The Impact of Cancer Treatment on Female Fertility: Achieving Pregnancy and Live Birth

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Disclosures

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Research support from Beckman Coulter, Ansh labs
Chemotherapy reduces the annual breast cancer death rate by 38%

We now need to add the ‘ageing’ delays of endocrine Rx
Childhood cancer survivors by current age

Long-term survival rate from childhood cancer is 80%
1 in 700 adults is a childhood cancer survivor

Skinner et al 2006 Lancet Oncology 7:489
The broader ‘survivorship’ agenda

• Most cancer survivors have significant health issues
  – Oeflinger et al NEJM 2006

• Reduced chance of marriage/cohabitation with brain/CNS cancers
  – Frobisher et al Int J Cancer 2007

• Concerns about bringing up a family after cancer
  – Recurrence, life expectancy
  – Goncalvez et al HRUpdate 2014
Chemotherapy: immediate and late effects on the ovary

• Depletion of growing follicles
  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
Consider:
• diagnosis / treatment plan
• expected outcome of fertility treatment
• prognosis of the cancer treatment
Fertility:
‘Good links are required between paediatric oncology units and fertility services’

‘Consider ovarian tissue cryopreservation (within the context of a clinical trial) in girls at high risk of premature ovarian insufficiency (D)’
Effects of cancer therapy on the ovary

Biomarkers: AMH, AFC, menses
Clinical outcomes: fertility, age at menopause

Blood vessels → Primordial Follicles → AMH → Growing Follicles → Cancer Treatment

Post treatment amenorrhea

AMH

Premature ovarian insufficiency

Potential fertility/subfertility

Infertility

Estrogen deficiency

Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab
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

Focal cortical fibrosis in ovaries exposed to chemotherapy

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

The variability in ovarian activity after cancer treatment

Key variables: age and treatment

Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab
Age-related changes in the ovarian reserve

Can we individualise based on ovarian reserve?
AMH reflects the number of small growing follicles

>60% from 3-8 mm antral follicles

Jepperson, Anderson et al 2013 MHR 19, 519
Anderson RA 2012 Clin Endocrinol 77, 652
AMH identifies ovarian damage in childhood cancer survivors despite regular cycles

Bath LE et al 2003 Human Reprod 18 2368
Prediction of ovarian function after chemotherapy

In relation to predictive markers here

Recruited n=56

Chemotherapy 42

No chemo
- Goserelin + Tam 8
- Tamoxifen 5
- Gos + anastrozole 1

Chemotherapy 42

6-9 months

Post chemo
- Tamoxifen 26
- Goserelin + Tam 8
- Arom inhib 11
- None 4

Surgery

‘Late’ analysis
- 35 at 4 years
- 33 at 5 years (79%) recurrence, TAH/BSO

USS:
- 27 pretreatment
- 21 at 5 years

Analyse ovarian activity here

Anderson RA et al 2006 Human Reprod 21, 2583
Effect of chemotherapy in eBC acute toxicity and long-term prediction

Anderson RA et al 2006 Human Reprod 21, 2583
Prediction of long-term ovarian function: pretreatment assessment

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

Anderson and Cameron 2011 JCE&M 96, 1336
Breast cancer prospective cohort 2

Prediction of post chemo ovarian function

60 women recruited

1 woman excluded: ineligible

59 women included

Chemotherapy (table 1)
Endocrine therapy
Tamoxifen (44)
Tamoxifen + Goserelin (6)
Tamoxifen + anastrozole (1)
Goserelin (1)

4 women withdrew before 1 year:
disease recurrence (n=1)
oophorectomy (1)
choice (2)

55 women at 1 year

9 women withdrew before 2 years:
disease recurrence (2)
hyst/oophorectomy (3)
choice (4)

46 women at 2 years

Anderson et al 2013 Eur J Cancer 49, 3404
Clinical application: predictive mosaic chart in eBC

- Sensitivity: 98.2%
- Specificity: 80.0%

For correct classification of amenorrhoea

n=75

Anderson et al 2013 Eur J Cancer
AMH profiles after chemotherapy

Are AMH levels here discriminatory?

Is AMH a good diagnostic here?
GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial

R. C. F. Leonard¹*, 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 ± 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?

Li et al 2011 Fertil Steril 96, 774
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 >25 IL/L).
N=96 and 28 respectively; median ± 95% confidence intervals.

Anderson et al 2017 Eur J Cancer
Importance of age for recovery of ovarian function after chemotherapy

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

Data from OPTION trial

Anderson RA et al 2017 Eur J Cancer
AMH and FSH at end of treatment for prediction of POI at 24 months
OPTION control group, n=32

AMH AUC 0.89
sensitivity 91%, specificity 82%

FSH AUC 0.77
sensitivity 100%, specificity 55%

Anderson RA et al 2017 Eur J Cancer
AMH profiles after chemotherapy

Clinical importance: identification of permanent POI may allow optimisation of endocrine treatment post chemo.

AMH good diagnostic here

AMH levels here are discriminatory if >40yrs
AMH: application in childhood cancer

22 girls age 0.3-15yr
17 prepubertal

Brougham et al 2012 JCE&M 97, 2059
AMH in 3 girls with cancer

Age 1.2; neuroblastoma

Age 2.4; rhabdomyosarcoma

Age 14.6: Hodgkin’s lymphoma

How predictive is this?

Brougham et al 2012 JCE&M 97, 2059
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

Hagen et al 2012 Fertil Steril
AMH and fertility in older women

Cumulative probability of conception stratified by AMH levels

Adjusted for age, smoking, contraception, BMI, race, prev pregnancy

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

Steiner AZ et al, 2017, JAMA
What about low toxicity regimens? RATHL trial in Hodgkin Lymphoma

Stage II (adverse), III, IV, IPS 0-7, Over 18, PS 0-3

PET 1(Staging)

2 cycles ABVD
Full dose, on schedule

PET 2 +ve

4 cycles BEACOPP-14 or 3 eBEACOPP

PET 2 -ve

Randomise

PET 3 +ve

4 cycles ABVD

PET 3 -ve

4 cycles AVD

RT or salvage regimen

2 cycles BEACOPP-14 or 1 eBEACOPP

Follow-up (no RT)

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)

**RATHL ovarian substudy**

- Median age: 26 31

**Figure: Flowchart of study enrollment and selection**

1. Registered for the ovarian sub study: N=74
2. Off study before/at PET2: N=7 Not included in the analysis
3. Remained on study: N=67
   - ABVD/AVD: N=57 ABVD n=24 AVD n=33
   - BEACOPP: N=10 BEACOPP-14 n=4 BEACOPP-esc n=6
4. Registered in RATHL: N=1214
5. Female, age<45: N=415
   - Off study before/at PET2: N=24 Not included in the analysis
6. Remained on study: N=391
7. FSH≤25 at baseline: N=356 ABVD/AVD n=307 BEACOPP n=49
   - FSH missing or FSH>25 at baseline: N=35
     - Not included in the FSH analysis Missing n=29 FSH>25 n=6
8. FSH post-treatment: N=321 ABVD/AVD n=282 BEACOPP n=39

Anderson RA et al 2018 Lancet Oncol
Effects of A(B)VD and BEACOPP on ovarian function

Blue: ABVD
Red: BEACOPP
(after 2 cycles of ABVD)

Anderson RA et al 2018 Lancet Oncol
Main relationships: AMH, age, recovery

AMH pretreatment vs age

AMH pretreatment vs 2 yr levels

Spearman r=0.71, p=0.0002
Slope = 1.05
Overall, AMH at recovery reflects pretreatment level

Anderson RA et al 2018 Lancet Oncol
Is AMH recovery always good?

- AMH recovery by age: Older women show reduced recovery
  \[ r = -0.48, \ p = 0.001 \]
- AMH recovery by pretreatment AMH: Women with low AMH show full recovery
  \[ r = -0.02, \ p = 0.9 \]

Anderson RA et al 2018 Lancet Oncol
Confirmation of impact of age on recovery

By age

<table>
<thead>
<tr>
<th>Age</th>
<th>% recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>140</td>
</tr>
<tr>
<td>35+</td>
<td>100</td>
</tr>
</tbody>
</table>

P<0.0001

By median AMH (9.8 pmol/l)

<table>
<thead>
<tr>
<th>AMH</th>
<th>% recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above</td>
<td>120</td>
</tr>
<tr>
<td>Below</td>
<td>100</td>
</tr>
</tbody>
</table>

ns

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

Anderson RA et al 2018 Lancet Oncol
FSH recovery after A(B)VD is also dependent on age

recovery to <25IU/L

<table>
<thead>
<tr>
<th>Age at EOT</th>
<th>Pretreatment</th>
<th>EOT</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;35</td>
<td>83% (77 – 88)</td>
<td>96% (93 – 98)</td>
<td>98% (95-99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 35+</td>
<td>54% (43 – 66)</td>
<td>83% (73 – 91)</td>
<td>93% (85-97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anderson RA et al 2018 Lancet Oncol
Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary

M. McLaughlin¹,², T.W. Kelsey³, W.H.B. Wallace⁴, R.A. Anderson⁵, and E.E. Telfer¹,²,⁸

ABVD Tissue shows clustering of follicles
Also seen in pre-pubertal tissue

McLaughlin et al 2016 Human Reprod
Effects of cancer therapy on the ovary

Biomarkers: AMH, AFC, menses
Clinical outcomes: fertility, age at menopause
Infertility despite menses resuming after chemotherapy

- Breast (n = 169)*
- HD (n = 128)*
- NHL (n = 123)*
- GI (n = 50)*
- Leukemia (n = 60)

Proportion of women

Age at diagnosis

Letourneau et al 2012 Cancer 118, 1710
Live birth to female childhood cancer survivors: chemo only

Pregnancy: HR 0.87 (0.81-0.94)

Alkylators only at highest dose
Busulfan and Lomustine

Chow et al Lancet Oncol 2016
Parenthood in female survivors of Hodgkin lymphoma in childhood and adolescence

Number with first parenthood/number in age group
Hodgkin’s lymphoma survivors
German population (×1000) p value
15/1539 190/2246 645/2335 1284/2362 1609/2228 2208/2847 2596/3244
0.001 0.13

0/19 4/35 23/84 69/129 78/110 40/66 14/21

0.53 0.96 0.84 0.76
The impact of pelvic radiotherapy in girls with Hodgkin Lymphoma

Non significant or only minor effects of:
- procarbazine (to 11400 mg/m$^2$)
- cyclophosphamide (to 6000 mg/m$^2$)
- alkylating agent dose scores of 1–5
- treatment protocol
- age at treatment
Hazard ratio for menopause <40 yrs in treatment of HL

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

Swerdlow AJ et al 2014, J Natl Cancer Inst
Impact of age on time to regular cycle after treatment for Hodgkin Lymphoma

HD13: early favourable
2xABVD±bleomycin

HD14: early unfavourable
4xABVD or 2xBEACOPP

HD15: advanced
6-8 x BEACOPP esc or -14
Pregnancy after cancer in girls and women in Scotland: a population-based analysis

Richard A Anderson, David H Brewster, Rachael Wood, Sian Nowell, Tom W Kelsey, Colin Fischbacher, W Hamish B Wallace
Scottish Cancer Registry, Information Services Division, NHS National Services Scotland
Information Services Division, NHS National Services Scotland
eData Research & Innovation Service, NHS National Services Scotland and Farr Institute
Department of Oncology and Haematology, Royal Hospital for Sick Children, Edinburgh
Aims

• To provide a population based analysis of the impact of cancer on subsequent pregnancy in females
• All diagnoses
• All ages up to 40
Methods

Study population
- female patients aged 39 years or under at date of first cancer
- on Scottish Cancer Registry
- diagnosed 1981-2012: n=23,201
- Linked to hospital discharge records
  - subsequent pregnancies up until the end of 2014.
  - miscarriage, termination, singleton live or still birth
- Follow-up to the date of death or 31st December 2014.
- Controls: population based, age matched
- Not previously pregnant (n=10,271): 3x age matched controls
Population-based analysis of pregnancy after cancer

38% less likely to achieve a pregnancy after diagnosis than women in the general population

28.6% vs 46.4% of women achieve a pregnancy after a cancer diagnosis

-across all diagnostic groups

Impact of age at diagnosis

Impact of period of diagnosis

RA Anderson et al 2018 Human Reprod
# Population-based analysis of pregnancy after cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of women</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix uteri</td>
<td>3498</td>
<td>0.34</td>
<td>0.31-0.37</td>
</tr>
<tr>
<td>Breast</td>
<td>5173</td>
<td>0.39</td>
<td>0.36-0.42</td>
</tr>
<tr>
<td>Brain, CNS</td>
<td>1045</td>
<td>0.42</td>
<td>0.36-0.48</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1077</td>
<td>0.48</td>
<td>0.42-0.54</td>
</tr>
<tr>
<td>Ovary</td>
<td>1129</td>
<td>0.63</td>
<td>0.57-0.69</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>962</td>
<td>0.67</td>
<td>0.62-0.73</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>673</td>
<td>0.67</td>
<td>0.58-0.77</td>
</tr>
<tr>
<td>Thyroid</td>
<td>926</td>
<td>0.79</td>
<td>0.72-0.86</td>
</tr>
<tr>
<td>Skin</td>
<td>5252</td>
<td>0.87</td>
<td>0.84-0.90</td>
</tr>
</tbody>
</table>

RA Anderson et al 2018 Human Reprod
Overall impact: ‘missing’ pregnancies

Why is this?
Eg skin cancer:
Unlikely to be ‘biological’
Possibly ‘psychological’
-effect on life choices?
Females not pregnant before cancer

- 10,271 women vs 30,811 age-matched controls
- Competing risk analysis
- Proportion achieving a first pregnancy
  - 20.6% vs 38.7%
- Rate ratio 0.53 (CI 0.51-0.56)

RA Anderson et al 2018 Human Reprod
Chance of a first pregnancy after cancer

Leukaemia

Hodgkin lymphoma

Breast cancer

Age at diagnosis
# First vs all pregnancies after cancer

<table>
<thead>
<tr>
<th></th>
<th>No of women</th>
<th>SIR</th>
<th>95% CI</th>
<th>% pregnant before cancer</th>
<th>% achieving pregnancy after</th>
<th>% achieving first pregnancy after</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervix uteri</strong></td>
<td>3498</td>
<td>0.34</td>
<td>0.31-0.37</td>
<td>67.4</td>
<td>15.8</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td>5173</td>
<td>0.39</td>
<td>0.36-0.42</td>
<td>67.9</td>
<td>10.6</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Brain, CNS</strong></td>
<td>1045</td>
<td>0.42</td>
<td>0.36-0.48</td>
<td>30.3</td>
<td>19.9</td>
<td>11.7</td>
</tr>
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<td><strong>Leukaemia</strong></td>
<td>1077</td>
<td>0.48</td>
<td>0.42-0.54</td>
<td>21.6</td>
<td>21.8</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Hodgkin lymphoma</strong></td>
<td>962</td>
<td>0.67</td>
<td>0.62-0.73</td>
<td>36.1</td>
<td>60.8</td>
<td>38.2</td>
</tr>
<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>673</td>
<td>0.67</td>
<td>0.58-0.77</td>
<td>46.5</td>
<td>32.2</td>
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<td>57.8</td>
<td>48.8</td>
<td>33.8</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38.7</td>
</tr>
</tbody>
</table>
The changing risk to fertility in some cancers
Changing risk by age

Hodgkin lymphoma

Leukaemia

Breast ca

SIR, error bars ± CI

Data from RA Anderson et al 2018 Human Reprod
### Outcome of first pregnancies after cancer

<table>
<thead>
<tr>
<th>Singleton first pregnancies following cancer</th>
<th>Nulliparous women with cancer</th>
<th>Control women</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number % / rate *</td>
<td>Number % / rate*</td>
<td>Difference</td>
<td>Lower</td>
</tr>
<tr>
<td>Total</td>
<td>2071 100</td>
<td>11772 100</td>
<td>0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>203 9.8</td>
<td>1095 9.3</td>
<td>0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>Termination</td>
<td>231 11.2</td>
<td>1725 14.7</td>
<td>-3.5</td>
<td>-5.0</td>
</tr>
<tr>
<td>Still Birth</td>
<td>8 0.4</td>
<td>53 0.5</td>
<td>-0.1</td>
<td>-0.4</td>
</tr>
<tr>
<td>Live Birth</td>
<td>1629 78.7</td>
<td>8899 75.6</td>
<td>3.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Infant Death</td>
<td>12 7.4</td>
<td>43 4.8</td>
<td>2.5</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

* % of all first singleton pregnancies apart from infant deaths which is per 1000 live births
Fertility and women’s health: can we link short-term assessment to long term outcomes?

Supporting lifelong women’s health

AMH

Premature ovarian insufficiency

Infertility

Estrogen deficiency

Recovery, of variable duration

Potential fertility/subfertility

Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab
Conclusions

Fertility preservation is now ‘main stream’ medicine

Oncofertility assessment for all: definitely!

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
Long-term health outcomes from our interventions
Key collaborators and funding

David T Baird
Hamish Wallace
Paed oncologist, Edinburgh

David Cameron and colleagues, Edinburgh Breast Unit
Bob Leonard and OPTION investigators
Peter Johnson and RATHL investigators
David Brewster and Rachael Wood, ISD, NHS Scotland
Tom Kelsey, Mathematician, St Andrews University
Roche Diagnostics for assay reagents