Insights from Combined Age-related Models
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Section 0

BACKGROUND
Background

The lab in Edinburgh collects & analyses tissue:

• Cryopreserved human ovarian cortex
• Part of the Fertility Preservation service
• Tissue is retained for future re-implantation
• A small amount is assessed
  – For possibility of re-infection
  – Estimate ovarian reserve
• Standard calculation is Mean Follicle Density
  – Estimate of non-growing follicles (NGFS) per cubic millilitre of cortical tissue
Female cancer patients age <18 at diagnosis
01/01/1996 - 30/06/2012
n = 410

Offered cryopreservation
n = 34

Tissue cryopreserved
n = 20

Deceased
n = 1

<12 years old
n = 4

On COCP
n = 1

Procedure declined
n = 13

Poor communication
n = 1

Uterine factor
n = 1

Parental choice
n = 2

Too unwell
n = 9

Procedure unsuccessful
n = 1

Deceased
n = 1

<12 years old
n = 1

On COCP
n = 1

Still on treatment
n = 4

Insufficient information on follow-up
n = 42

Deceased
n = 81

<12 years old
n = 91

Not offered cryopreservation
n = 376

Lost to follow-up
n = 1

<12 years old
n = 2

Insufficient information on follow-up
n = 42

n = 141

n = 6

n = 14

= cryopreservation offered.
= reasons for not having tissue cryopreserved.
= patients in study eligible for ovarian function evaluation.
After 10 years: HR 0.018; p < 0.0000001
K-M for offered group 0.65 (95% CI 0.47-0.90)
K-M for not-offered group 0.99 (95% CI 0.98-1.00)
Ewings sarcoma localised T 7 Vertebrae (Age 12) – unexpected contamination of ovarian biopsy
- **Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation**

- **Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults**

- **Fertility preservation in pre-pubertal girls with cancer: the role of ovarian tissue cryopreservation**
  - W H B Wallace, T W Kelsey, R A Anderson
Section 1

THE PROBLEM
Unexpected MFD numbers

- Patients receiving ABVD chemotherapy appeared to have higher than expected MFD
- Patients receiving other chemo regimes appeared to have reduced MFD
- Untreated patients had normal MFD

But

1. Increased MFD is impossible according to our understanding of ovarian reserve
2. There was no age-related model for MFD in healthy subjects
“Women are born with a finite number of germ cells (GC), which cannot be replaced.”
   – Homepage of Richard Anderson

“NGFs are formed in large numbers in the fetal ovary in humans with peak population occurring at 20–22 weeks gestation”

“The human ovary contains a fixed number of non-growing follicles (NGFs) established before birth that decline with increasing age culminating in the menopause at 50–51 years.”
   – (Baker, 1963; Wallace and Kelsey, 2010; Mamsen et al., 2011)
• Follicular density in ovarian biopsy of infertile women: a novel method to assess ovarian reserve
  – A Lass et al.
• MFD routinely used from age 30 years up
• Sparse data and no normative results for younger ages
• Data collected at Copenhagen & Edinburgh for fertility preservation investigations
Section 2

A SOLUTION
Combine Existing Models

- We have a normative model of NGF population for all ages up to menopause
- *Human ovarian reserve from conception to the menopause*
  - W H B Wallace, T W Kelsey
- We also have an age-related model of ovarian volume
- *Ovarian volume throughout life: a validated normative model*
  - T W Kelsey, S K Dodwell, et al.
The NGF model is the standard reference

- Data-driven
- Aggregated data from multiple sources

Externally validated in 2015

The relation between variation in size of the primordial follicle pool and menopause: a cohort comparison of observed and predicted distribution of age at menopause

- M Depmann, J Faddy, et al.
- *Journal of Clinical Endocrinology and Metabolism* 100(6): 2015
The Wallace-Kelsey Model
(Five parameter asymmetric double-Gaussian cumulative curve)

log_{10}(y) = \frac{a}{4} \left[ 1 + \text{Erf} \left( \frac{x+b+\frac{c}{d\sqrt{2}}}{d\sqrt{2}} \right) \right] \left[ 1 - \text{Erf} \left( \frac{x+b-\frac{c}{e\sqrt{2}}}{e\sqrt{2}} \right) \right]

• The ovarian volume model is less ubiquitous
  – Data-driven, aggregated & simulated data
• AFC and AMH are preferred as indirect measures of remaining ovarian reserve
• However, 99% correlation between log-adjusted OV and log-adjusted NGF for ages 25 – 51 years
• Ovarian volume correlates strongly with the number of non-growing follicles in the human ovary
  – TW Kelsey, WHB Wallace
  – Obstetrics and Gynecology International (2012): 305025
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0071465
• A large ovary contains many NGFs
  – And a small one contains few NGFs
• We know the age of each patient
• We can predict NGF(age) and OV(age)
• Predicted MFD is simply NGF(age)/OV(age)
• But not all the ovary is cortical tissue
  – Estimate that 24% of a typical ovary consists of cortical tissue
• Prediction now is NGF/(24% of OV)
Modelling Limitations

- **Unsophisticated**
  - No attempt to use NGF and volume data to produce a 2-attribute predictor
  - But easy to explain to medical colleagues

- **No evidence that the assumption is true**
  - For the ages of interest, NGF numbers are falling and volumes are increasing
  - Potentially working against the assumption

- **The cortical proportion was an estimate**
  - As opposed to an agreed value from the literature
Section 3

RESULTS
MFD: observed vs predicted

- Expected MFD vs Observed MFD graph
- Points are scattered around the line of perfect prediction
- Most points are close to the line, indicating a good fit
MFD: Bland-Altman

Difference from Predicted MFD

Mean of Observed and Predicted MFD
• For our data:
  – 87% correlation of observed and expected
  – < 1% proportional error
  – Mean difference 2.6 NGFs

• Applied to Danish data
  – 90% correlation of observed and expected
  – 12% proportional error
  – Mean difference 3.3 NGFs

• An externally validated age-related model of mean follicle density in the cortex of the human ovary
  – M McLaughlin, TW Kelsey, et al.
Section 4

APPLICATION TO THE ORIGINAL PROBLEM
MFD: observed vs predicted

![Graph showing observed vs predicted MFD](image)
MFD: Bland-Altman

The diagram illustrates a scatter plot comparing the difference from predicted MFD against the mean of observed and predicted MFD. The plot shows a positive correlation, with most points clustering above the zero line, indicating that the predicted MFD values are generally lower than the observed MFD values.
• Blue dots are controls
  – Further external validation
• Green dots are COPDAC chemotherapy
  – Reducing the MFD, as expected
• Red dots are ABVD chemotherapy
  – Substantial & quantifiable increase in MFD for all 8 cases
• Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary
  – M McLaughlin, T W Kelsey, et al.
• Our understanding is wrong
• Regeneration of human ovarian reserve is possible
  – At a massive rate
• We have both evidence and a specific trigger
• We have no mechanism
  – But we’re working this
• We also have no evidence that the new cells are viable
  – No **clinical** evidence; **anecdotal** evidence exists
Summary

• Models can be combined to give transformational insights
  – The contributing models need to be strong
  – Lack of sophistication can work well

• A normative age-related model of MFD allows quantification of the effects of treatment
  – Using predicted MFD before treatment as the baseline

• Effect of first line cancer treatment on the ovarian reserve and follicular density in girls under the age of 18 years
  – M El Issaoui, V Giorgione, et al.
It's all very well “making discoveries”, “saving lives” and “improving the world”, Roger. But your research is making barely any impact on social media.

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Thank You

Any questions?