Assessing ovarian function after cancer

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Chemotherapy reduces the annual breast cancer death rate by 38%
Childhood cancer survivors by current age

Long-term survival rate from childhood cancer is 80%
1 in 700 adults is a childhood cancer survivor
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 insufficiency
  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
## Risks of chemo agents to fertility

<table>
<thead>
<tr>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Cisplatin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Carboplatin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Chlormethine</td>
<td>Doxorubicin</td>
<td>Dactinomycin</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Dacarbazine</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Thiotepa</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Gemcitabine</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Cytarabine</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>Daunorubicin</td>
<td>Fludarabine</td>
</tr>
<tr>
<td>Carmustine</td>
<td></td>
<td>Etoposide</td>
</tr>
<tr>
<td>Lomustine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from ASCO guidelines and others
Ovarian failure and radiation to the ovary

Chemaitilly, W. et al. J Clin Endocrinol Metab 2006;91:1723
Adverse effect of radiotherapy to uterus

Miscarriage

Percent

TBI  Cyclophos  Expected

5/8

8/44

Premature delivery

Percent

TBI  Cyclophos  Expected

6/16

4/56

Sanders et al 1996 Blood 87, 3045
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 amenorrhoea

AMH
Premature ovarian insufficiency

Potential fertility/subfertility
Infertility
Estrogen deficiency

Jayasinghe, Wallace and Anderson 2018
The variability in ovarian activity after cancer treatment

Key variables: age and treatment
Age-related changes in the ovarian reserve

Can we individualise based on ovarian reserve?

Wallace and Kelsey 2010 PLoS One 5; e8772
Live birth to female childhood cancer survivors: chemo only

Cumulative incidence [%]

Pregnancy: HR 0.87 (0.81-0.94)
Alkylators only at highest dose
Busulfan and Lomustine

# at risk:
Survivor 3093 3185 2353 1076 452 197 147
Sibling 1843 1580 1056 567 268 121 75

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

![Graph showing parenthood percentages by age group for Hodgkin's lymphoma survivors compared to the German population.](image)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Hodgkin's lymphoma survivors</th>
<th>German population</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-19</td>
<td>0/19</td>
<td>15/1539</td>
</tr>
<tr>
<td>20-24</td>
<td>4/35</td>
<td>190/2246</td>
</tr>
<tr>
<td>25-29</td>
<td>23/84</td>
<td>645/2335</td>
</tr>
<tr>
<td>30-34</td>
<td>69/129</td>
<td>1284/2362</td>
</tr>
<tr>
<td>35-39</td>
<td>78/110</td>
<td>1609/2228</td>
</tr>
<tr>
<td>40-44</td>
<td>40/66</td>
<td>2208/2847</td>
</tr>
<tr>
<td>45-49</td>
<td>14/21</td>
<td>2596/3244</td>
</tr>
</tbody>
</table>

Number with first parenthood/number in age group

Hodgkin's lymphoma survivors

German population (×1000)

p value

0.53 0.96 0.84 0.76 0.001 0.13

Brämswig JH et al 2015 Lancet Oncol 16, 557-675
Treatment-related aspects

Non significant or only minor effects of:

• procarbazine (to 11 400 mg/m²)
• cyclophosphamide (to 6000 mg/m²)
• alkylating agent dose scores of 1–5
• treatment protocol
• Abdominal/supradiaphragmatic radiation
• age at treatment

Brämswig JH et al 2015 Lancet Oncol 16, 557-675
Hazard ratio for menopause <40 yrs in treatment of HL

- ABVD with pelvic RT
- ABVD
- Alkylating, pelvic RT
- Alkylating, no pelvic RT
- Pelvic RT
- No alkylating, no pelvic RT

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 BEACOPP esc or -14
Infertility despite menses resuming after chemotherapy

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

Proportion of women vs. Age at diagnosis

Letourneau et al 2012 Cancer 118, 1710
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.
Population-based analysis of pregnancy after cancer

All females with cancer in Scotland 1981-2012, aged 0-40 yrs
23,201 cancer survivors
Linked to national maternity database

38% less likely to achieve a pregnancy after diagnosis than women in the general population - across all diagnostic groups

<table>
<thead>
<tr>
<th>Diagnosis</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’
Probably ‘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)

<table>
<thead>
<tr>
<th></th>
<th>0 yrs</th>
<th>5 yrs</th>
<th>10 yrs</th>
<th>20 yrs</th>
<th>30 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>10271</td>
<td>6435</td>
<td>4344</td>
<td>2122</td>
<td>570</td>
</tr>
<tr>
<td>Controls</td>
<td>30811</td>
<td>20167</td>
<td>14294</td>
<td>6858</td>
<td>1990</td>
</tr>
</tbody>
</table>

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

Leukaemia

Hodgkin lymphoma

Breast cancer

Age at diagnosis

- 35-39
- 30-34
- 25-29
- 0-14
- 15-24

- 35-39
- 30-34
- 25-29
- 15-24

- 0-14
- 15-24
- 25-29
- 35-39
- 30-34
The changing risk to fertility in some cancers
## 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</td>
<td>% / rate *</td>
<td>Number</td>
<td>% / rate*</td>
</tr>
<tr>
<td>Total</td>
<td>2071</td>
<td>100</td>
<td>11772</td>
<td>100</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>203</td>
<td>9.8</td>
<td>1095</td>
<td>9.3</td>
</tr>
<tr>
<td>Termination</td>
<td>231</td>
<td>11.2</td>
<td>1725</td>
<td>14.7</td>
</tr>
<tr>
<td>Still Birth</td>
<td>8</td>
<td>0.4</td>
<td>53</td>
<td>0.5</td>
</tr>
<tr>
<td>Live Birth</td>
<td>1629</td>
<td>78.7</td>
<td>8899</td>
<td>75.6</td>
</tr>
<tr>
<td>Infant Death</td>
<td>12</td>
<td>7.4</td>
<td>43</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* % of all first singleton pregnancies apart from for infant deaths which is per 1000 live births

RA Anderson et al 2018 Human Reprod
The variability in ovarian activity after cancer treatment

Key variables: age and treatment
Premature loss of ovarian function: Infertility and POI

Can we individualise based on ovarian reserve?

Wallace and Kelsey 2010 PLoS One 5; e8772
AMH reflects the number of small growing follicles
The AMH normal range from birth to menopause

Key features
- Detectable in girls of all ages
- Rise through childhood
- Peak at 24 yrs

Breast cancer prospective cohorts

Prediction of post chemo ovarian function

In relation to predictive markers here

Chemotherapy (table 1)
- Tamoxifen (44)
- Tamoxifen + Goserelin (6)
- Tamoxifen + anastrozole (1)
- Goserelin (1)

Analyse ovarian activity here

60 women recruited

1 woman excluded: ineligible

59 women included

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
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
Clinical application: predictive mosaic chart in eBC

- Sensitivity: 98.2%
- Specificity: 80.0%
- For correct classification of amenorrhea

n=75

Anderson et al 2013 Eur J Cancer
Can AMH diagnose POI after chemo?

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

Red, not POI
Blue: POI (amenorrhoea plus FSH >25IU/L).
N=96 and 28 respectively; median ± 95% confidence intervals.

Anderson et al 2017 Eur J Cancer
Ovarian function after chemotherapy: age and treatment-dependant

AMH for
- Pre chemo prediction
- Post chemo diagnosis
AMH: application in childhood cancer

Medium/low risk

High risk

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

Can this predict their reproductive lifespan?

Brougham et al 2012 JCE&M 97, 2059
AMH and prediction of menopause

AMH at baseline

Menopause by AMH centile

257 ovulatory women, 21-46yr
Reassessed after 11 years (19% menopausal)

Low age specific AMH
Shift towards younger age at menopause

High age specific AMH
Shift towards higher age at menopause

Broer SL et al 2011 JCE&M
AMH and fecundability

AMH quintiles, middle 3 combined

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

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
PET 2 + ve

4 cycles BEACOPP-14 or 3 eBEACOPP

PET 3 - ve
PET 3 + ve

RT or salvage regimen

PET 3

4 cycles ABVD
4 cycles AVD

Randomise

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)

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

AMH

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?

Older women show reduced recovery

Women with low AMH show full recovery

Anderson RA et al 2018 Lancet Oncol
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)

Anderson RA et al 2018 Lancet Oncol
FSH recovery to <25IU/L after A(B)VD is dependent on age

Kaplan-Meier estimates at 1 year
83% (77 – 88) in <35 yrs
54% (43 – 66) in ≥35 yrs

at 2 years
96% (93 – 98) in <35 yrs
83% (73 – 91) in ≥35 yrs

At 3 years: 98% (95-99) vs 93% (85-97)

Anderson RA et al 2018 Lancet Oncol
FERTILITY RISK ASSESSMENT
(Includes Intrinsic and Extrinsic factors)

Pre-pubertal
Testis biopsy

Pubertal
Able to produce a suitable semen sample

Post-pubertal
Testis Tissue Cryopreservation

Patient Assessment

Pre-pubertal

FEMALE

Ovarian biopsy

Post-pubertal
Ovarian stimulation

MALE

Able to produce a suitable semen sample

NO
Testis biopsy
Testis biopsy/Gamete extraction

YES
Sperm Cryopreservation

Intervention

Storage

Experimental
Established

Anderson RA et al 2015 Lancet Diabetes Endocrinol
Ovarian strip autotransplantation

Oophorectomy

Strip reimplantation on ovarian pedicle

Ovarian transplant model

Oophorectomy
Cryopreservation of cortical strips
Reimplantation

High basal FSH
60-70% of follicles lost

Gosden et al 1994
First baby after ovarian cryopreservation

New mother Quarda Touirat, speaking at a press conference on Friday, said: "I'm very happy, it's what I've always wanted. It was a dream."

"Our findings suggest that cryopreservation of ovarian tissue should be offered to all young women diagnosed with cancer."

Donnez et al., Lancet 2004
‘many experts believe that there is now enough evidence to support the use of ovarian-tissue cryopreservation as a valid and effective technique rather than as an experimental approach’

‘Selection criteria clearly need to be applied, the most important being:
• age of less than 35 years
• a realistic chance of surviving for 5 years
• at least a 50% risk of POI’
The need for patient selection

Percent of women with POI after pre-chemo unilat oophorectomy

Overall n=143, mean 58 months followup

Schmidt KT et al 2013 RBMOnline 26, 272
Pregnancy after treatment (and unilat oophorectomy)

- 57 women had tried to conceive
  - 41 succeeded (72%)

- 68 pregnancies overall
  - 45 babies
  - 5 ongoing
  - 15 miscarriages
  - 1 ectopic
  - 1 termination

Need for better selection!
15 year, population-based analysis of criteria for ovarian cryopreservation

Female cancer patients age <18 at diagnosis 01/01/1996 - 30/6/2012  

\[ n = 410 \]

Offered cryopreservation  
\[ n = 34 \]

- Tissue cryopreserved  
\[ n = 20 \]

- Procedure declined  
\[ n = 13 \]

- Procedure unsuccessful  
\[ n = 1 \]

- Deceased  
\[ n = 1 \]

Not offered cryopreservation  
\[ n = 376 \]

- Deceased  
\[ n = 81 \]

- <12 years old  
\[ n = 91 \]

- On COCP  
\[ n = 17 \]

- Lost to follow-up  
\[ n = 1 \]

- On COCP  
\[ n = 1 \]

- Still on treatment  
\[ n = 4 \]

- Insufficient information on follow-up  
\[ n = 42 \]

- Parental choice  
\[ n = 2 \]

- Too unwell  
\[ n = 9 \]

- Uterine factor  
\[ n = 1 \]

- Poor communication  
\[ n = 1 \]

- <12 years old  
\[ n = 14 \]

- <12 years old  
\[ n = 6 \]

- <12 years old  
\[ n = 141 \]

Do the ‘Offered’ group have a higher prevalence of POI?  
(robust criteria of amen >4mo +high FSH x2/low E2)

Wallace, Smith, Kelsey, Edgar and Anderson 2014 Lancet Oncology 15, 1129
Cumulative incidence of POI

15-year probability 35% [95% CI 10–53] vs 1% [0–2] p<0.0001

Hazard ratio 56.8 [95% CI 6.2–521.6] at 10 years

Wallace, Smith, Kelsey, Edgar and Anderson 2014 Lancet Oncology 15, 1129
Conclusions

• Fertility preservation is becoming ‘main stream’

• Need for accurate, patient-specific risk to fertility and ovarian function
  – Extrinsic issues: proposed treatment
  – Intrinsic issues: age and ovarian reserve

• Development of evidence-based algorithms to enable truly informed patient choice
• And (cost-)effective care
Key collaborators

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

Hamish Wallace
Paed oncologist, Edinburgh

Tom Kelsey
St Andrews