Patient selection for fertility preservation: age vs ovarian reserve

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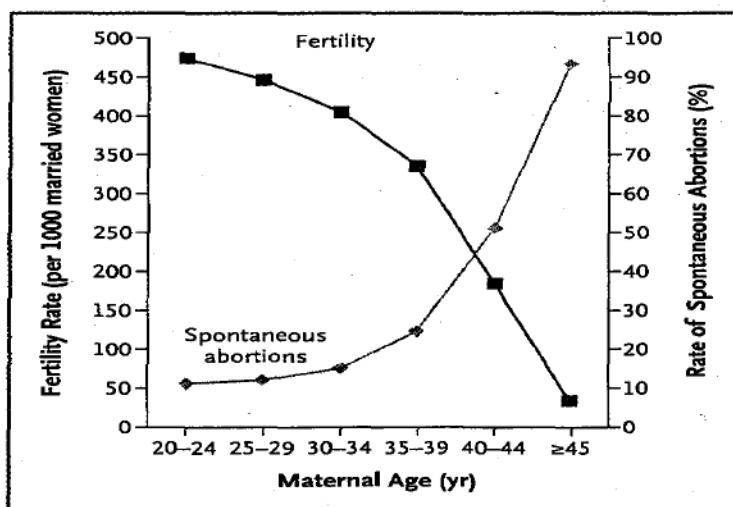
Disclosures

- Research support/consultancy work for Roche Diagnostics, Beckman Coulter

What are the questions?

How best to use age and AMH to guide fertility preservation decisions

- Prediction of loss of fertility
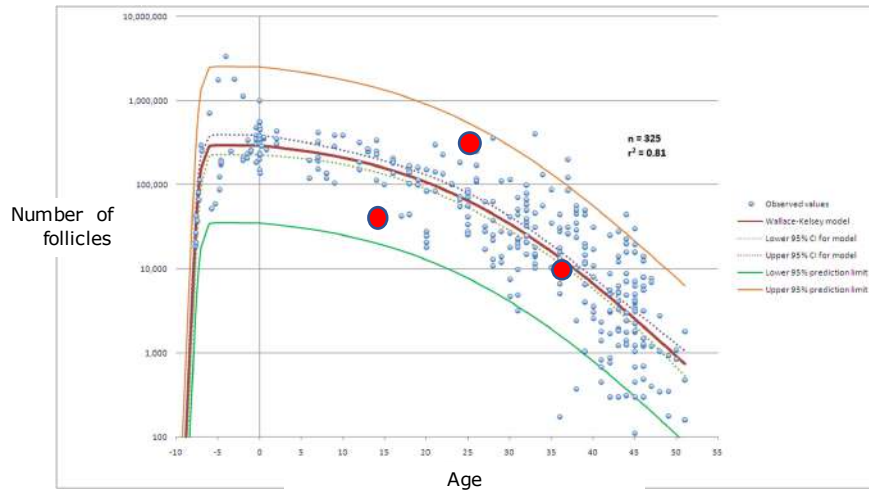- Will our intervention be effective?
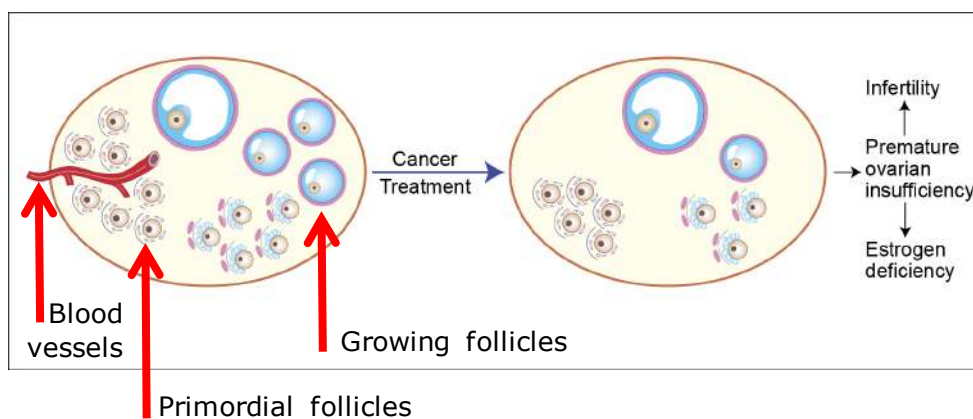
Fertility by age

Both quantity and quality decline

Heffner L. Advanced Maternal Age – How old is too old? N Engl J Med 2004;

The finite nature of female reproduction

Number of follicles

Age

Wallace and Kelsey 2010 PLoS One 5; e8772

Effects of cancer therapy on the ovary

Blood vessels

Primordial follicles

Growing follicles

Cancer Treatment

Infertility

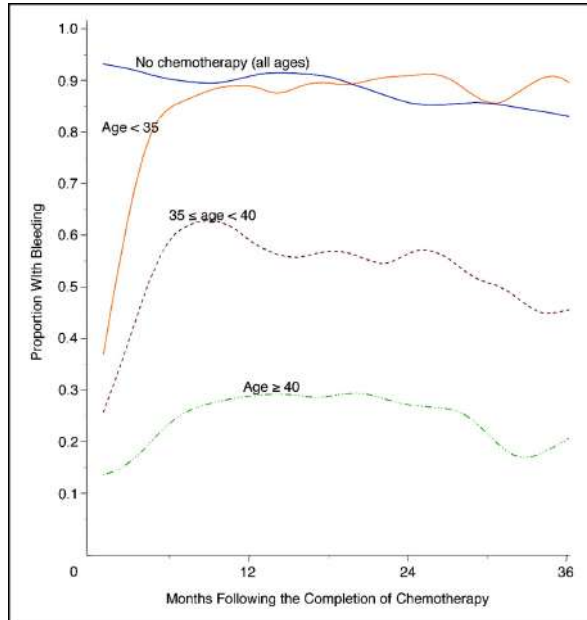Premature ovarian insufficiency
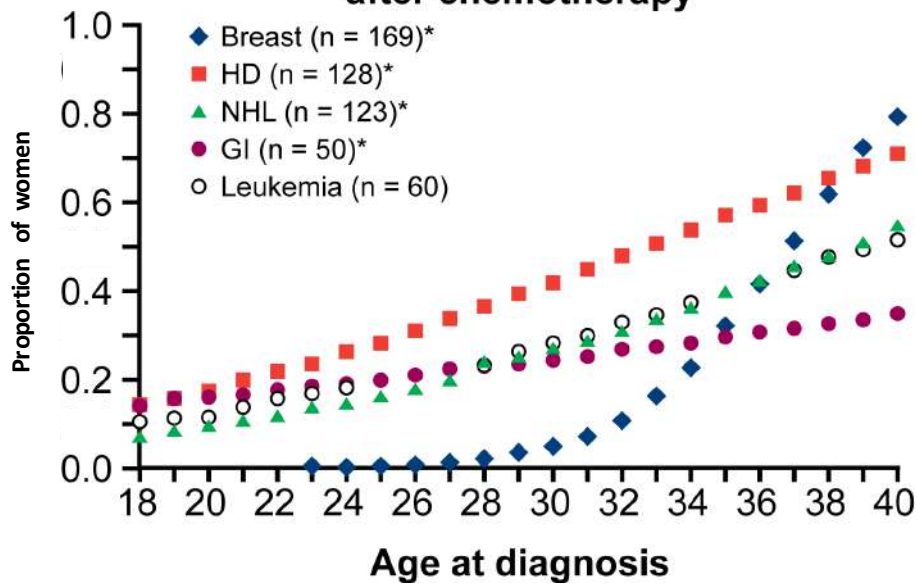
Estrogen deficiency

'Biomarker' outcomes   **'Clinical' outcomes**

Effect of age

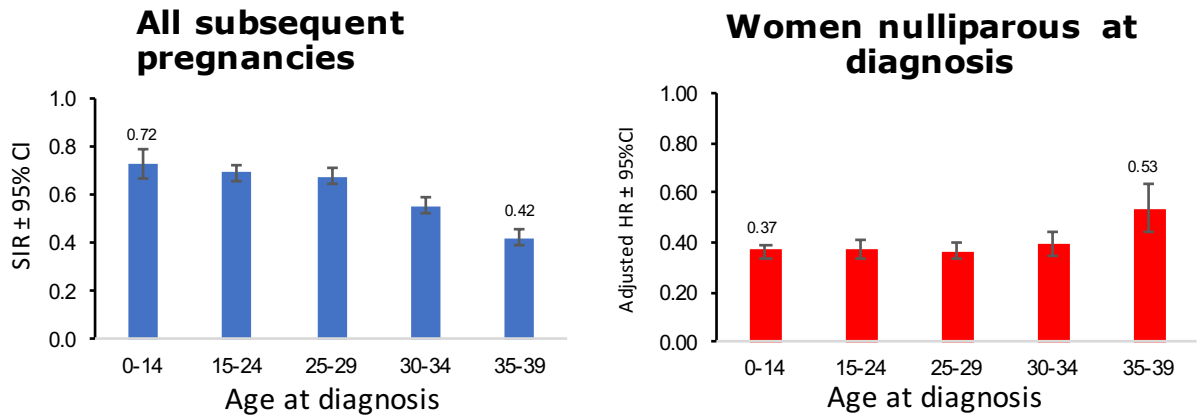Prevalence of ongoing menses after chemo for early breast cancer

Petrek et al 2006 J Clin Oncol 24 1045

Letourneau et al 2012 Cancer 118, 1710

Overall impact of cancer on subsequent pregnancy

All subsequent pregnancies

Women nulliparous at diagnosis

Complex interaction of biological and social factors: opportunity and decision-making
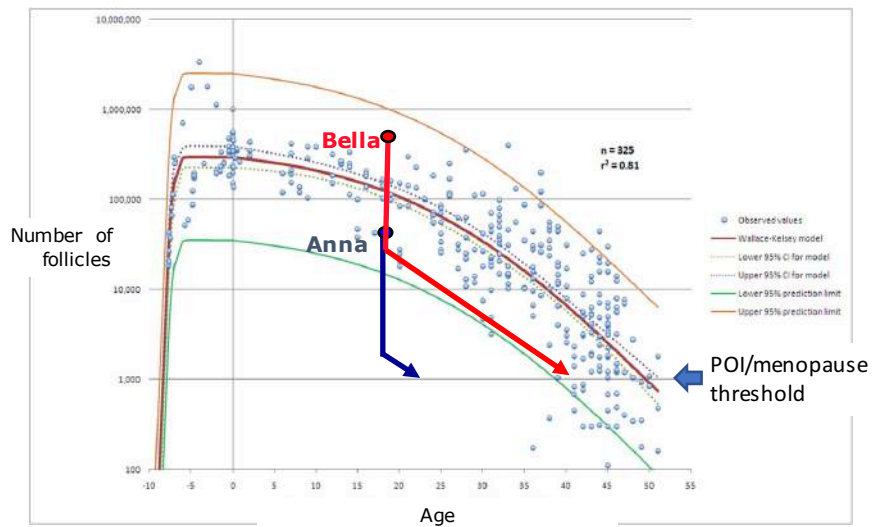
Anderson et al, unpublished
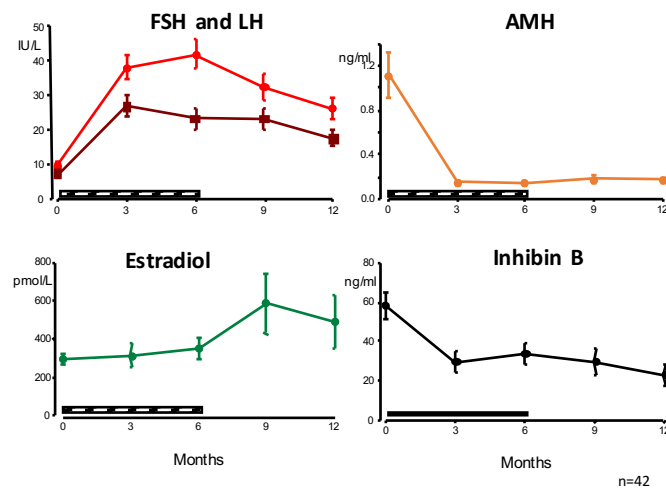
Effects of cancer therapy on the ovary
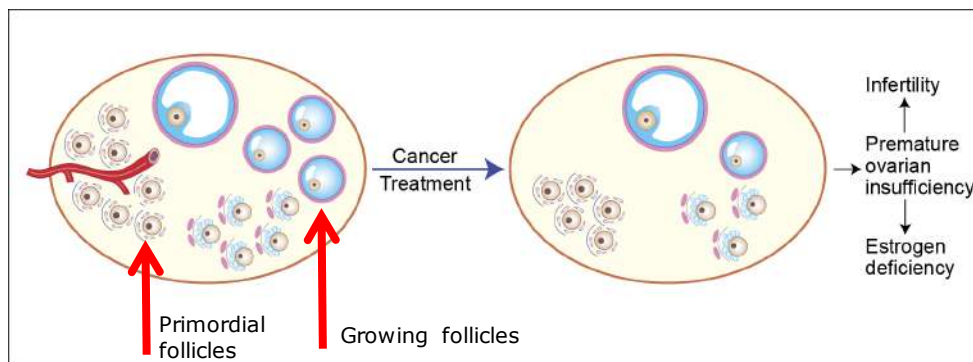
Short term/surrogates: biomarkers of ovarian function

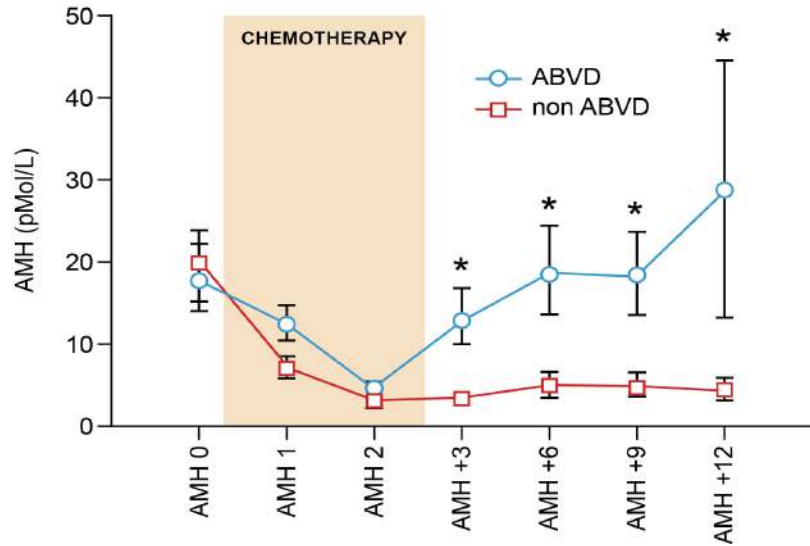# The impact of individual susceptibility

Wallace and Kelsey 2010 PLoS One 5; e8772

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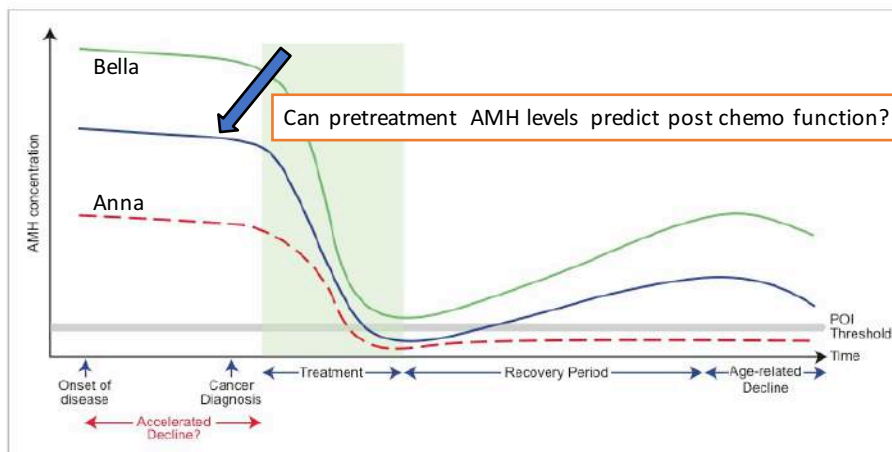

Anderson RA et al 2006 Human Reprod 21, 2583

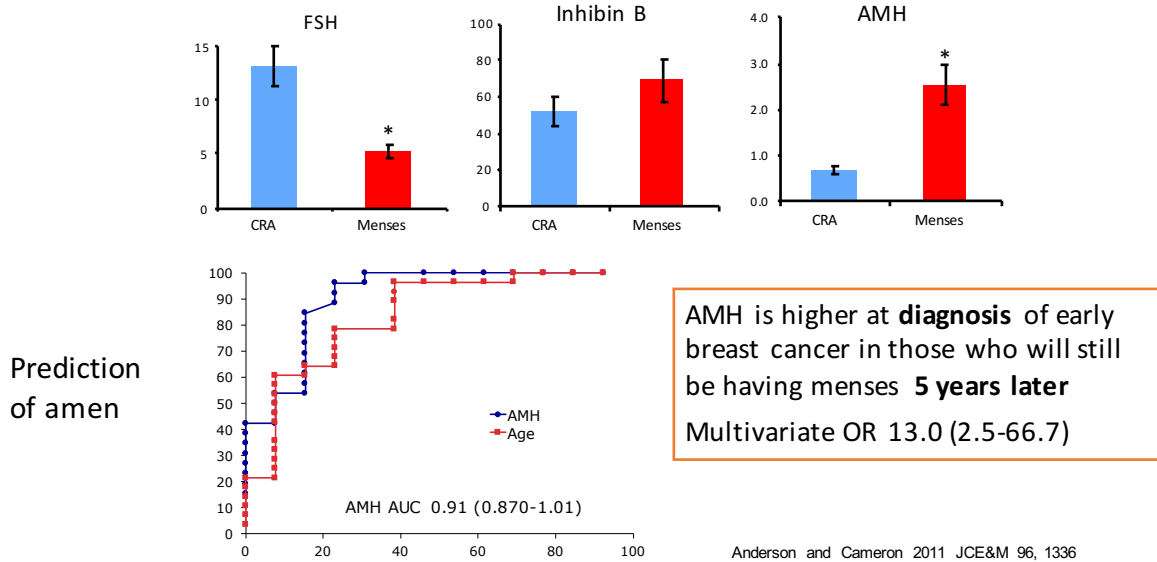## AMH differentiates high and low risk chemo
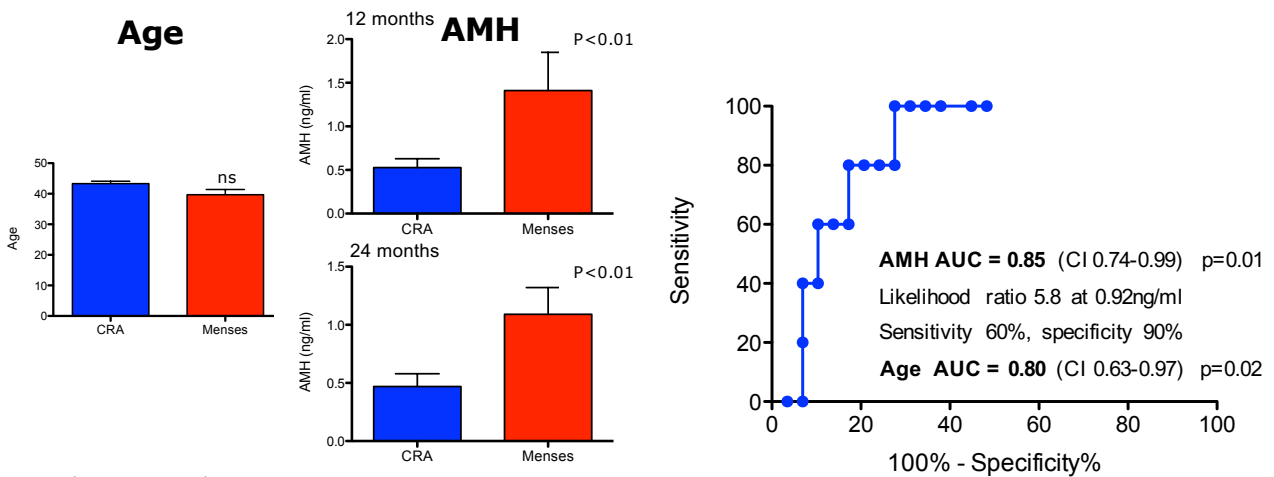

N=26, HL and NHL

Decanter C et al 2009 RBMOnline

AMH profiles in the oncology patient

Can pretreatment AMH levels predict post chemo function?

Prediction of long-term ovarian function: pretreatment assessment

FSH

Inhibin B

AMH

Prediction of amen

AMH AUC 0.91 (0.870-1.01)

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

Multivariate OR 13.0 (2.5-66.7)

Anderson and Cameron 2011 JCE&M 96, 1336

Validation cohort: pretreatment age, hormones by CRA at 12 and 24 months

Age

12 months **AMH**

P<0.01

24 months

P<0.01

AMH AUC = 0.85 (CI 0.74-0.99) p=0.01

Likelihood ratio 5.8 at 0.92ng/ml

Sensitivity 60%, specificity 90%

Age AUC = 0.80 (CI 0.63-0.97) p=0.02

Multivariate analysis:
AMH remains significant after adjusting for age, tamoxifen, smoking, BMI

Anderson et al 2013 Eur J Cancer

Importance of age for ovarian function after chemotherapy
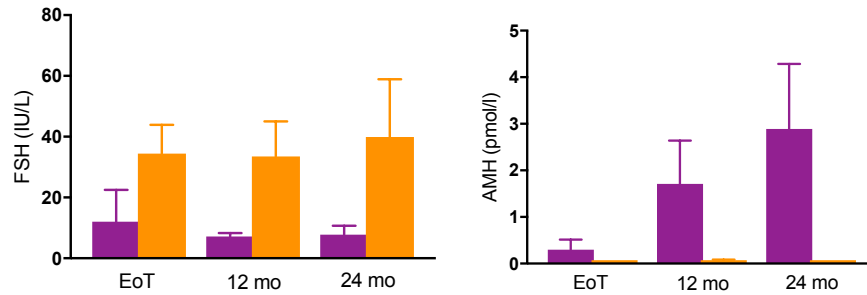
Women aged ≤ 40 (purple) vs >40 years (orange)
n=62 and 81, median ± 95% CI.

Data from OPTION trial
of GnRHa in early
breast cancer
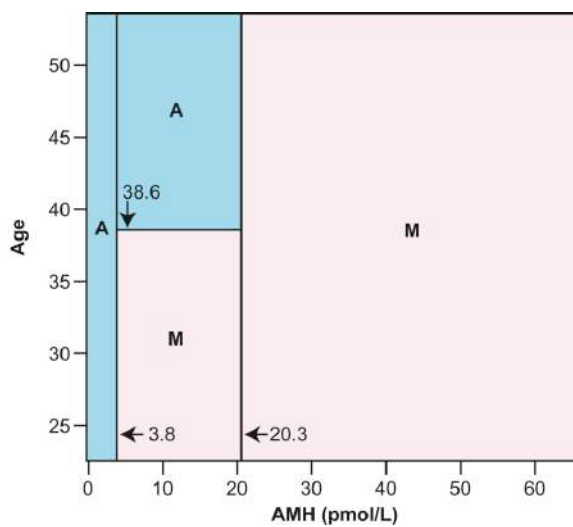
Anderson RA et al 2017 Eur J Cancer in press

Pretreatment AMH with age predicts loss of ovarian function after chemotherapy for early breast cancer

sensitivity 98.2% specificity
80.0%
for correct classification

n=75

Anderson and Cameron 2011 JCE&M
Anderson et al 2013 Eur J Cancer

Slide 1:

CLINICAL TRIAL

Biomarker prediction of chemotherapy-related amenorrhea in premenopausal women with breast cancer participating in E5103

Kathryn J. Ruddy · Anne O'Neill · Kathy D. Miller · Bryan P. Schneider ·
Emily Baker · Joseph A. Sparano · Chau Dang · Donald W. Northfelt ·
George W. Sledge Jr. · Ann H. Partridge

Early breast cancer treated with cyclophos/doxorubicin/paclitaxel
Plus bevacizumab/placebo
n=120

Table 5 Multivariate model for 18-month CRA ($n = 120$)

Characteristic	OR	95 % CI	p value
AMH	0.41[a]	0.18–0.95	0.04
Age	1.18[b]	1.04–1.34	0.008
Race (white vs. other)	0.77	0.12–4.84[a]	0.79
Received bevacizumab (yes vs. no)	0.93	0.19–4.51	0.93
Tamoxifen use (yes vs. no)	2.25	0.59–8.55	0.23

12 month: AMH and age significant by univariate, only age by multivariate

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Slide 2:

Return of ovarian function after chemo for eBC

Scores for
- age <40 yr
- AMH >0.7 ng/ml
- BMI >25 kg/m^2
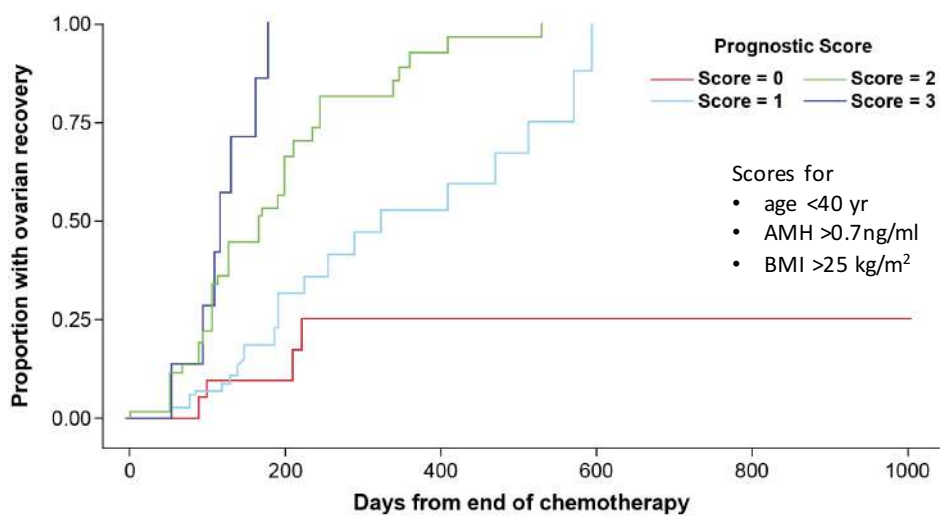
From Su et al 2014 Cancer
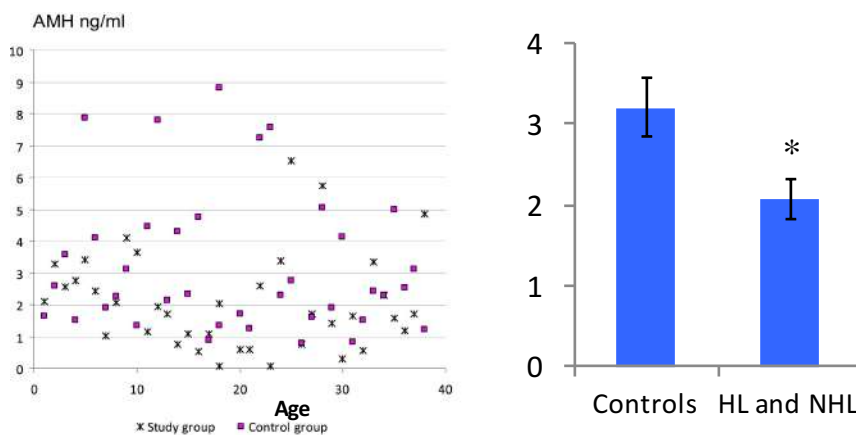
AMH and age predict POI in eBrCa
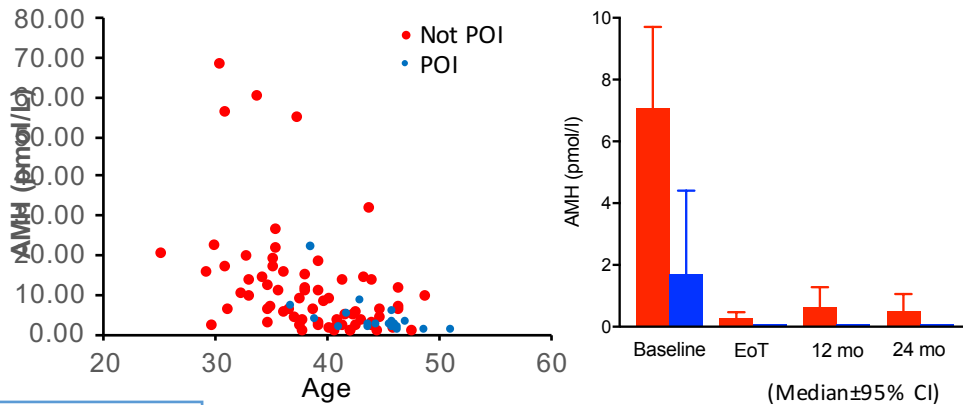
Data from OPTION trial of GnRHa in early breast cancer

ROC AUC 0.77
AMH <7.5pmol/l:
sensitivity 95%, specificity 49%

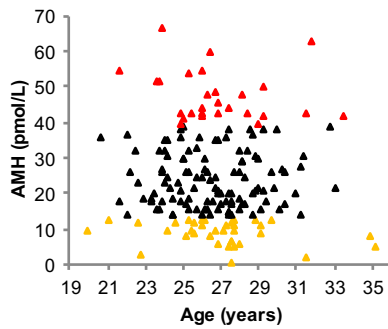(Median±95% CI)

Anderson RA et al 2017 Eur J Cancer
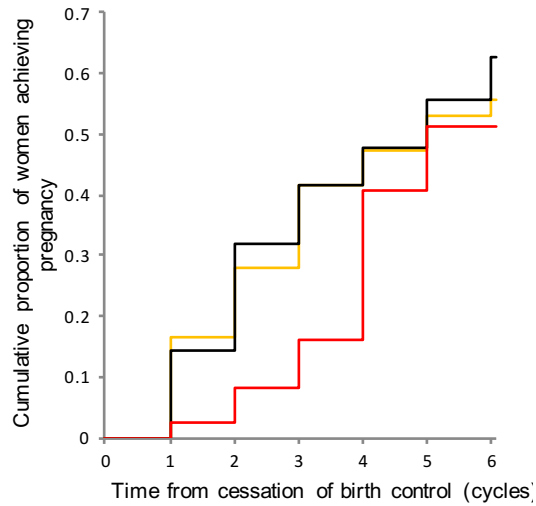
Reduced AMH in lymphoma at diagnosis

Controls, n=38
Hodgkin lymphoma, n=31
Non-Hodkin lymphoma, n=7

Lawrenz B et al, 2012 Fertil Steril 98, 141-144

AMH does not predict fecundability in young women

AMH quintiles, middle 3 combined

Hagen et al 2012 Fertil Steril

JAMA | Original Investigation

Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age

Anne Z. Steiner, MD, MPH; David Pritchard, MS; Frank Z. Stanczyk, PhD; James S. Kesner, PhD; Juliana W. Meadows, PhD; Amy H. Herring, ScD; Donna D. Baird, PhD, MPH

Table 3. Association Between Biomarkers of Ovarian Reserve and Predicted Probability of Conceiving in the Time to Conceive Cohort Study

Biomarker	No. of	Conceived During Study,	Cumulative Probability of Conception, % (95% CI)[b]		Hazard Ratio (95% CI)[c]	
			By 6 Cycles	By 12 Cycles	Unadjusted	Adjusted[b]
Antimüllerian hormone, ng/mL						
<0.7	84	53 (63)	65 (56-73)	84 (76-91)	0.96 (0.72-1.28)	1.19 (0.88-1.61)
0.7-8.4	579	381 (66)	62 (57-66)	75 (70-79)	1 [Reference]	1 [Reference]
≥8.5	74	44 (59)	59 (45-69)	66 (57-77)	0.97 (0.71-1.33)	0.88 (0.64-1.21)

But over a longer timeframe?

981 women aged 30 to 44, trying to conceived max 3 months at study entry
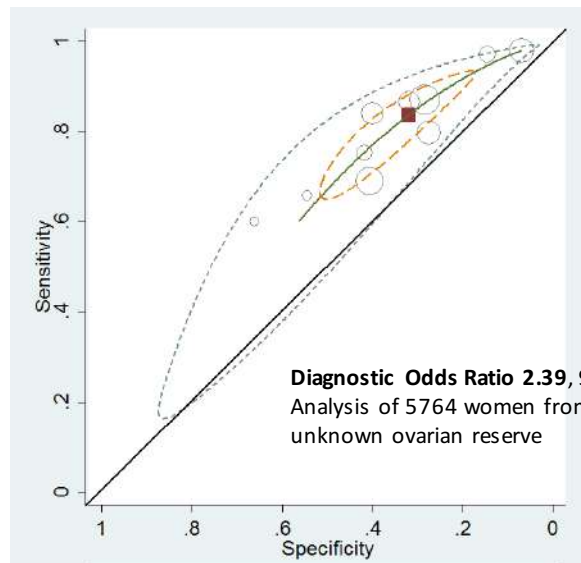
Steiner AZ et al, 2017, JAMA

AMH predicts oocyte yield in IVF

'In COS, AMH predicts number of oocytes': D Seifer 2002
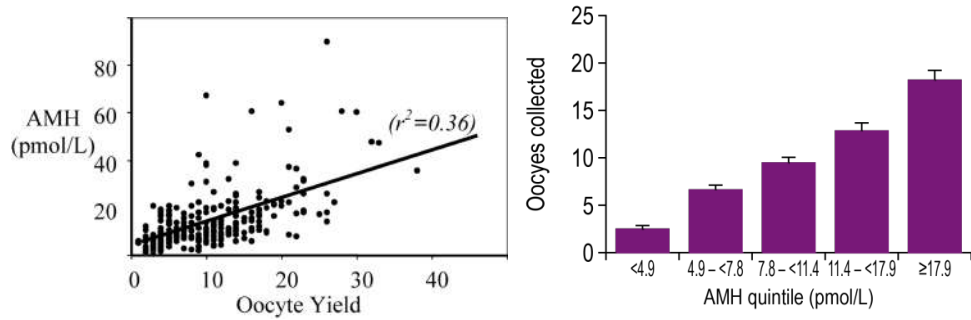
Fleming R et al. Hum. Reprod. 2006 21:1436
Nelson SM et al. Hum. Reprod. 2007 22:2414

AMH poorly predicts live birth after IVF

Diagnostic Odds Ratio 2.39, 95% CI: 1.85-3.08
Analysis of 5764 women from 10 studies of women with
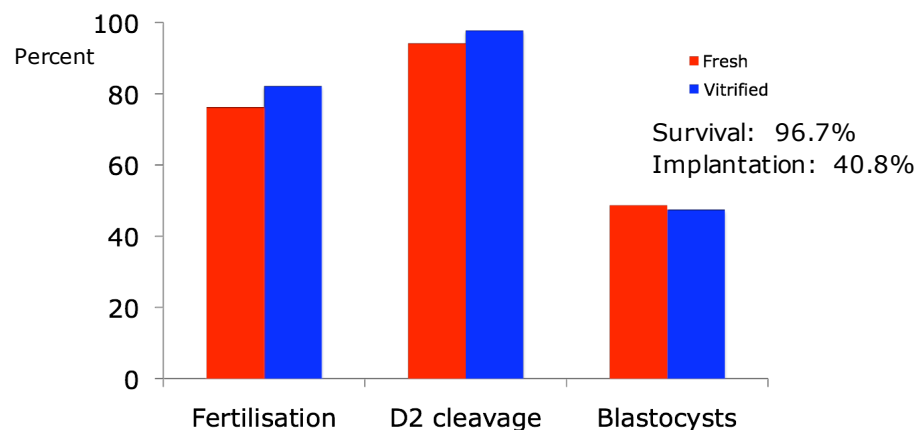unknown ovarian reserve

Iliodromitri, Kelsey, Wu, Anderson and Nelson HRUpdate 2014, 20, 560

What are the questions?

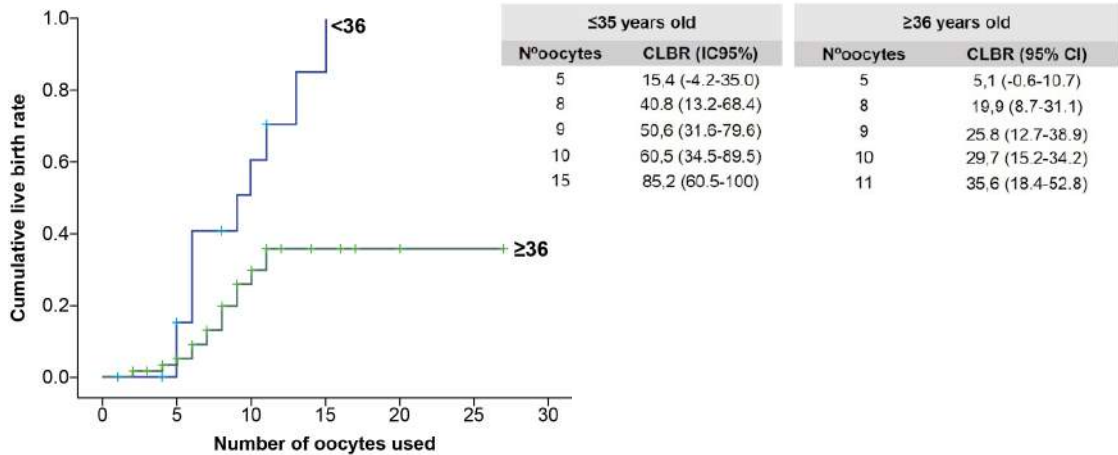How best to use age and AMH to guide fertility preservation decisions

- Prediction of loss of fertility

- Will our intervention be effective?

Comparison of fresh and vitrified oocytes

Survival: 96.7%
Implantation: 40.8%

Cobo et al 2008 Fertil Steril 89; 1657

How successful is oocyte cryostorage at making babies?

|	≤35 years old		≥36 years old	
N°oocytes	CLBR (IC95%)		N°oocytes	CLBR (95% CI)
5	15,4 (-4.2-35.0)		5	5,1 (-0.6-10.7)
8	40,8 (13.2-68.4)		8	19,9 (8.7-31.1)
9	50,6 (31.6-79.6)		9	25.8 (12.7-38.9)
10	60,5 (34.5-89.5)		10	29,7 (15.2-34.2)
15	85,2 (60.5-100)		11	35,6 (18.4-52.8)

Overall n=1468 stored, 137 returned, mostly non-medical

Cobo A etal 2016, Fertil Steril 105, 755-764

How many eggs do you get in women with cancer?

UK, 2000-2014, n=306

breast cancer (33 yr)
haematological (28 yr)
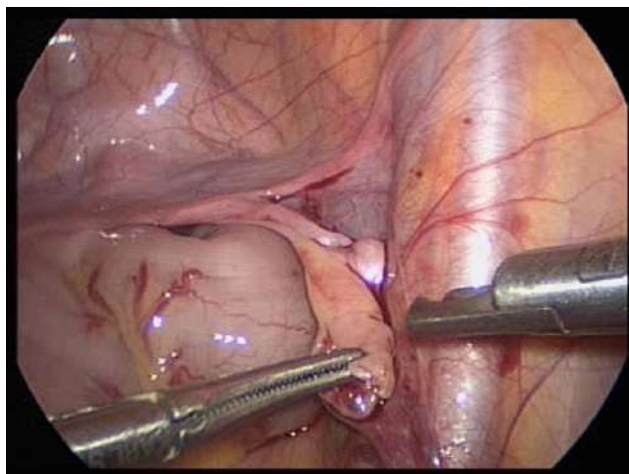gynae cancer (31 yr)
GI (30 yr)
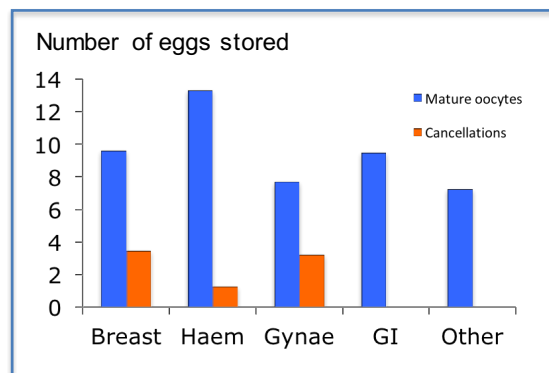
Alvarez and Ramanathan 2016 Hum Reprod

Pregnancy outcomes

- 32 ETs in 22 patients
- Mean storage duration 31 months
- Pregnancy rate 43.8%, LBR 18.8% per cycle
- Cumulative PR 54.5% per patient, LBR 22.7% (8 babies)
- Miscarriage rate 57.1%

Alvarez and Ramanathan 2016 Hum Reprod

## What about with ovarian tissue cryopreservation?

95 transplantations in 74 women with POI

|	
Age at cryopreservation (years) mean ± SD	30 ± 5.9
Age at transplantation (years)	34 ± 5.2
Breast cancer n/total (%)	14/40 (35.0%)
Hodgkin lymphoma n/total (%)	10/40 (25.0%)
Other malignancies n/total (%)	14/40 (35.0%)
Benign diseases n/total (%)	2/40 (5.0%)
Chemotherapy n/total (%)[a]	35/40 (87.5%)
Radiotherapy of the pelvis n/total (%)	5/40 (12.5%)
Active tissue 1 year after transplantation n/total (%)	25/40 (62.5%)
Pregnancies n/total (%)	11/40 (27.5%)
Deliveries n/total (%)	9/40 (22.5%)

H. Van der Ven et al. Hum. Reprod. 2016;31:2031-2041

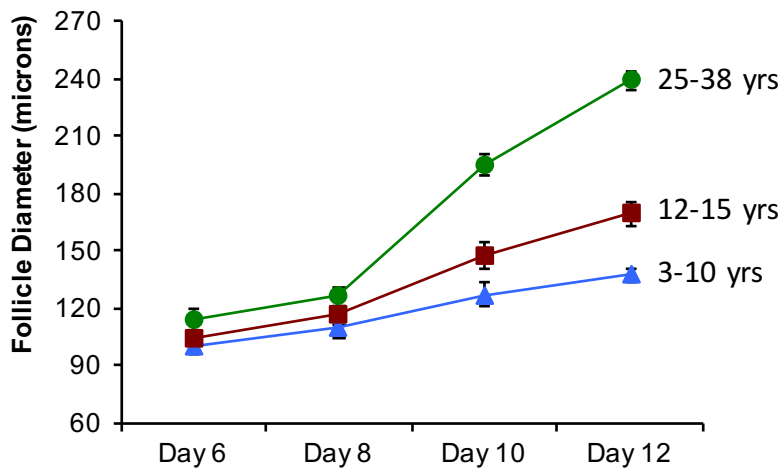# Age and ovarian transplant success

0/2 in 40+
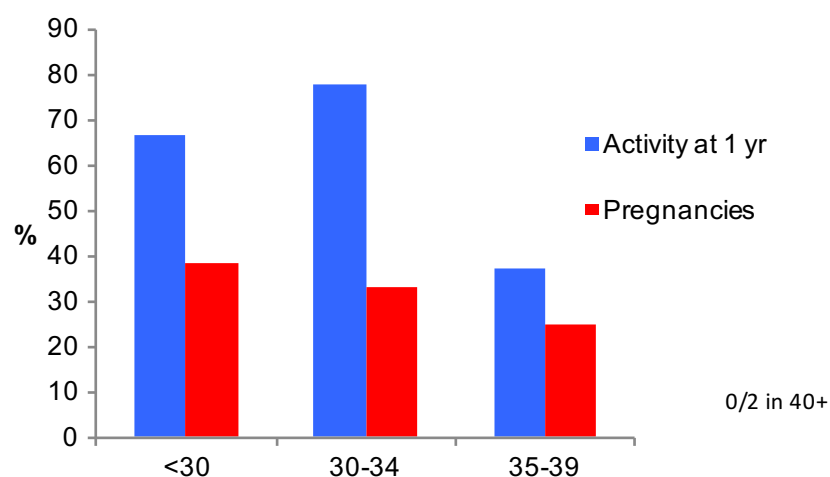
H. Van der Ven et al. Hum. Reprod. 2016;31:2031-2041

The other end of the age range?
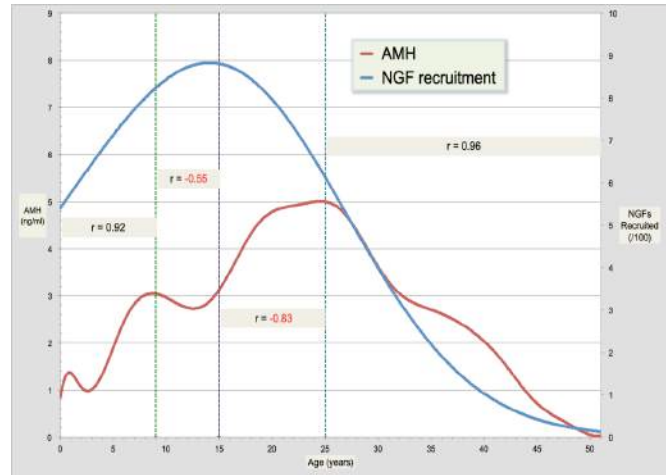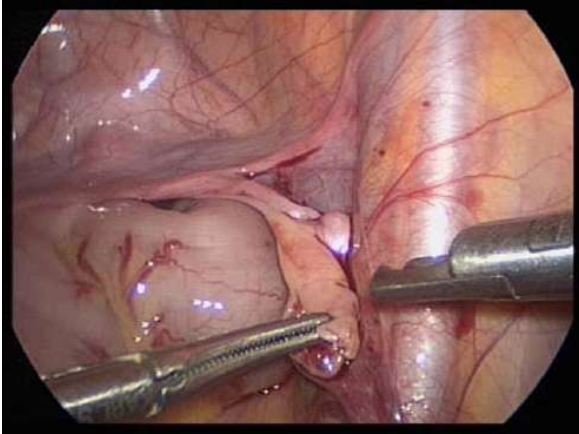
Adapted from Kelsey et al 2012 Mol Hum Reprod 18:79-87
Fleming et al 2102 Fertil Steril 1097

Isolated follicle growth is altered in girls

n = 15 (3-10yrs); n = 70 (12-16yrs)
Adult follicles (n=44) from Caesarian section
Antral cavities form at approx 200mm: 30% in adults

Anderson RA et al Hum Reprod 2014

Conclusions

- Age is the key predictor of female fertility
- Both in health and after cancer
- AMH can also predict POI after cancer
- AMH does not predict short-term fecundability or IVF success
- Does it predict post-cancer reproductive lifespan: the ability to conceive in the future

Assessment for fertility preservation

- **Intrinsic factors**
  - Health of patient
  - Consent (patient/parent)
  - Age
  - Assessment of ovarian reserve
- **Extrinsic factors**
  - Nature of predicted treatment
    - (high/medium/low/uncertain risk)
  - Expertise/funding available

Key collaborators

David Cameron and colleagues, Edinburgh Breast Unit
Bob Leonard and OPTION collaborators

Hamish Wallace

Tom Kelsey

Evelyn Telfer
and Marie McLaughlin

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