FERTILITY PRESERVATION IN THE (YOUNG) CANCER PATIENT

Professor W Hamish B Wallace
University of Edinburgh &
Royal Hospital for Sick Children,
Edinburgh, Scotland, UK

hamish.wallace@nhs.net

ESMO
Madrid
27 September 2014
No Conflicts of Interest to Declare
Improved Five Year Survival (1966-2000)

Figure 3.1: Survival of childhood cancer patients diagnosed 1966-2000, by period of diagnosis

- 1996-2000
- 1991-1995
- 1986-1990
- 1981-1985
- 1976-1980
- 1971-1975
- 1966-1970

% still alive vs. Years since diagnosis
Risk assessment for fertility preservation

- **Intrinsic factors**
  - Health status of patient
  - Consent (patient/parent)
  - Age
  - Assessment of ovarian reserve

- **Extrinsic factors**
  - Nature of predicted treatment
    - (high/medium/low/uncertain risk)
  - Expertise/options available

After Wallace WH, Critchley HO and Anderson RA
Optimizing reproductive outcome in children and young people with cancer.
*J Clin Oncol* 2012; 30: 3-5.
# Risk of infertility

<table>
<thead>
<tr>
<th>Low risk (&lt;20%)</th>
<th>Medium risk</th>
<th>High risk (&gt;80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>AML</td>
<td>Total Body Irradiation</td>
</tr>
<tr>
<td>Wilms’ tumour</td>
<td>Osteosarcoma</td>
<td>Pelvic/testes RT</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>Ewing’s sarcoma</td>
<td>Chemo pre BMT</td>
</tr>
<tr>
<td>Sx, RT &lt; 24Gy</td>
<td>STS: stage II/III</td>
<td>Metastatic Ewing's</td>
</tr>
<tr>
<td>Soft tissue sarcoma (stage1)</td>
<td>Neuroblastoma</td>
<td>HL (Pelvic RT)</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma HL (Low stage)</td>
<td>NHL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain tumour RT &gt; 24 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HL (High Stage)</td>
<td></td>
</tr>
</tbody>
</table>

Wallace et al., The Lancet Oncology, 2005
Young females with cancer
Ovarian reserve: Conception to Menopause

Ovarian reserve: Conception to Menopause

Wallace and Kelsey 2010 PLoS One 5; e8772
Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer.

Sensitivity 98.2%
Specificity 80.0%
For correct classification of amenorrhea

n=75
## Key features of the 3 options for fertility preservation for women

<table>
<thead>
<tr>
<th>Technique</th>
<th>Main advantages</th>
<th>Main disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo cryopreservation</td>
<td>Established technique</td>
<td>May incur delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sperm required: partner or donor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed potential for future fertility</td>
</tr>
<tr>
<td>Oocyte cryopreservation</td>
<td>Does not require sperm</td>
<td>May incur delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not appropriate for pre-pubertal child</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited numbers of eggs can be stored in time available</td>
</tr>
<tr>
<td>Ovarian tissue cryopreservation</td>
<td>Minimal delay</td>
<td>Requires surgical procedure</td>
</tr>
<tr>
<td></td>
<td>No lower age limit</td>
<td>Malignant contamination in some conditions precludes reimplantation</td>
</tr>
<tr>
<td></td>
<td>Allows for spontaneous and repeated conception</td>
<td>In vitro follicle growth unlikely to be available for several years.</td>
</tr>
<tr>
<td></td>
<td>Greater allowance for future developments</td>
<td></td>
</tr>
</tbody>
</table>
Ovarian tissue cryopreservation: World-wide experience

* At least 30 pregnancies worldwide after othotopic reimplantation of frozen-thawed ovarian cortex
* Success rate is unclear as the denominator is unknown
* No pregnancies reported following the reimplantation of ovarian tissue harvested pre-pubertally
* Young children are potentially ideal candidates

- To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer
- Expert Panel
- The questions to be addressed by the guideline were determined by the Panel
- Systematic review of the available literature

Lee et al. JCO 2006
Loren et al. JCO 2013

• Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
• Refer patients who express an interest in fertility preservation to reproductive specialists
• Address fertility preservation as early as possible, before treatment starts
• Document fertility preservation discussions in the medical record
• Encourage patients to participate in registries and clinical studies

Lee et al. JCO 2006
Loren et al. JCO 2013
Fertility Preservation ASCO Guidelines update (2013) (Females)

- Embryo (2006) and oocyte cryopreservation (2013) should be considered as established fertility preservation methods.
- There is insufficient evidence of the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method.
- Other methods (e.g., ovarian tissue cryopreservation) are still experimental.

Lee et al. JCO 2006
Loren et al. JCO 2013
Ovarian cryopreservation & ovarian function

Edinburgh experience in children (<18 yrs)
1996-2012
Can we develop useful criteria for fertility preservation in children and adolescents?

Development of ‘Edinburgh criteria’ since 1996
• Age <35 years
• No previous chemotherapy (or low risk)
• High (>50%) risk of ovarian failure
  • High dose alkylating agents
  • Radiotherapy to pelvis
• Good (>50%) chance of survival

Can this predict those at high risk of POI?
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

Deceased
n = 1

<12 years old
n = 4

On COCP
n = 1

Not offered cryopreservation
n = 376

Deceased
n = 81

<12 years old
n = 91

On COCP
n = 17

<12 years old
n = 3

<12 years old
n = 2

Still on treatment
n = 4

Insufficient information on follow-up
n = 42

Lost to follow-up
n = 1

Does the ‘Offered’ group have a higher prevalence of POI?
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
Conclusion

• Ovarian cryopreservation was offered to 9% of our patients, and performed in 5%
• The procedure was safe and without complications
• No patients have asked for re-implantation of their tissue – to date
• All patients who have thus far developed premature ovarian insufficiency were identified except one patient
• The Edinburgh Selection Criteria have proved to be helpful in selecting those patients at highest risk of POI
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)
Isolated human sperm cells (1500x)
Albert Tousson – Nikon Small world
Males: Fertility preservation

• Young men who can produce semen should have the opportunity of sperm banking before treatment begins
• Sperm retrieval should be considered if the chances of infertility are high and the testes are >10mls
  • Storage of gametes is governed by the HFE act 1990
  • Written informed consent from a competent male is required

• There is currently no option to preserve fertility in the pre-pubertal boy
Fertility Preservation ASCO Guidelines update (2013) (Males)

• Present sperm cryopreservation (sperm banking) as the only established fertility preservation method
• Do not recommend hormonal therapy in men; it is not successful in preserving fertility
• Inform patients that other methods (eg, testicular tissue cryopreservation) are experimental
• Advise men of a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy

Lee et al. JCO 2006
Loren et al. JCO 2013
Acknowledgements

• Richard Anderson
• David T Baird
• Tom Kelsey
• Evelyn Telfer
• Marie McLaughlan
• Alice Grove Smith
• George Galea

• Rod Mitchell
• Louise Bath
• Chris Kelnar
• Angela Edgar
• Mark Brougham
• Fraser Munro
THANK YOU
Ovarian cortical strips

- rich in primordial follicles
- survive cryopreservation
- technique validated in sheep

Baird DT et al., Endocrinology (1999)
## Live births following cryopreservation of ovarian tissue and transplantation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (yrs)</th>
<th>Surgical method</th>
<th>Reimplantation</th>
<th>Pregnancy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>25</td>
<td>Unilateral ovarian biopsy</td>
<td>Orthotopic</td>
<td>Spontaneous, live birth</td>
<td>Donnez, 2004</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>31</td>
<td>Unilateral ovarian biopsy (after 1st course chemo)</td>
<td>Ortho and heterotopic</td>
<td>Spontaneous, miscarriage then livebirth</td>
<td>Demeestere 2007</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>27</td>
<td>Whole ovary</td>
<td>Orthotopic</td>
<td>Livebirth male Week 37 B.Wt 2.6 Kg</td>
<td>Andersen et al 2008</td>
</tr>
<tr>
<td>Ewings Sarcoma</td>
<td>36</td>
<td>Whole ovary</td>
<td>Orthotopic</td>
<td>Livebirth Female Term B Wt 3.2 Kg</td>
<td>Andersen et al 2008</td>
</tr>
</tbody>
</table>
Technology or evidence led?

• When there is uncertainty about a new experimental procedure, it is important for it to be evaluated in IRB-approved clinical trials.

• Unlikely to be feasible or ethical to perform an RCT in a well characterized group of young women to test laparoscopic collection of ovarian cortex versus versus either dummy laparoscopy or no intervention.

• It is highly unlikely that IRBs would pass such a study, or that such a randomized study would be able to recruit sufficient patients.
**Table 2: Patient characteristics and ovarian function in those patients where ovarian tissue was cryopreserved**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age at cryopreservation (years)</th>
<th>Method of ovarian tissue collection</th>
<th>Complications from procedure</th>
<th>Duration since cryopreservation (years)</th>
<th>Age at last assessment (years)</th>
<th>Current Ovarian Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hodgkin's Lymphoma</td>
<td>14.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.8</td>
<td>30.2</td>
<td>Not POI</td>
</tr>
<tr>
<td>2</td>
<td>Ewing's Sarcoma (pubic bone)</td>
<td>14.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>16.6</td>
<td>25.6</td>
<td>POI (+1 child)</td>
</tr>
<tr>
<td>3</td>
<td>Sacral Ependymoma</td>
<td>11.3</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.8</td>
<td>24.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>4</td>
<td>Hodgkin's Lymphoma</td>
<td>13.7</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.6</td>
<td>28.9</td>
<td>Not POI</td>
</tr>
<tr>
<td>5</td>
<td>Hodgkin's Lymphoma</td>
<td>11.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>14.7</td>
<td>On COCP</td>
<td>Not POI</td>
</tr>
<tr>
<td>6</td>
<td>Chronic Granulocytic Leukaemia</td>
<td>9.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>12.2</td>
<td>21.7</td>
<td>Not POI</td>
</tr>
<tr>
<td>7</td>
<td>Rhabdomyosarcoma</td>
<td>5.3</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>8.2</td>
<td>13.1</td>
<td>POI</td>
</tr>
<tr>
<td>8</td>
<td>Ewing's Sarcoma (pelvic)</td>
<td>9.8</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>6.7</td>
<td>15.6</td>
<td>POI</td>
</tr>
<tr>
<td>9</td>
<td>Uterine Cervix Rhabdomyosarcoma</td>
<td>16.4</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>5.1</td>
<td>17.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>10</td>
<td>Hodgkin's Lymphoma</td>
<td>14.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.2</td>
<td>17.2</td>
<td>POI</td>
</tr>
<tr>
<td>11</td>
<td>Abdominal Embryonal Rhabdomyosarcoma</td>
<td>7.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>Deceased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ewing's Sarcoma</td>
<td>12.1</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.9</td>
<td>15.2</td>
<td>POI</td>
</tr>
<tr>
<td>13</td>
<td>Hodgkin's Lymphoma</td>
<td>12.7</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.3</td>
<td>14.3</td>
<td>POI</td>
</tr>
<tr>
<td>14</td>
<td>Metastatic Mesothelioblastoma</td>
<td>8.1</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>2.9</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hodgkin's Lymphoma</td>
<td>15.2</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.9</td>
<td>16.9</td>
<td>Not POI</td>
</tr>
<tr>
<td>16</td>
<td>Alveolar Rhabdomyosarcoma</td>
<td>10.5</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.4</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Embryonal Rhabdomyosarcoma</td>
<td>3.0</td>
<td>Oophorectomy</td>
<td>None</td>
<td>1.4</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Ewing's Sarcoma</td>
<td>12.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.4</td>
<td>13.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>19</td>
<td>Undifferentiated Sarcoma</td>
<td>12.3</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.0</td>
<td>13.4</td>
<td>Not POI</td>
</tr>
<tr>
<td>20</td>
<td>Wilms Tumour</td>
<td>1.2</td>
<td>Oophorectomy</td>
<td>None</td>
<td>0.6</td>
<td>Not assessed</td>
<td></td>
</tr>
</tbody>
</table>

All tissue collected before chemotherapy/radiotherapy administered (except patients 1 and 10). Ovarian function was not assessed in those patients who were under the age of 12 years at the time of the study.

*Hodgkin's Lymphoma collected after relapse of disease 21 months post initial radiotherapy

*Ewing's Sarcoma collected after relapse of disease 7 months post initial radiotherapy

*Uterine Cervix diagnosis changed to Mullerian Adenosarcoma shortly after tissue cryopreserved

*All metastatic deposits found on cortical strip
Offered Cryopreservation and Accepted

n = 14

Not POI
n = 8
Age 21.9 yr (13.3 – 30.7)

POI
n = 6
Age: 13.4 yr (11.2 – 15.3)
Interval: 1.7 yr (0.4 – 6.2)
Offered Cryopreservation - procedure declined

n = 6

Not POI
n = 5
Age 16.7 yr (15.0 – 21.3)

POI
n = 1
Age: 13.4 yr
Interval: 7.9 yr
Not offered Cryopreservation

n = 141

Not POI
n = 140
Age 17.9 yr (12.3 – 32.2)

POI
n = 1
Age: 15.0 yr
Interval: 2.9 yr
HR = 0.026, p < 10^{-5}
HR = 0.026, p < 10^{-7}
HR = 0.021, p < 10^{-9}
HR = 0.018, p < 10^{-11}

Cumulative probability of not POI vs. Years since diagnosis
Cryopreservation of ovarian cortical tissue – Edinburgh criteria

Selection criteria (1995, modified 2000)
- Age < 35 years
- No previous chemotherapy/radiotherapy if age > 15 years
- Mild, non gonadotoxic chemotherapy if < 15 years
- A realistic chance of surviving five years
- A high risk of premature ovarian insufficiency
- Informed consent (Parent and where possible Patient)
- Negative HIV and Hepatitis serology
- No existing children
Algorithm for Tissue Cryopreservation

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>SEMEN ANALYSIS</th>
<th>TESTICULAR BIOPSY</th>
<th>INTRA-OPERATIVE ANALYSIS</th>
<th>METHOD OF CRYOPRESERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pubertal</td>
<td>Unsuitable for semen cyropreservation</td>
<td>Biopsy with NO intra-operative analysis</td>
<td>No sperm/ sperm unlikely*</td>
<td>Immature tissue freezing (DMSO)</td>
</tr>
<tr>
<td>Pubertal</td>
<td>Unable to produce sperm (eg &lt;12) or Oligozoospermia/ Azoospermia</td>
<td>Biopsy with intra-operative analysis</td>
<td>Sperm detected/ sperm likely*</td>
<td>Immature tissue freezing (DMSO) + Mature tissue freezing (Glycerol)</td>
</tr>
<tr>
<td></td>
<td>Suitable for semen cyropreservation</td>
<td></td>
<td></td>
<td>Sperm freezing</td>
</tr>
</tbody>
</table>
Cryopreservation of pre-pubertal testis tissue prior to cancer treatment

• Boys undergoing cancer treatment with >80% risk of infertility

• Biopsy to be taken with routine procedure

• Storage by Tissue Services according to ‘mature’ or ‘immature’ protocol

• Small piece of tissue to be used for research

Ethical Approval Granted – September 2013
Human Testis Xenografting