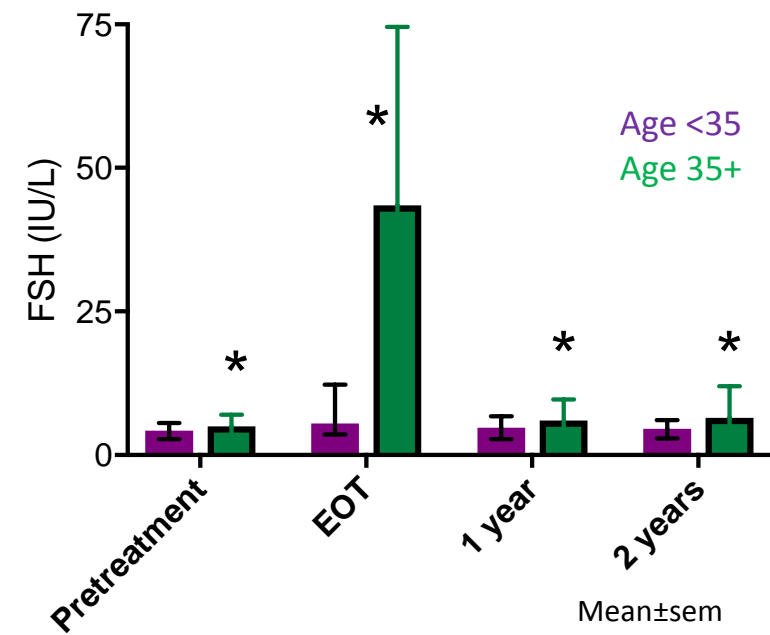
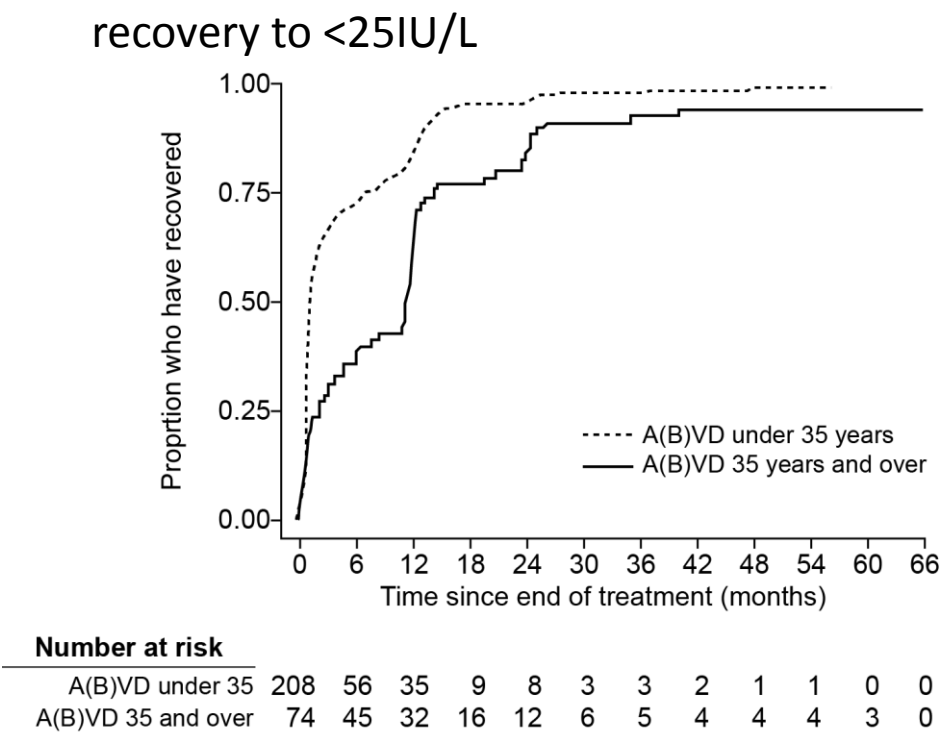
Confirmation of impact of age on recovery



Multiple linear regression analysis vs AMH recovery:
age (beta -0.43, $p=0.004$)
pretreatment AMH (beta -0.15, $p=0.3$)

Different to breast cancer data: older population, more toxic treatment

FSH recovery after A(B)VD is also dependent on age



| % recovered | Age <35 | 35+ |
|-------------|---------------|---------------|
| At 1 year | 83% (77 – 88) | 54% (43 – 66) |
| At 2 years | 96% (93 – 98) | 83% (73 – 91) |
| At 3 years | 98% (95-99) | 93% (85-97) |

Conclusions

AMH is a valuable index of ovarian function in oncology patients

Pretreatment assessment

Post treatment: immediate, and long term

Need for accurate, patient-specific risk to fertility and ovarian function

Extrinsic issues: proposed treatment

Intrinsic issues: age and ovarian reserve

Rational and effective use of FP techniques

Truly informed consent for interventions



Key collaborators and funding

Hamish Wallace, and colleagues, Paediatric oncology, Edinburgh

David Cameron and colleagues, Edinburgh Breast Unit

Bob Leonard and OPTION investigators

Peter Johnson and RATHL investigators

Tom Kelsey, Mathematician, St Andrews University

Beckman Coulter and Roche Diagnostics for assay reagents

