

## Reproductive function in cancer survivors

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managed by **bio**scientifica European Society
of Endocrinology
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#### **CONFLICT OF INTEREST**

**Professor W.Hamish Wallace** 

I declare that I have no potential conflict of interest.

## Improved Five Year Survival (1966-2000)



# 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

Wallace WH, Critchley HOD & Anderson RA. JCO, 2012

## **Risk of infertility**

Low risk (<20%)	Medium risk	High risk (>80%)
ALL Wilms' tumour Brain tumour Sx, RT < 24Gy Soft tissue sarcoma (stage1) Hodgkin's Lymphoma HIL(Low stage)	AML Osteosarcoma Ewing's sarcoma STS: stage II/III Neuroblastoma NHL Brain tumour RT>24Gy HL (High Stage)	Total Body Irradiation Pelvic/testes RT Chemo pre BMT Metastatic Ewing's <b>HLL (Pelvic RT)</b>

Wallace, Anderson, Irvine. Lancet Oncology 2005

# Radiation-induced ovarian damage

#### Human oocyte (Primordial follicle)

 $LD_{50} < 2 Gy$ 

Wallace, Thomson, Kelsey. (2003) Hum Reprod.



#### Parenthood in 590 adult female survivors treated with five successive protocols for Hodgkin lymphoma during childhood and adolescence. A prospective, longitudinal and long-term study.

Professor Jürgen H. Brämswig, M.D., Marianne Riepenhausen, Ph.D. Professor Günther Schellong, M.D.



Lancet Oncology (in press)

Parenthood in female HL-survivors <18 years at diagnosis is similar to parenthood in the 16-39 year old female German population and not affected by gonadotoxic chemotherapy.

It is reduced only in women >40 years and in women who

#### **Ovarian Reserve?**



#### The Wallace-Kelsey Model (Five parameter asymmetric double-Gaussian cumulative curve)



 $log_{10}(y) = \frac{a}{4} \left[ 1 + \operatorname{Erf}\left(\frac{x+b+\frac{c}{2}}{d\sqrt{2}}\right) \right] \left[ 1 - \operatorname{Erf}\left(\frac{x+b-\frac{c}{2}}{e\sqrt{2}}\right) \right]$ 

Wallace & Kelsey (2010) PloS ONE

ESHRE, Lille, 2012

#### **Ovarian reserve: Conception to**

#### Menonalise



Wallace & Kelsey (2010) PloS ONE

## Prediction of Ovarian Reserve (AMH)

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

But there was no validated reference model for AMH available

Anderson, Nelson, Wallace (2011) Maturitas

#### A validated model of serum anti-Mullerian hormone (AMH) from conception to menopause



Kelsey et al. PLoS ONE 2011

## AMH in childhood cancer



Brougham et al 2012 JCE&M

## AMH in 3 girls with cancer



## Summary

AMH is detectable before puberty

AMH falls rapidly during cancer treatment in both pre-pubertal and pubertal girls

AMH levels recover in those patients at low/medium risk of gonadotoxicity

AMH fails to recover in those at high risk. This could be indicative of future reproductive impairment

Brougham et al 2012 JCE&M

## Fertility preservation options: established and experimental





#### Ovarian tissue cryopreservation: World-wide experience

At least 40 pregnancies worldwide after othotopic reimplantation of frozenthawed ovarian cortex Success rate is unclear as the denominator is unknown

No pregnancies reported following the reimplantation of ovarian tissue harvested prepubertally Young children are potentially ideal candidates



Donnez, J. & Dolmans, M.-M. Nat. Rev. Endocrinol. 9, 735–749 (2013)

## Ovarian Cryopreservation & Ovarian Function

Edinburgh experience in children (< 18 yrs) 1996-2012

#### 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 ovarian failure

Informed consent (parent and where possible patient)

Negative HIV and Hepatitis serology No existing children

#### 15 year, population-based analysis of criteria for ovarian cryopreservation



Do the 'Offered' group have a higher prevalence of POI?

n = 14





#### **Cumulative incidence of POI**



Walllace....and Anderson 2014 Lancet Oncology

## 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

#### Vitruvian man



Leonardo da Vinci 1490



#### 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 established option to preserve fertility in the pre-pubertal boy....

#### Challenges

Provide fertility counseling to all young patients with cancer

Cryopreserve ovarian tissue from the right (high risk) patients

Define the success rate of the procedures

Develop IVG/M as a safe alternative to reimplantation through basic research



#### cknowledgements

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## **Thank You**

