Fertility preservation: Considerations for the young patient with cancer

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Epidemiology of Childhood Cancer

- Cumulative Risk of childhood cancer: 1 in 444 boys; 1 in 594 girls (1500 cases/yr in UK)
- >80% of children with cancer will survive five years, 70% are ten year survivors
- 1 in 570 young adults (20-34 years) is a childhood cancer survivor in UK
- Fertility remains a prime concern for those who survive
Risk assessment for Fertility preservation

* **Intrinsic factors**
  * Heath status of patient
  * Consent (Patient/Parent)
  * Assessment of ovarian reserve

* **Extrinsic factors**
  * Nature of predicted treatment
    * High/Medium/Low/Uncertain Risk
  * Time available
  * Expertise available
## 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 (stage I)</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; 24Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HL (High Stage)</td>
<td></td>
</tr>
</tbody>
</table>

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Wallace et al. Lancet Oncology 2005
Laura Age 15

- Nodular sclerosing Stage IVB Hodgkin lymphoma
- Bilateral supraclavicular, right axillary, anterior mediastinal, paratracheal, right hilar, posterior mediastinal, coeliac, portal, retroperitoneal, internal and external iliac and deep inguinal lymph nodes
- Bone marrow infiltration

- Treatment
  - EuroNet-PHL-C1 Protocol:
    - Treatment Group 3 (TG3)
  - Ovarian Cryopreservation

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Aims

Can involved field RT be omitted in FDG-PET scan negative patients after two courses of OEPA in all treatment groups?

Can procarbazine be substituted for intermediate and advanced stage disease groups by Dacarbazine?

Maintaining event free survival for all > 90%
**EuroNet-PHL-C-1**

**Chemotherapy randomisation**

- **TG-1**
  - 2 COPP
  - 4 COPDAC

- **TG-2**
  - 2 COPDAC
  - 4 COPP

- **TG-3**
  - 4 COPDAC

- **RA**
- **2 x OEPA**
- **IR**

- **No Radiotherapy**
- **IF-RT**

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EuroNet-PHL-C-1
Chemotherapy randomisation

2 x OEPA

RA

2 x OEPA

IR

TG-1

TG-2

R

2 COPDAC

TG-3

R

4 COPDAC

No Radiotherapy

IF-RT

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Response assessment PET scan

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Laura: Response assessment

- > 50% decrease in the volume of all involved areas
- Largely PET scan negative
- -but still positive in a few small areas on central review
- Involved Field Radiotherapy

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Involved field Radiotherapy

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Estimated dose to organs at risk

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>Maximum dose received</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>spinal cord</td>
<td>2139.7 cGy</td>
<td>1916.2 cGy</td>
</tr>
<tr>
<td>heart</td>
<td>2116.1 cGy</td>
<td>1701.4 cGy</td>
</tr>
<tr>
<td>left kidney</td>
<td>2169.1 cGy</td>
<td>1439.8 cGy</td>
</tr>
<tr>
<td>right kidney</td>
<td>2022.2 cGy</td>
<td>639.3 cGy</td>
</tr>
<tr>
<td>lung</td>
<td>2148.5 cGy</td>
<td>1168.9 cGy</td>
</tr>
<tr>
<td>right breast</td>
<td>2195.1 cGy</td>
<td>476.7 cGy</td>
</tr>
<tr>
<td>left breast</td>
<td>2156.4 cGy</td>
<td>654.6 cGy</td>
</tr>
<tr>
<td>liver</td>
<td>2153.4 cGy</td>
<td>830.2 cGy</td>
</tr>
<tr>
<td>thyroid</td>
<td>2047.2 cGy</td>
<td>1999.0 cGy</td>
</tr>
</tbody>
</table>
After Treatment: with a famous guest!
Effective and mean ovarian sterilizing doses of radiotherapy at increasing age

19 Gy will sterilize at 7 years

11 Gy will sterilize at 42 years

Wallace WH et al. IJRBP (2005)
The Human Ovary
The Wallace-Kelsey Model

\[
\log_{10}(NGF) = \frac{5.56}{4} \left[ 1 + \text{Erf} \left( \frac{age + 25.6 + \frac{52.7}{2}}{0.074\sqrt{2}} \right) \right] \left[ 1 - \text{Erf} \left( \frac{age + 25.6 - \frac{52.7}{2}}{24.5\sqrt{2}} \right) \right]
\]

\[n = 325\]
\[r^2 = 0.81\]
Ovarian reserve: Conception to Menopause (NGF population)


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Percentage of NGF population remaining with increasing age
Prediction of ovarian reserve

- Anti Mullerian Hormone (AMH) is an important product of the adult ovary, produced by the granulosa cells of small growing follicles
- AMH has little variation across and between menstrual cycles
- AMH is the best currently available marker of the number of small-growing follicles in the ovary
A validated model of serum anti-Mullerian hormone from conception to menopause (a single data set of healthy females (n=3260) from twenty different sources)

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Kelsey et al. PLoS ONE (in press)
AMH (Normal range)
## 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</td>
</tr>
<tr>
<td></td>
<td>Allows for spontaneous and repeated conception</td>
<td>precludes reimplantation</td>
</tr>
<tr>
<td></td>
<td>Greater allowance for future developments</td>
<td>In vitro follicle growth unlikely to be available for several years.</td>
</tr>
</tbody>
</table>
Cryopreservation: World-wide experience

- At least 17 pregnancies worldwide after othotopic reimplantation of frozen-thawed ovarian cortex
- Success rate is unclear as the denominator is unknown (?25%)
- No pregnancies reported following the re-implantation of ovarian tissue harvested pre-pubertally
- Young children are potentially ideal candidates

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## 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>
Cryopreservation of ovarian cortical tissue

Selection criteria (1995, modified 2000)

- Age < 30 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 ovarian failure
- Informed consent (Parent and where possible Patient)
- Negative HIV and Hepatitis serology
- No existing children
Consent

- We emphasize in the information sheet that the procedure is voluntary and experimental, and not part of routine practice.
- We obtain informed consent for disposal of ovarian tissue if it is no longer required or the patient dies.
- In the event of the patient's death the material is disposed of or, if consent has been obtained, it may be used for ethically approved research studies.
- Separately, we ask if an additional small amount can be taken at the time of collection for research studies.
- Our practice constitutes research and has been approved by the local institutional review board (IRB).
Reimplantation?

- It is important to be aware that reimplantation of ovarian cortical tissue is a separate procedure.
- Consent for harvesting ovarian tissue from children often will have been obtained from their parents.
- Informed consent for reimplantation can be obtained from the patients at a much later date when they are competent to assess the complex issues themselves.
Ewings sarcoma localised T 7 Vertebrae (Age 12) – Unexpected Contamination of ovarian biopsy

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Re-implantation or IVG and maturation?

- Contamination of the cryopreserved tissue with malignant cells, particularly in haematological malignant disease – shown in a rodent lymphoma model – to cause recrudescence of the original disease

- Oocyte maturation in vitro, followed by IVF, would eliminate this risk
Isolated human sperm cells (1500x)
Albert Tousson – Nikon Small world

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Strategies for fertility preservation in males undergoing treatment for cancer

- Clinical practice
- Sperm banking
  - Ejaculation
  - Rectal electrostimulation?
  - Testicular/epididymal aspiration
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 prepubertal boy.
Summary

Males

- Sperm banking must be considered in all males before treatment that carries a risk of long-term gonadal damage

- There is currently no option to preserve fertility in the pre-pubertal boy (more research required)
Females

- It remains difficult to predict which patients are at high risk of a premature menopause
- Cryopreservation of ovarian tissue before treatment is the best option for girls and young women
- Orthotopic reimplantation works but so far there have been very few live births.
- Accelerated IVG of human oocytes is likely to become a realistic possibility.
- Research-based egg and ovarian tissue storage facilities be developed at a number of collaborating sites in Europe.
Thank you
Activation towards maturation of NGFs

Correlation Coefficients (r)

Birth - 24.5 years
AMH vs NGF population: $r = -0.93$
AMH vs NGF recruitment: $r = 0.52$

24.5 - 51 years
AMH vs NGF population: $r = 0.83$
AMH vs NGF recruitment: $r = 0.88$

Percentage of peak (%) vs Age (years)
Relationship of baseline AMH level (ng/ml) with age at diagnosis
Summary of Talk

- Who is at risk of infertility?
- Assessment of Ovarian Reserve
- What can be offered to those at high risk of infertility?
- Our Edinburgh experience of ovarian cryopreservation
- Ethical and consent issues
Prediction of ovarian reserve

- There is increasing information on the ability of AMH to detect chemotherapy-induced loss of ovarian reserve in survivors of cancer in childhood.

- And limited data from prospective studies illustrate its ability to reflect acute gonadotoxicity.

- There is a need for more research on markers of ovarian reserve to improve our assessment of the individual patient before the onset of potentially gonadotoxic treatment.

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Ethical issues

- Ethical considerations for children are different and more challenging from those involving adults who are assumed to be competent.
- Interventions in children can only be ethical if they can be considered to be therapeutic and in the best interests of the minor.
• We are drowning in information, while starving for wisdom. The world henceforth will be run by synthesizers, people able to put together the right information at the right time, think critically about it, and make important choices wisely.
The assessment of ovarian reserve reserve (for the individual patient)

A photomicrograph of developing oocytes, as they move along the spiral of an anglerfish's ovary. **James E. Hayden**

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