FERTILITY PRESERVATION IN GIRLS AND WOMEN WITH CANCER

Richard A Anderson
Elsie Inglis Professor of Clinical Reproductive Science
University of Edinburgh
LEARNING OBJECTIVES

Effects of cancer treatment on female fertility
Options for fertility preservation in girls and women
Polychemotherapy reduces the annual breast cancer death rate by about 38%
Long-term survival rate from childhood cancer is 80%
1 in 700 adults is a childhood cancer survivor


Cancer in Adolescents and Young Adults (AYA) Working Group
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 (POI)

- Chapman RM, Sutcliffe SB and Malpas JS (1979)
- JAMA 242, 1877-1881
PRIMORDIAL FOLLICLES: THE GUARDIANS OF FEMALE FERTILITY AND FEMININITY

Human ovary, 17 weeks

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ACUTE OVARIAN FAILURE AFTER CHEMOTHERAPY


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INFERTILITY DESPITE MENSES RESUMING AFTER CHEMOTHERAPY

# RISK OF INFERTILITY BY DISEASE/TREATMENT

<table>
<thead>
<tr>
<th>Low (&lt;20%)</th>
<th>Medium</th>
<th>High (&gt;80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>Acute myeloid leukaemia</td>
<td>Total Body Irradiation</td>
</tr>
<tr>
<td>Wilms’ tumour</td>
<td>Osteosarcoma</td>
<td>Pelvic/testes RT</td>
</tr>
<tr>
<td>Soft tissue sarcoma (stage I)</td>
<td>Ewing's sarcoma</td>
<td>Chemo pre BMT</td>
</tr>
<tr>
<td>Brain tumour (Surgery, RT &lt;24Gy)</td>
<td>STS: stage II/III</td>
<td>Metastatic Ewing’s</td>
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<tr>
<td>Hodgkin Lymphoma (low stage)</td>
<td>Hodgkin Lymphoma (high stage)</td>
<td>Hodgkin Lymphoma (pelvic RT)</td>
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<tr>
<td></td>
<td>Non-Hodgkin Lymphoma</td>
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</tbody>
</table>

HAZARD RATIO FOR MENOPAUSE <40 YEARS IN TREATMENT OF HODGKIN LYMPHOMA

All adjusted for age, overall n=2127
PARENTHOOD IN FEMALE SURVIVORS OF CHILDHOOD HODGKIN LYMPHOMA


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TREATMENT-RELATED ASPECTS

Non significant / 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

OVARIAN FAILURE AND RADIATION TO THE OVARY

STERILISING RADIATION DOSE (50% RISK) AND AGE


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THE UTERUS
ADVERSE EFFECT OF RADIOTHERAPY TO UTERUS

Miscarriage

<table>
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<tr>
<th></th>
<th>TBI</th>
<th>Cyclophos</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>5/8</td>
<td>8/44</td>
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</table>

Premature delivery

<table>
<thead>
<tr>
<th></th>
<th>TBI</th>
<th>Cyclophos</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>6/16</td>
<td>4/56</td>
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</tbody>
</table>

HOW TO DETECT UTERINE DAMAGE?
Consider:
- Diagnosis / treatment plan
- Expected outcome of fertility treatment
- Prognosis of the cancer treatment
WHO GETS FERTILITY PRESERVATION?

Offer to all
‘Insurance policy’

Offer to those
with clear need

Issues of costs, equality of access, informed decision making at a time of extreme stress etc.
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/funding available

CHEMOTHERAPY-RELATED AMENORRHOEA: BREAST CANCER


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PREMATURE LOSS OF OVARIAN FUNCTION:
INFERTILITY AND POI

Can we individualise based on ovarian reserve?

AMH REFLECTS THE NUMBER OF SMALL GROWING FOLLICLES

Anderson RA, Clin Endocrinol 2012;77:652-655
THE AMH NORMAL RANGE FROM BIRTH TO MENOPAUSE

Key features
- Detectable in girls of all ages
- Rise through childhood
- Peak at 24 years
- Decline to menopause

REDUCED OVARIAN RESERVE IN CHILDHOOD CANCER SURVIVORS WITH REGULAR CYCLES


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AMH DIFFERENTIATES HIGH AND LOW RISK CHEMOTHERAPY

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60 women recruited

1 woman excluded: ineligible

59 women included

46 women at 2 years

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

46 women at 1 year

55 women at 1 year

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

In relation to predictive markers here

Breast cancer prospective cohorts

Prediction of post chemo ovarian function

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

Analyse ovarian activity here

Sensitivity 98.2% specificity 80.0% for correct classification of amenorrhea

n=75

At diagnosis of early breast cancer AMH is higher in those women who will still be having menses 5 years later.
AMH AND PREDICTION OF MENOPAUSE

AMH at baseline

Menopause by AMH centile

Low age specific AMH
Shift towards younger age at menopause

High age specific AMH
Shift towards higher age at menopause

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


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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 MFH, et al. JCE&M 2012;97:2059-2067
AMH: APPLICATION IN CHILDHOOD CANCER

22 girls age 0.3-15 yr
17 prepubertal

Brougham MFH, et al. JCE&M 2012;97:2059-2067
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FERTILITY RISK ASSESSMENT
(Includes Intrinsic and Extrinsic factors)

**MALE**
- Pre-pubertal
- Pubertal
- Post-pubertal

- Able to produce a suitable semen sample
  - **NO**
    - Testis biopsy
  - **YES**
    - Testis biopsy/Gamete extraction

- Testis Tissue Cryopreservation

**FEMALE**
- Pre-pubertal
- Post-pubertal

- Ovarian biopsy
- Ovarian stimulation

- Partner/Donor sperm

**Storage**
- Sperm Cryopreservation
- Ovarian Tissue Cryopreservation
- Oocyte Cryo
- Embryo Cryo

**Patient Assessment**
- **Experimental**
- **Established**


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COMPARISON OF FRESH AND VITRIFIED OOCYTES


Survival: 96.7%
Implantation: 40.8%
EMBRYO CRYOPRESERVATION
established option
But....
### HOW DO CANCER PATIENTS RESPOND IN IVF CYCLES?

<table>
<thead>
<tr>
<th></th>
<th>Cancer (n=227)</th>
<th>Controls (n=1258)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of mature oocytes</td>
<td>9.0±6.5</td>
<td>10.8±6.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Fertilisation</td>
<td>7.98±5.2%</td>
<td>8.08±5.1%</td>
<td>ns</td>
</tr>
<tr>
<td>Poor responders</td>
<td>7.8%</td>
<td>5.9%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Meta-analysis of 7 studies

REDUCED AMH IN LYMPHOMA

Controls, n=38  Hodgkin lymphoma, n=31  Non-Hodgkin lymphoma, n=7

WHAT STIMULATION REGIMEN TO USE?

Time and safety

- Urgency of starting: when in cycle?
- Short protocol needed

- Minimise risk of ovarian hyperstimulation (OHSS)
- Avoid high oestrogen exposure in breast cancer?
NON-CONVENTIONAL OPTIONS

<table>
<thead>
<tr>
<th>Non-conventional Options</th>
<th>Conventional (n = 87; 101 cycles)</th>
<th>Random start (n = 24; 24 cycles)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.9 ± 5.2</td>
<td>34.6 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>AFC</td>
<td>13 (9-19)</td>
<td>11.5 (6-16)</td>
<td>NS</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>9 (8-10)</td>
<td>11 (10-12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FSH dose (IU)</td>
<td>3,386 ± 1,085</td>
<td>4,201 ± 1,147</td>
<td>0.001</td>
</tr>
<tr>
<td>Mature oocytes</td>
<td>11 (6-16)</td>
<td>9 (5-14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mature oocyte/AFC ratio</td>
<td>0.8 (0.5-1.1)</td>
<td>0.8 (0.6-1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilization</td>
<td>0.77 ± 0.22</td>
<td>0.87 ± 0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

No data on birth rate

FERTILITY PRESERVATION IN 1035 WOMEN OVER 5 YEARS


Oncology
475 women
Age 31.9 ± 5.1
MII oocytes: 8.2

Non-oncology
560 women
Age 36.7 ± 4.2
MII oocytes: 9.8
HOW MANY HAVE RETURNED?

- 26 non-oncology women have attempted pregnancy
- Mean interval 20.5 months
- 84% oocyte survival rate
- 1 woman no embryo transfer
- Pregnancy rate 30.7% (cumulative 70.9%)

OVARIAN STRIP AUTOTRANSPLANTATION

Oophorectomy

Strip reimplantation on ovarian pedicle


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RESTORATION OF FERTILITY AFTER AUTOTRANSPLANTATION OF CRYOPRESERVED OVARIAN BIOPSIES
OVARIAN TRANSPLANT MODEL

Oophorectomy
Cryopreservation of cortical strips
Reimplantation

High basal FSH
60-70% of follicles lost


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TEAMWORK REQUIRED!

- Paediatric Oncology
- Haematology (sickle cell disease)
- Others e.g. Rheumatology
- IVF unit Oocyte/embryo storage
- Tissue Services
- Research lab
- Repro Med specialist
- Operation: Theatre/Aesthetic
- Oncology

Regulatory aspects: HFEA vs HTA, IRAS, Hospital R&D
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."

### SUMMARY OF 60 REPLACEMENTS

<table>
<thead>
<tr>
<th>Team</th>
<th>Patients</th>
<th>Pregnancy</th>
<th>Live birth</th>
<th>No. of patients</th>
<th>No. of live births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Natural</td>
<td>IVF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Denmark</td>
<td>25</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Spain</td>
<td>22</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>11 women</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

- 93% achieved ovarian activity after a median of 4 months
- 18% of women achieved a pregnancy


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PREGNANCY AFTER HETEROTOPIC TRANSPLANTATION

Twin pregnancy at 8 weeks of gestation

8-cell and 5-cell embryos

Live birth after autograft of ovarian tissue cryopreserved during childhood

Isabelle Demestere\textsuperscript{1,2,*}, Philippe Simon\textsuperscript{3}, Laurence Dedeken\textsuperscript{4}, Federica Moffa\textsuperscript{1,6}, Sophie Tsépélidis\textsuperscript{1,2,7}, Cécile Brachet\textsuperscript{5}, Anne Delbaere\textsuperscript{1,2}, Fabienne Devreker\textsuperscript{1,5}, and Alina Ferster\textsuperscript{4}

Sickle cell disease, unilateral oophorectomy for cryopreservation age 13 (thelarche age 10, premenarchal)
Prior to HSCT

Tissue replaced age 25, menses after 5 months; normalised FSH, AMH undetectable
Natural conception 2 years later
REPLACEMENT FOR PUBERTY?

BUT
- Rapid onset of oestrogenisation
- Early progesterone exposure
- Waste of oocytes
- Malignant contamination?

Anderson, Hindmarsh and Wallace
Eur J Cancer 2013

OVARIAN CONTAMINATION: VERTEBRAL EWING’S SARCOMA
THE NEED FOR PATIENT SELECTION

Percent of women with POI after pre-chemo unilat oophorectomy

Overall n=143, mean 58 months follow up

Schmidt KT, et al. RBM Online 2013;26:272-279
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 termination

Schmidt KT, et al. 2013 RBM Online 26, 272
CAN WE DEVELOP USEFUL CRITERIA?

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

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

CUMULATIVE INCIDENCE OF POI


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OTHER OPTIONS: OVARIAN PROTECTION

GnRH agonist administration during chemo
- Increasing evidence for efficacy (reduced risk of POI) in breast cancer
- No evidence in other cancers
- Limited evidence of preservation of fertility

Ovarian transposition
- May be an option where radiotherapy field is well defined
- Risk of vascular compromise to ovary
- No high-quality evidence of effectiveness

CONCLUSIONS

Fertility preservation is becoming ‘main stream’
Need for accurate, patient-specific risk to fertility and ovarian function
  • Extrinsic issues: proposed treatment
  • Intrinsic issues: ovarian reserve
Development of evidence-based algorithms to enable truly informed patient choice

Options:
Oocyte and embryo vitrification: established, for postpubertal woman
Ovarian tissue cryo: remains experimental, especially in girls
Ovarian protection: limited evidence of efficacy