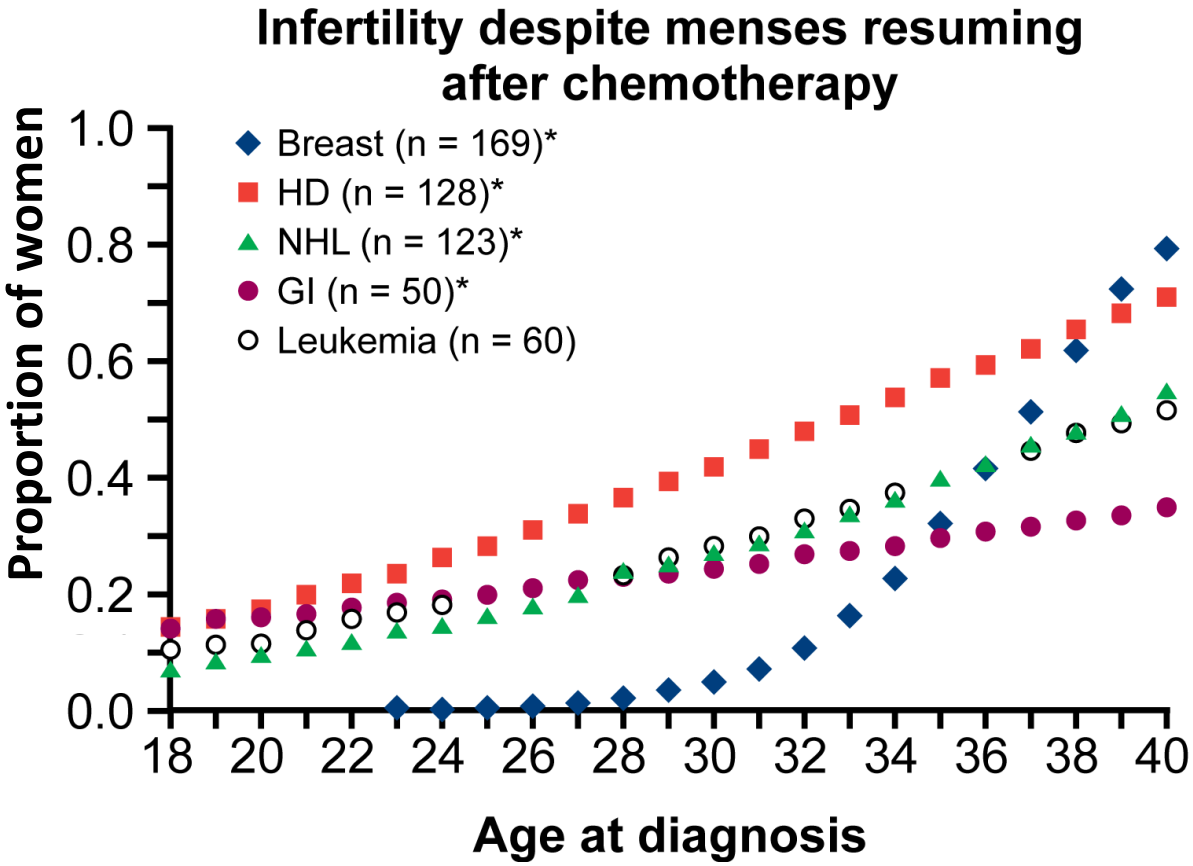
Taking fertility preservation from the lab to the patient and to the population

Richard A Anderson

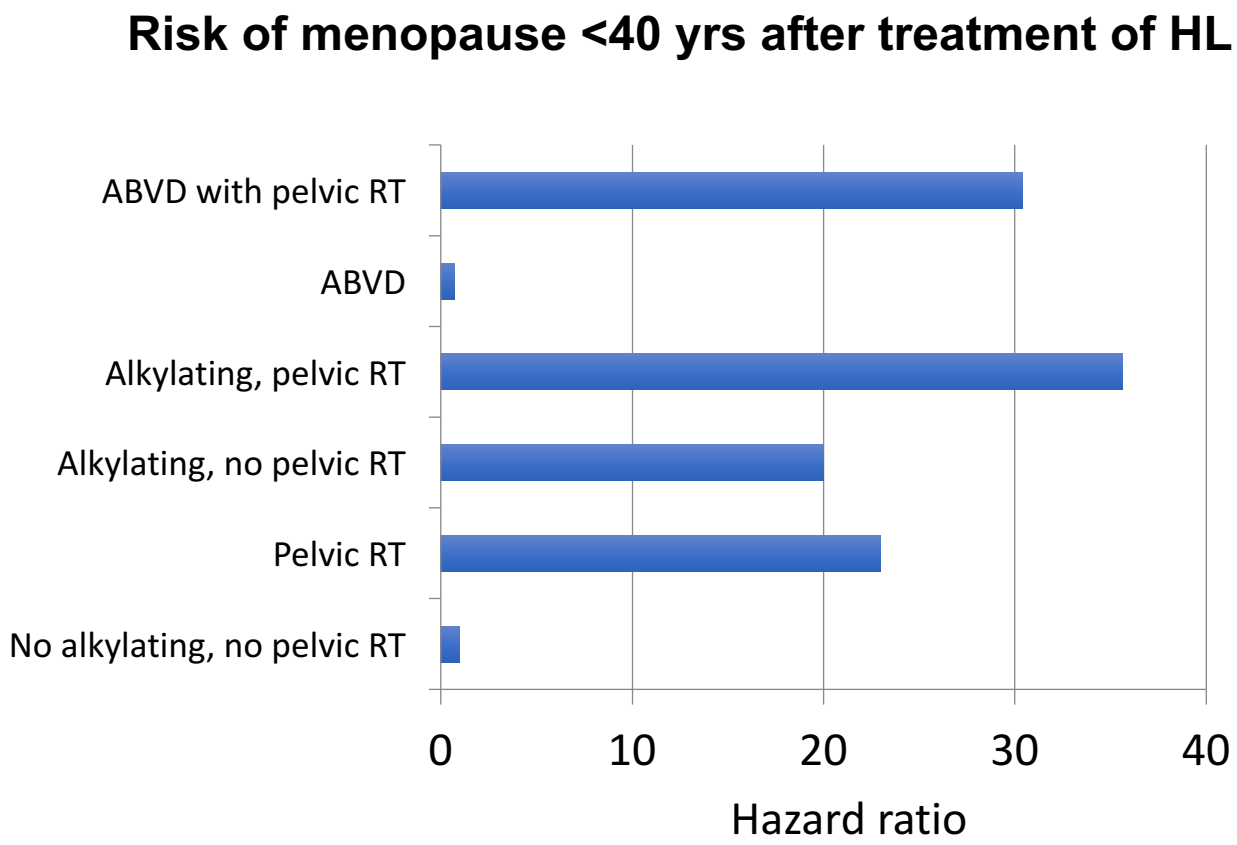
Elsie Inglis Professor of Clinical Reproductive Science
University of Edinburgh

MRC Centre for Reproductive Health

Cancer treatment damages female reproductive function

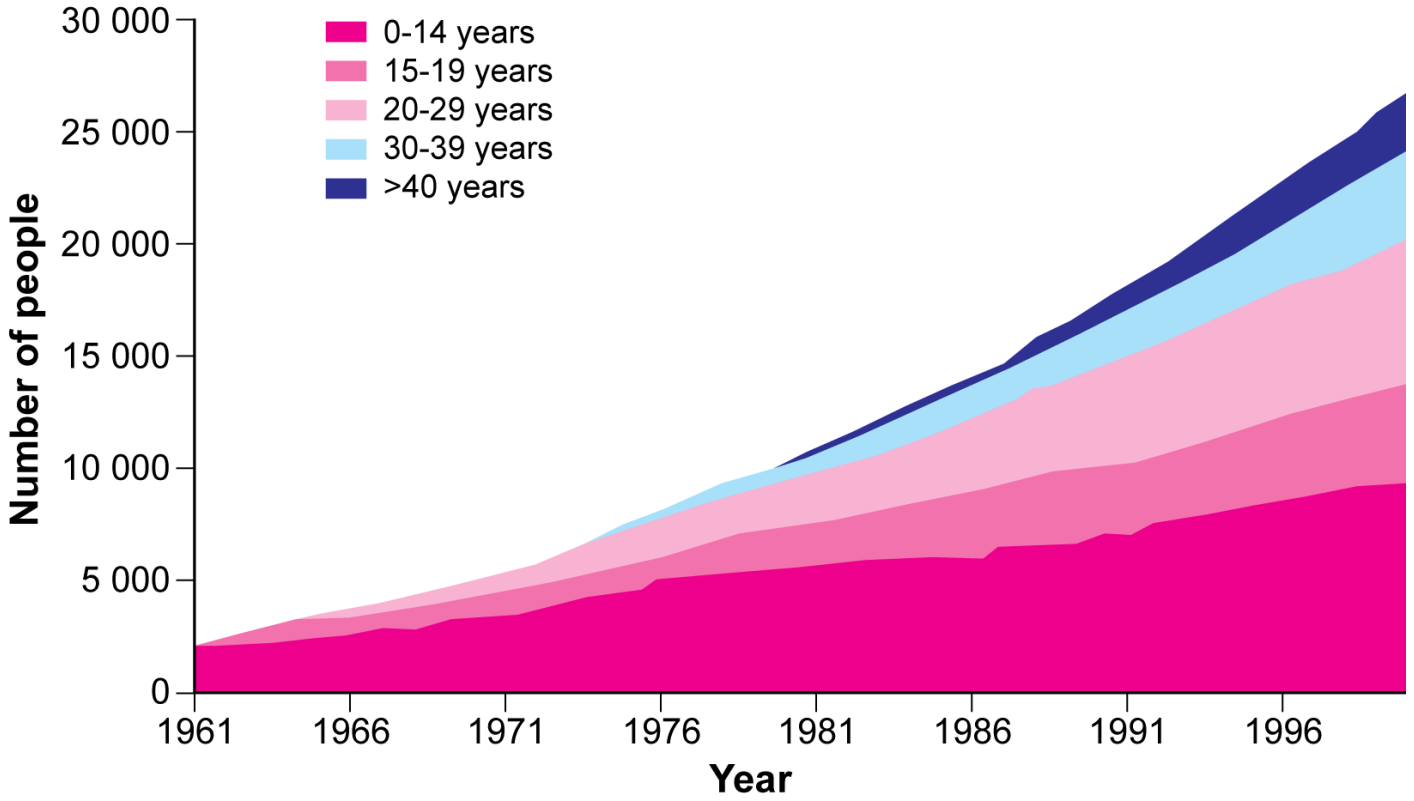


Letourneau et al 2012 Cancer 118, 1710



Swerdlow AJ et al 2014, J Natl Cancer Inst

Childhood cancer survivors by current age

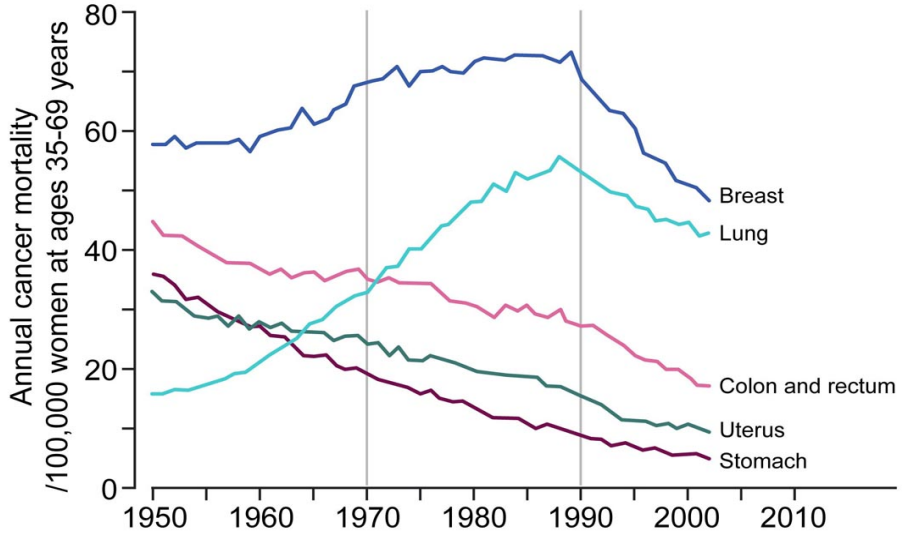


Long-term survival rate from childhood cancer is **80%**

1 in 700 adults is a childhood cancer survivor

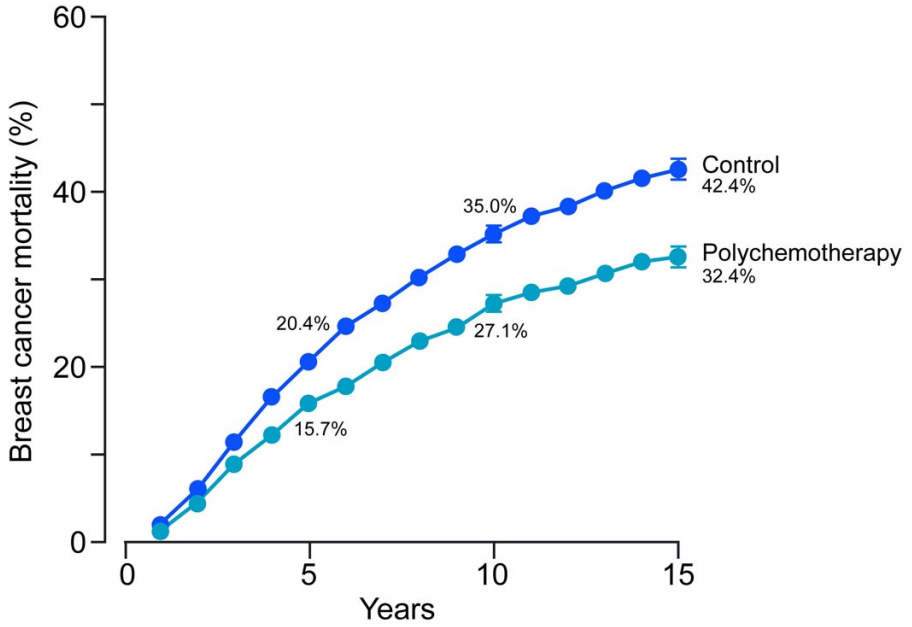
Skinner et al 2006 Lancet Oncology 7:489

Improving survival: minimising 'late effects'



Chemotherapy reduces the annual breast cancer death rate by 38%

We now need to add the 'ageing' delays of endocrine Rx

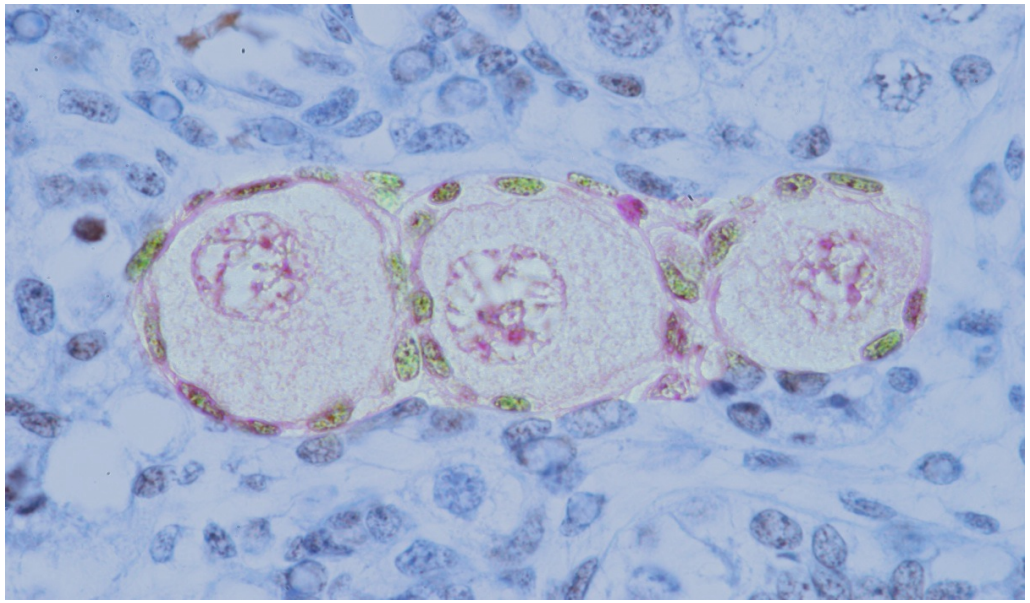


Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2005;365:1687

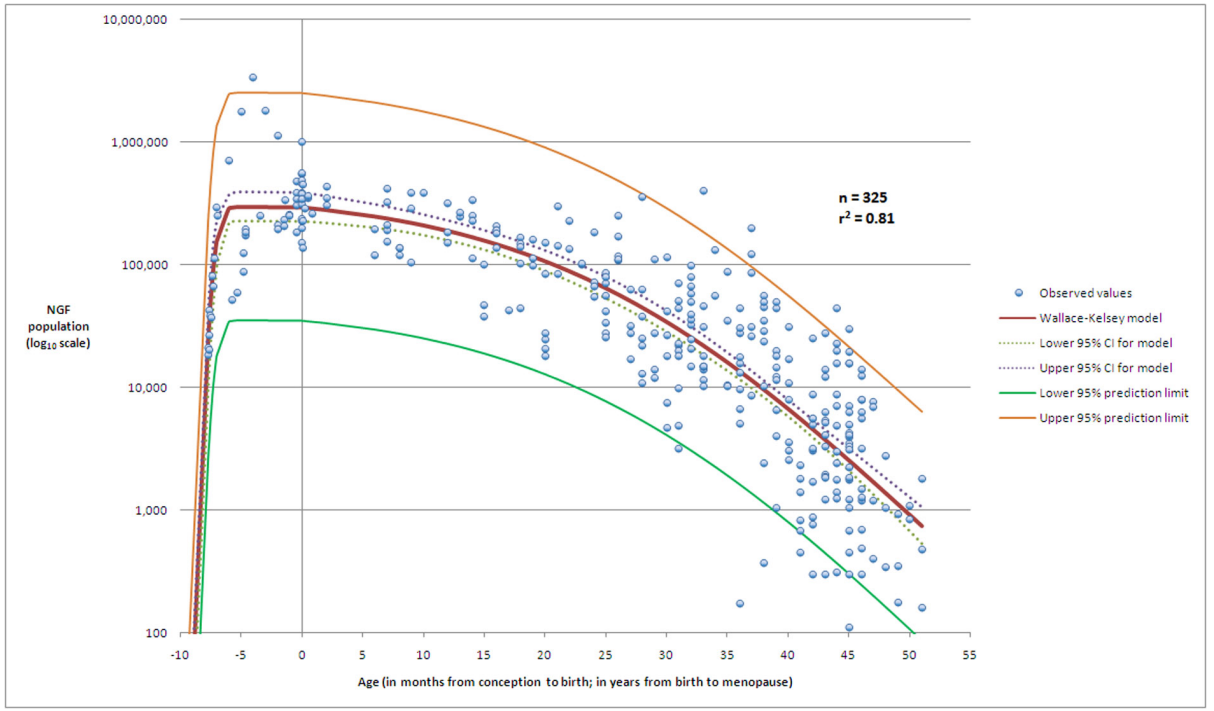
Reproductive impact within a broader 'survivorship' agenda

- Most cancer survivors have significant health issues
  - Oeflinger et al NEJM 2006
- Reduced chance of marriage/cohabitation
  - brain/CNS cancers
  - Frobisher et al Int J Cancer 2007
- Concerns about bringing up a family after cancer
  - Recurrence, life expectancy
  - Goncalvez et al HRUpdate 2014

The primordial follicle: guardian of fertility

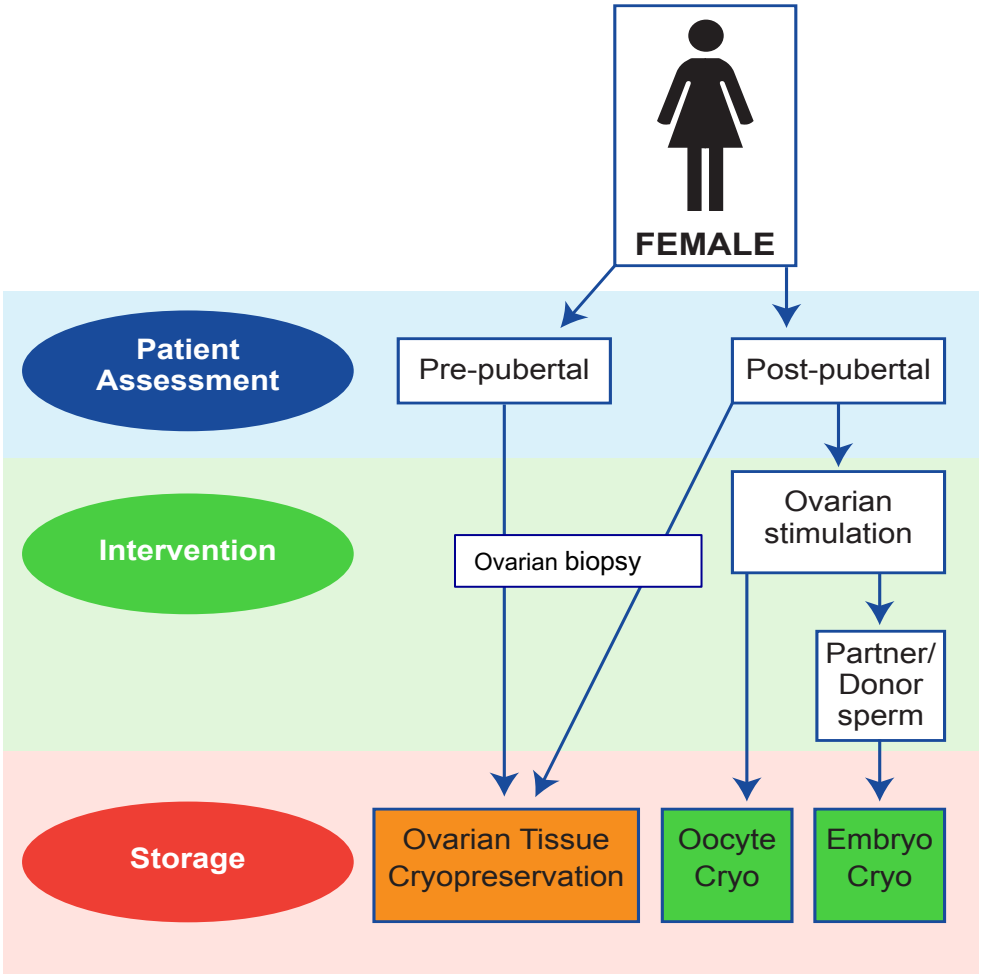


Human ovary, 17 weeks gestation

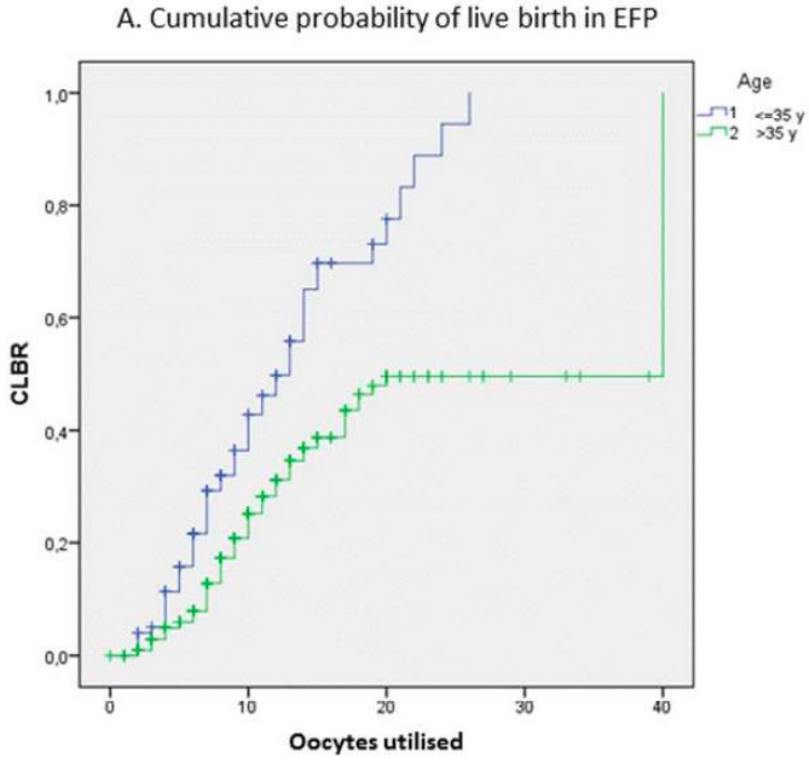


Wallace and Kelsey 2010 PLoS One 5; e8772

Options for female fertility preservation



Anderson, Mitchell et al 2015 Lancet Diabetes Endocrinol



Age ≤35		Age >35	
N°oocytes	CLBR(95%CI)	N°oocytes	CLBR(95%CI)
5	15.8 (8.4-23.1)	5	5.9 (3.6-8.3)
8	32.0 (22.1-41.9)	8	17.3 (13.3-21.3)
10	42.8 (31.7-53.90)	10	25.2 (20.2-30.1)
15	69.8 (57.4-82.2)	15	38.8 (32.0-45.6
20	77.6 (64.4-90.9)	20	49.6 (40.7-58.4)
24	94.4 (84.3-100.4)		

Cobo A et al, 2018, Human Reprod

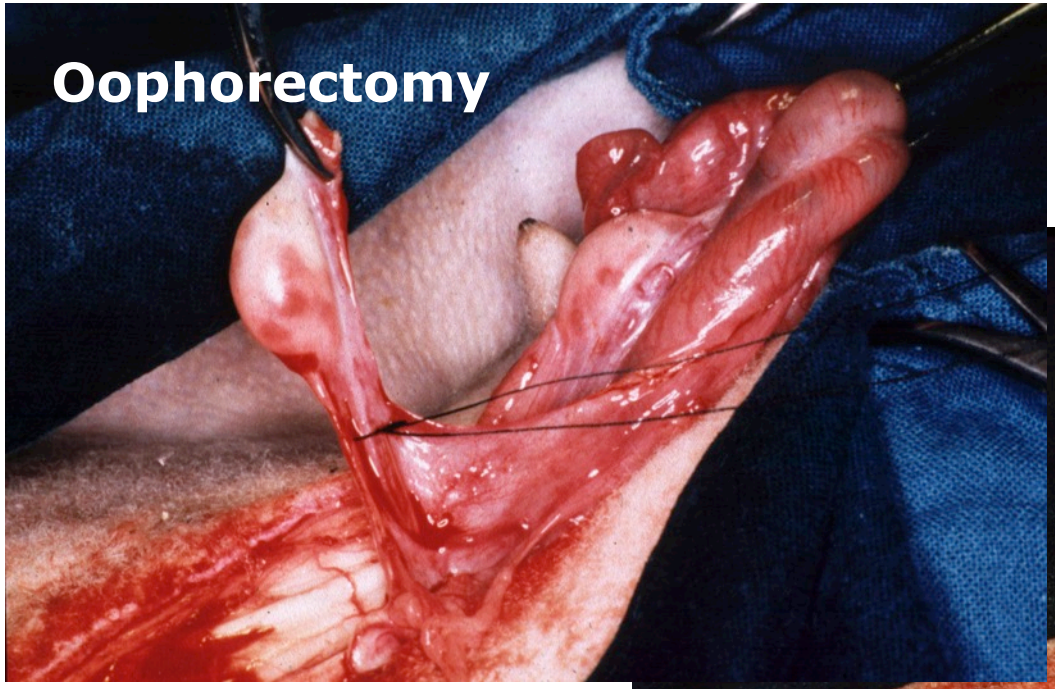
The development of ovarian tissue cryopreservation

David T Baird

Roger G Gosden

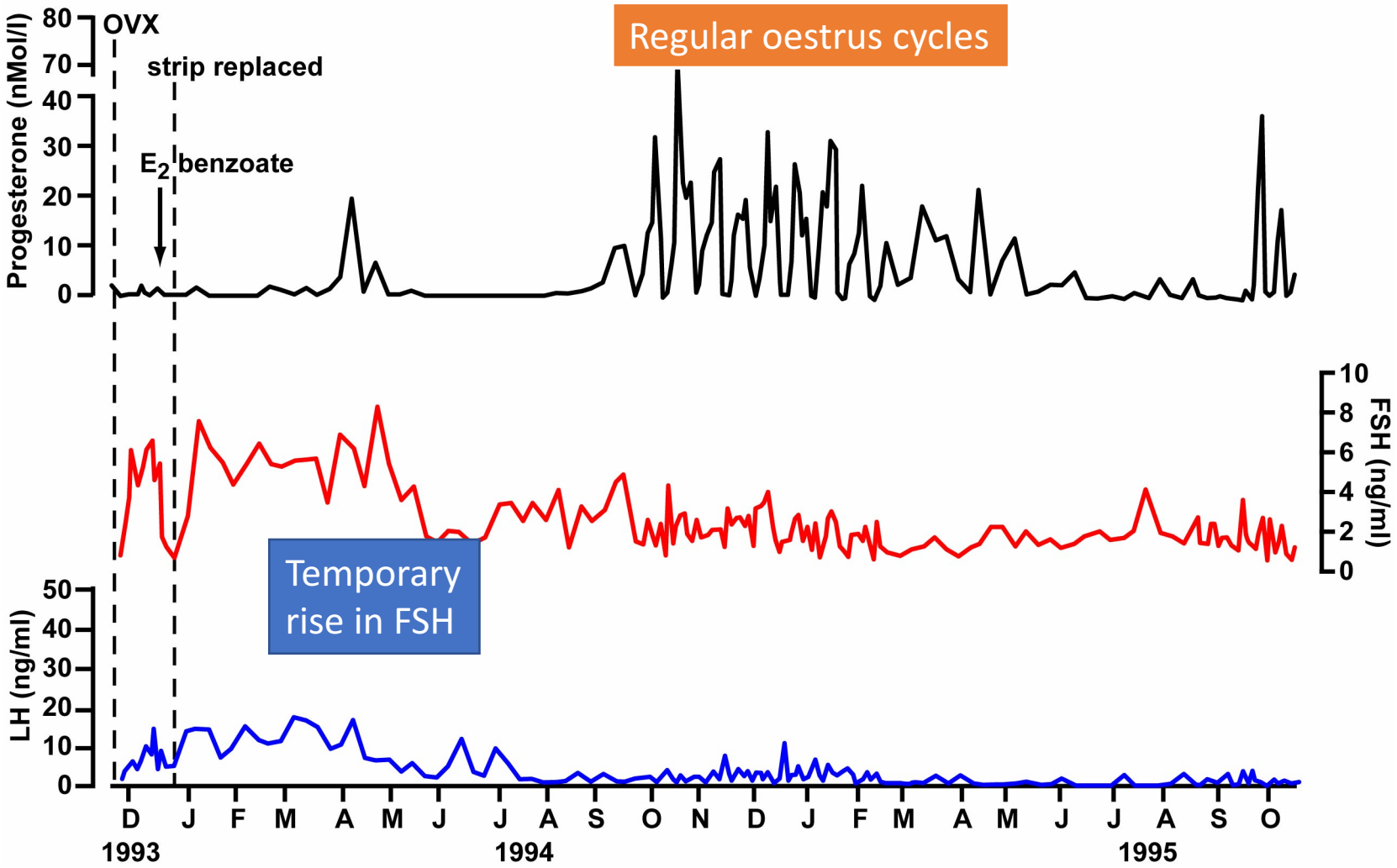
A human-sized mono-ovulatory mammal

Ovarian strip autotransplantation



Gosden, Baird, Wade & Webb, 1994: *Hum Reprod*; **9**: 597-603

Autotransplantation of frozen ovarian tissue



Baird DT et al Endocrinology. 1999;140(1):462-471

Restoration of fertility after autotransplantation of cryopreserved ovarian biopsies

Development of a a clinical service: Teamwork and dialogue required

Others eg Rheumatology

Haematology

Paediatic Oncology

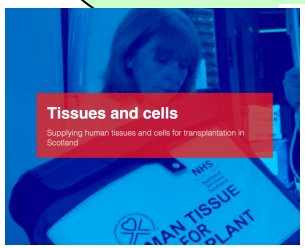
Oncology

Repro Med team

First human ovarian cryostorage in 1993

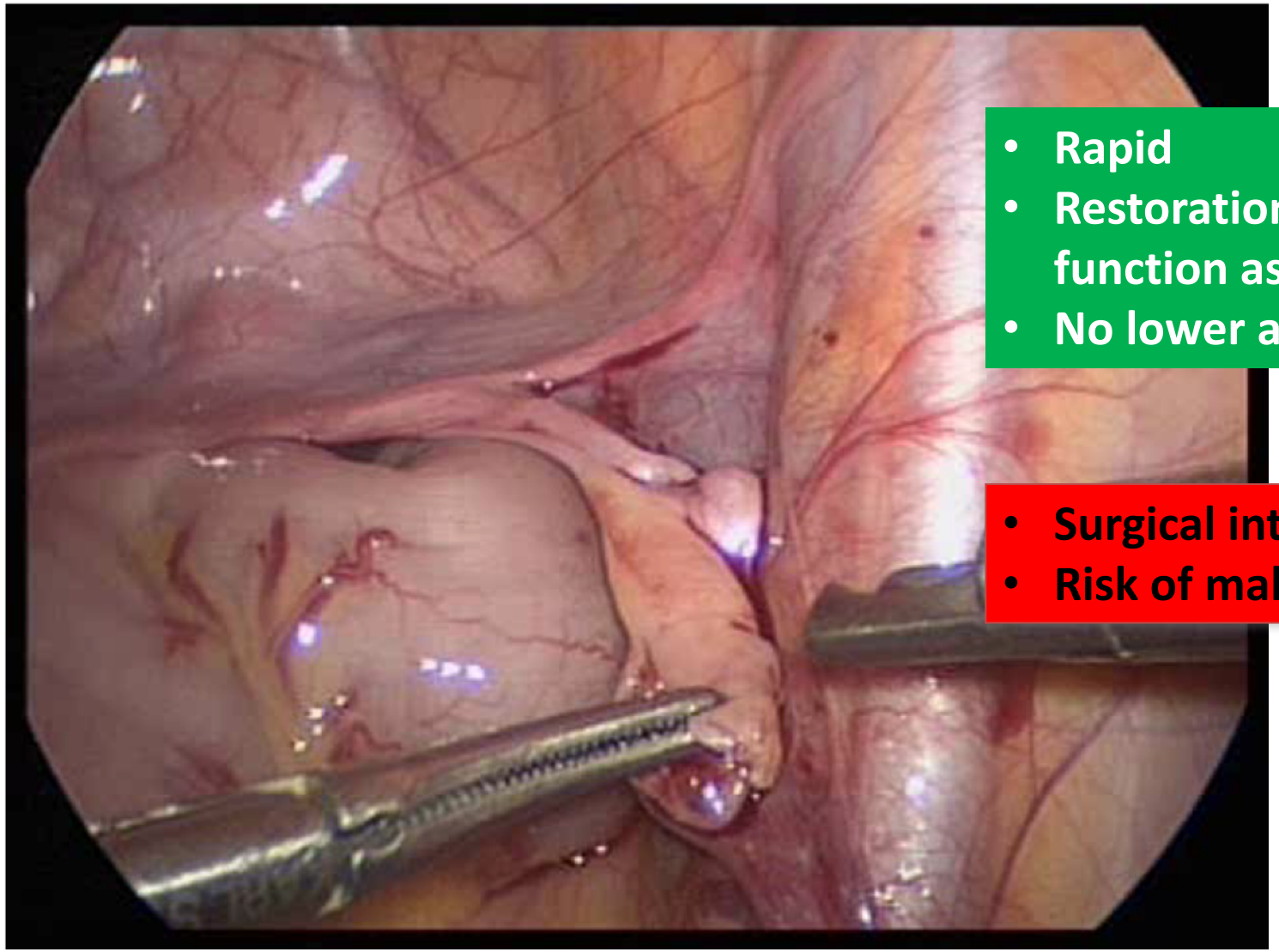
Tissue Bank

Research lab



HTA Human Tissue Authority
The regulator for human tissue and organs

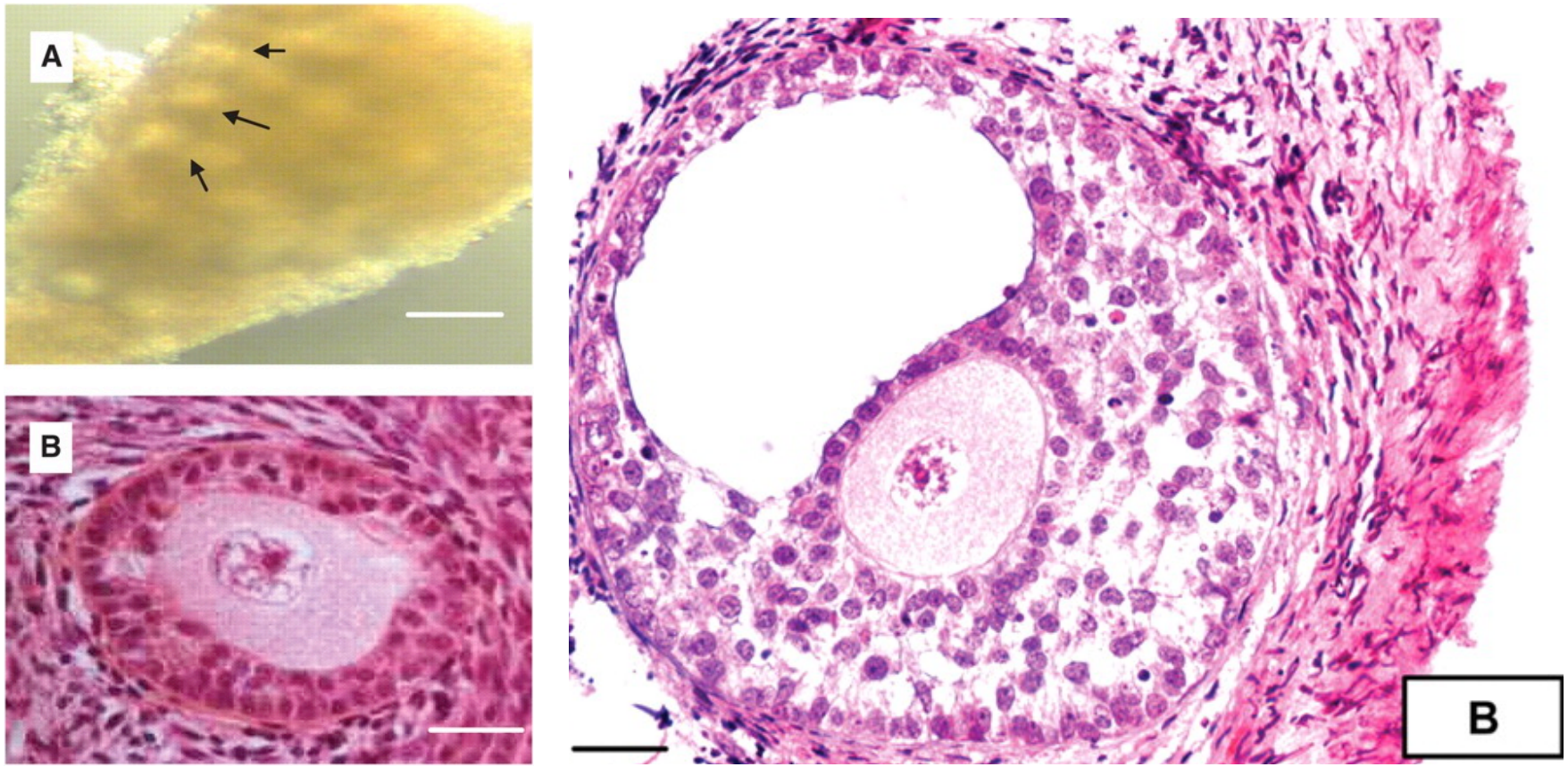
Ovarian tissue storage-girls too



- **Rapid**
- **Restoration of endocrine function as well as fertility**
- **No lower age limit**

- **Surgical intervention**
- **Risk of malignant contamination**

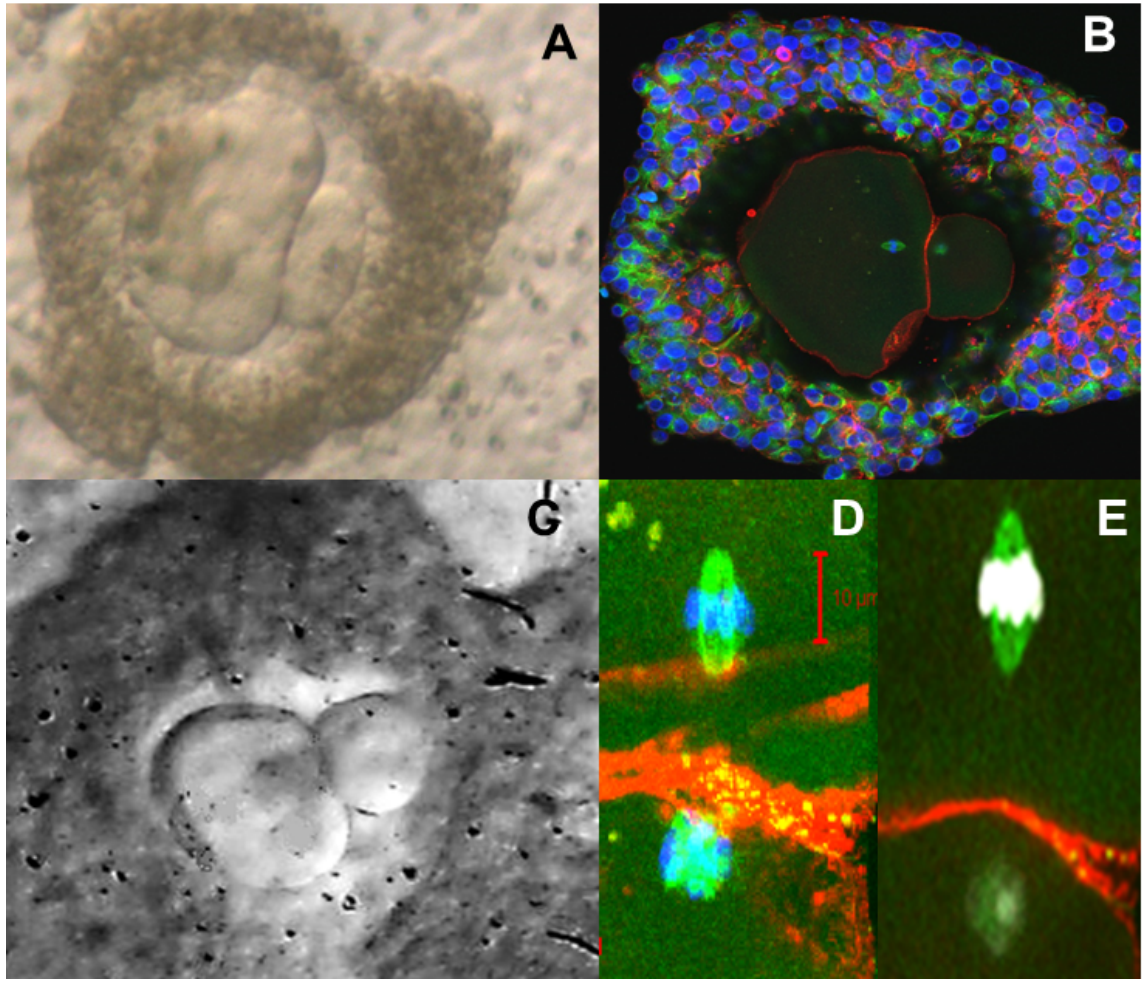
in vitro growth and maturation?



In vitro grown human follicles cultured first in cortical strips for 6 days then isolated at the pre-antral stage and cultured for a further 4 days with 100 ng/ml activin A.

Telfer EE et al. Hum. Reprod. 2008 23:1151-1158

The end result: metaphase II oocytes

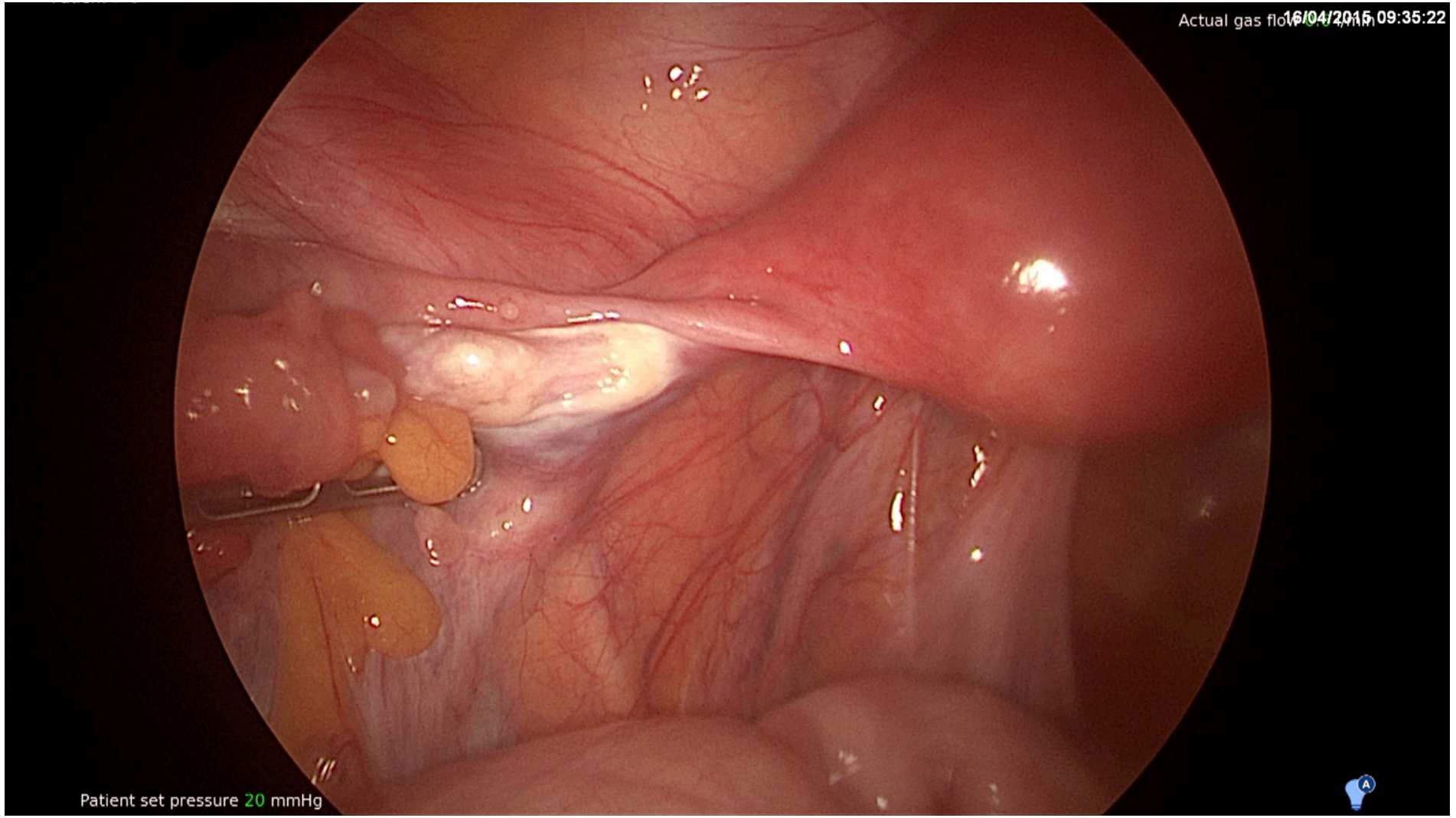


McLaughlin et al 2018 Mol Hum Reprod

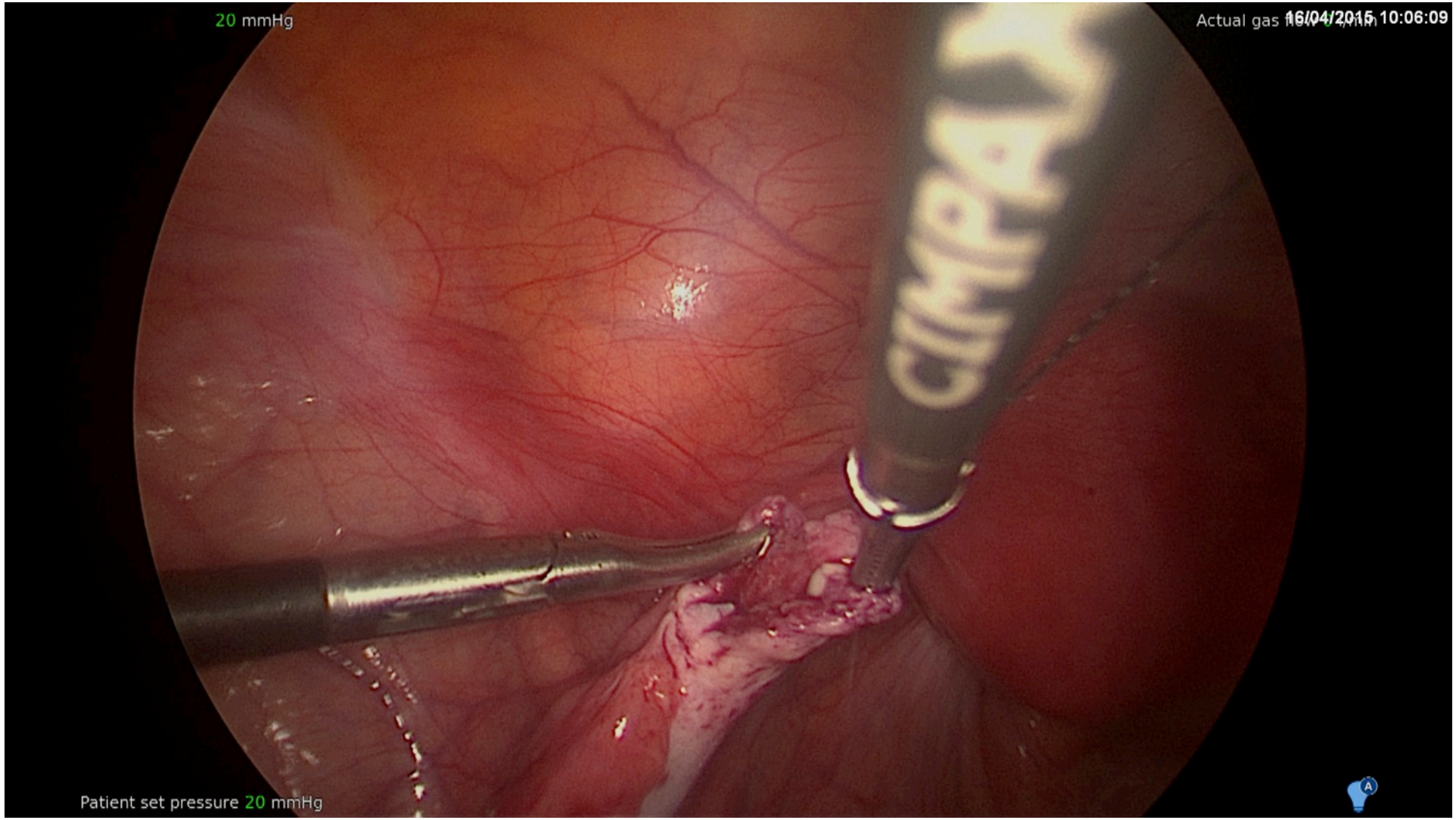
Evelyn Telfer

Can these be fertilized, developmental competence?

2004 Wilms tumour: ovarian tissue cryopreservation age 23
2015: ovarian tissue replacement

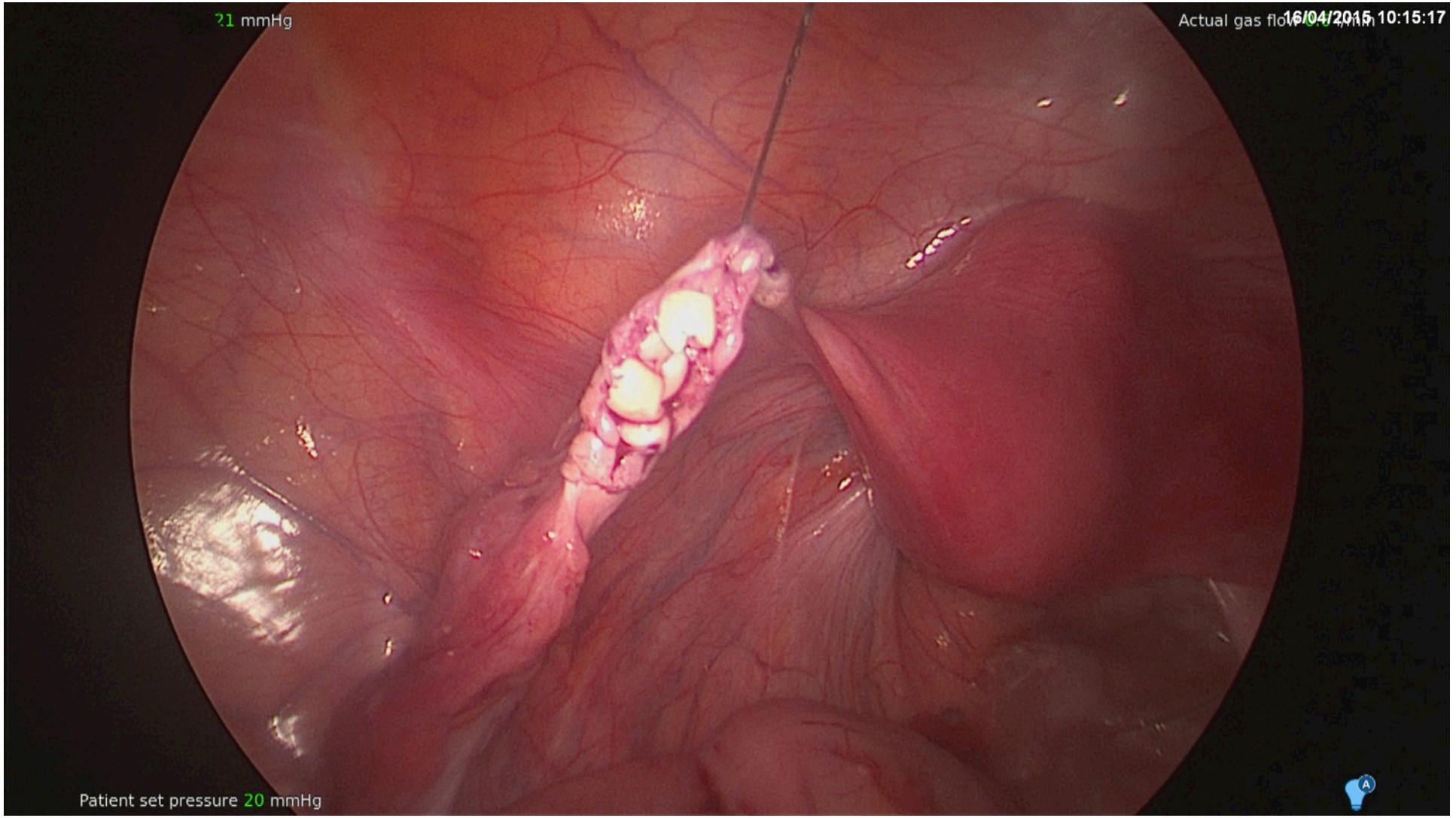


April 2015



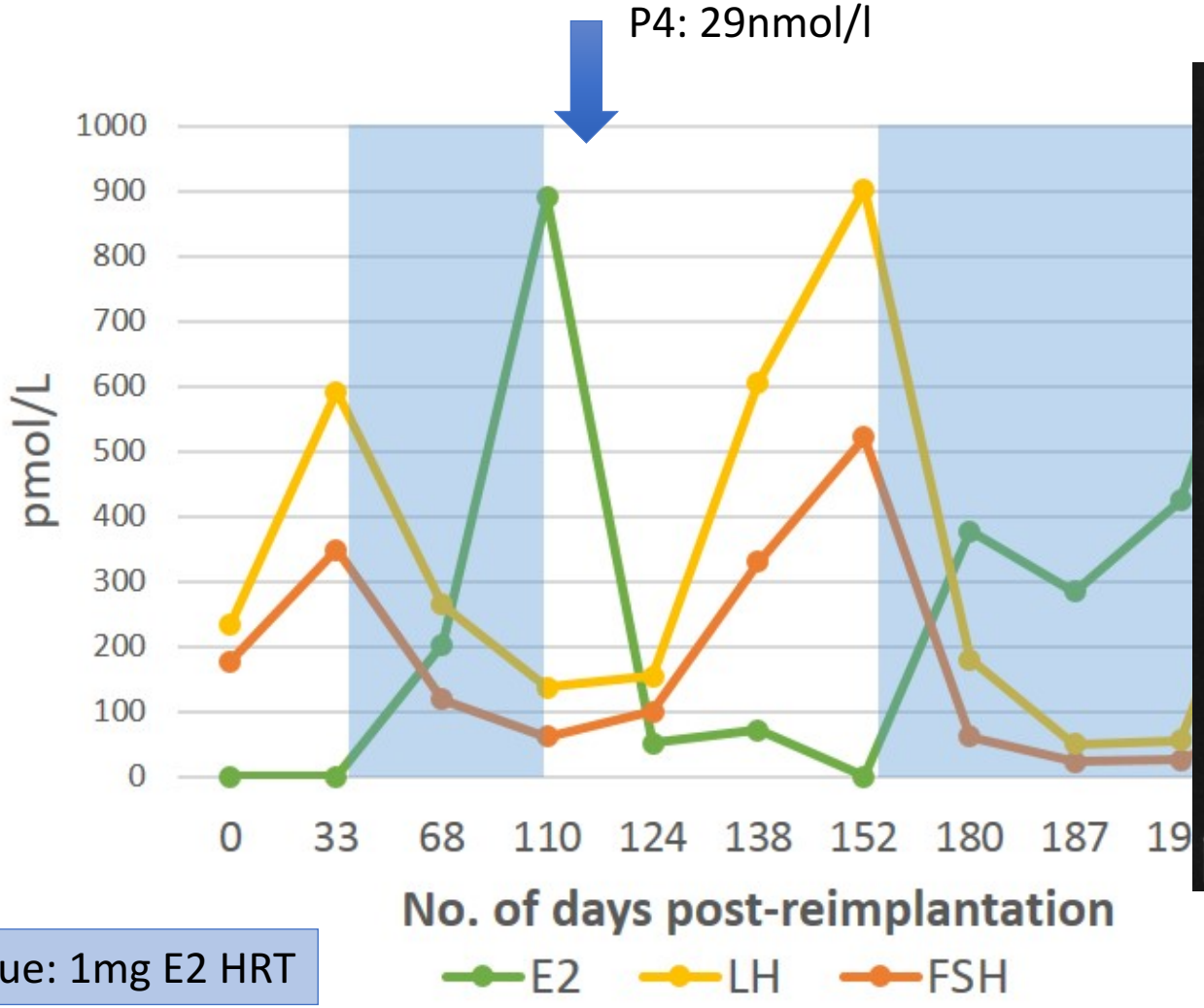
April 2015

Replacement of ovarian tissue



April 2015

Subsequent ovarian activity



Blue: 1mg E2 HRT

P4: 34nmol/l

Pregnancy, 7 weeks gestation

Dunlop CE et al 2016 JARG

Can we develop useful criteria?
for ovarian tissue cryopreservation

- Development of ‘Edinburgh criteria’ since 1996
- Age <35 years (initially 30)
- 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

Anderson Wallace and Baird 2008 Reproduction 131, 681
Wallace…..and Anderson 2014 Lancet Oncology 15, 1129

Articles

Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation

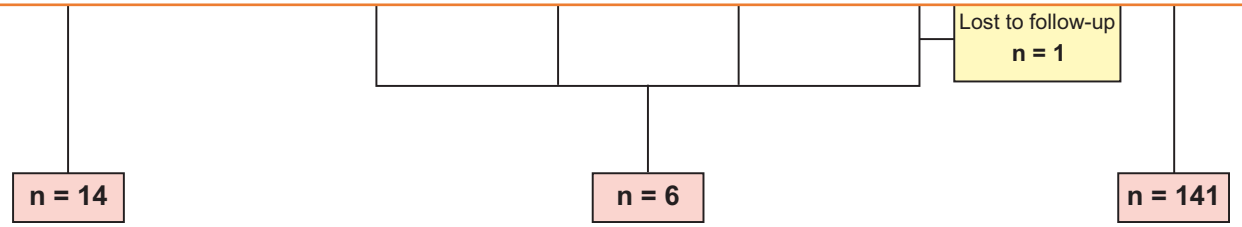
W Hamish B Wallace, Alice Grove Smith, Thomas W Kelsey, Angela E Edgar, Richard A Anderson

Summary

Background Ovarian tissue cryopreservation with later reimplantation has been shown to preserve fertility in adult women, but this approach remains unproven and experimental in children and adolescents. We aimed to assess the use of the Edinburgh selection criteria for ovarian tissue cryopreservation in girls and young women with cancer to determine whether we are offering this invasive procedure to the patients who are most at risk of premature ovarian insufficiency.

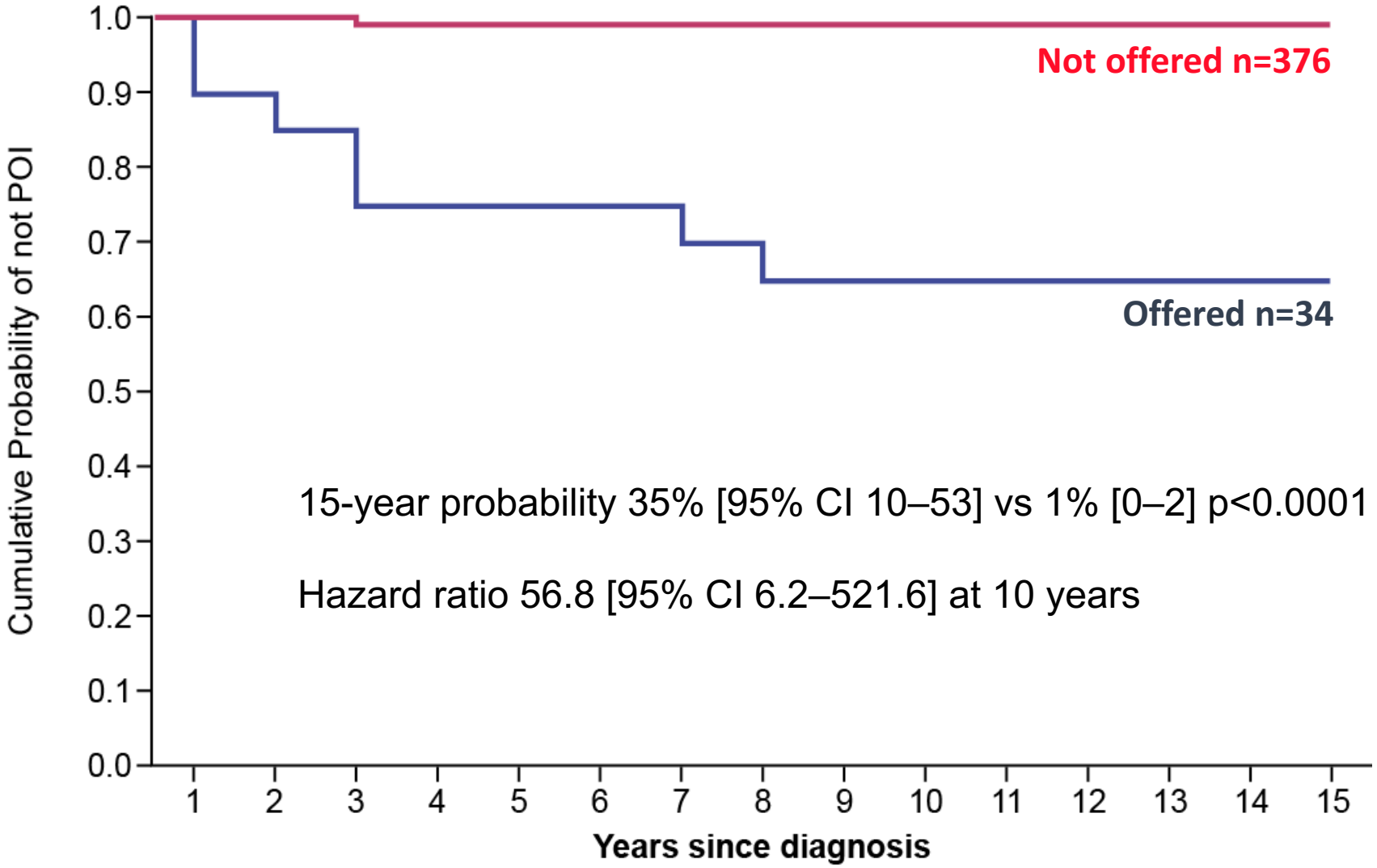
Lancet Oncol 2014
Published Online
August 15, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70334-1

(robust criteria of amen >4mo +high FSH x2/low E2)



Walllace…..and Anderson 2014 Lancet Oncology 15, 1129

Are we offering it to the right patients?



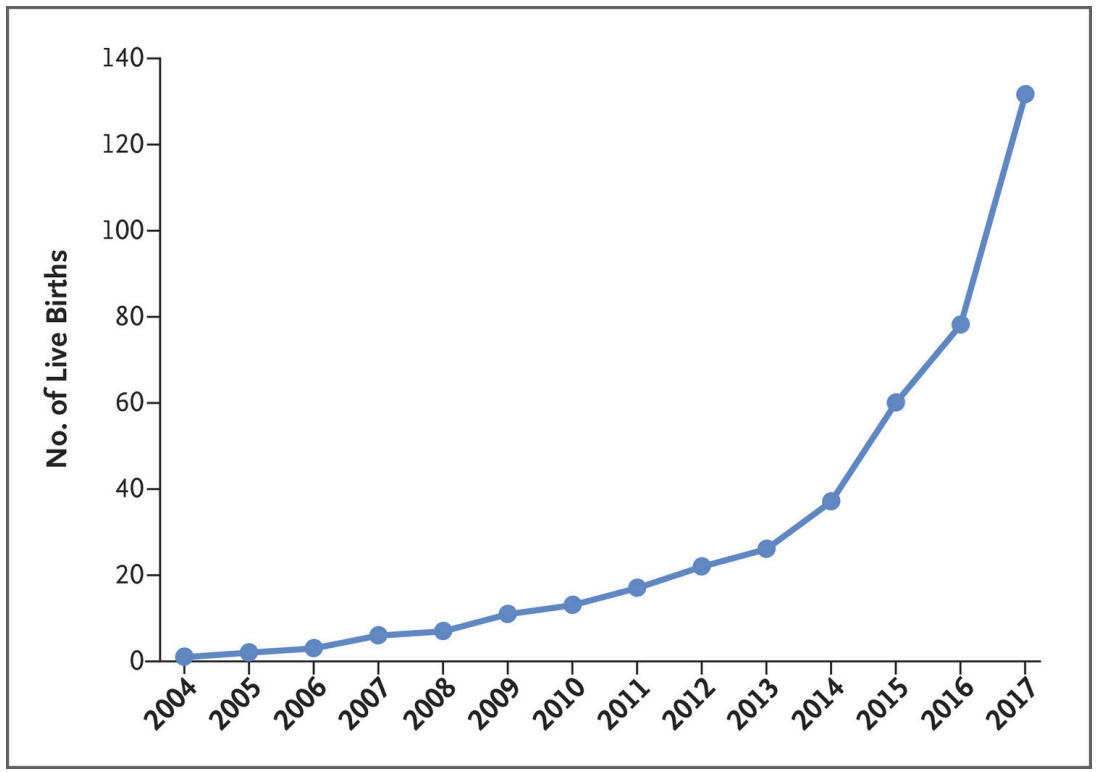
Walllace…..and Anderson 2014 Lancet Oncology 15, 1129

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Fertility Preservation in Women

Jacques Donnez, M.D., Ph.D., and Marie-Madeleine Dolmans, M.D., Ph.D.



'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'

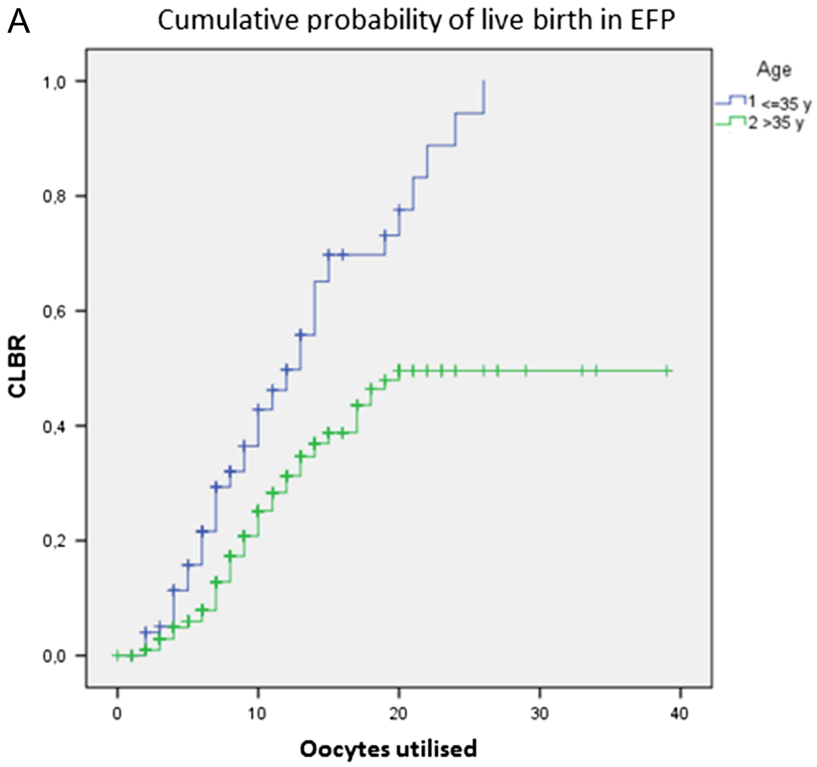
'Selection criteria clearly need to be applied, the most important being:

- age of less than 35 years
- a realistic chance of surviving for 5 years
- at least a 50% risk of POI'

Donnez J, Dolmans M. N Engl J Med 2017;377:1657-1665

Cumulative probability of live birth after oocyte vitrification

A



Age ≤35. N = 123		Age >35. N = 518	
Nºoocytes	CLBR(95%CI)	Nºoocytes	CLBR(95%CI)
5	15.8 (8.4-23.1)	5	5.9 (3.6-8.3)
8	32.0 (22.1-41.9)	8	17.3 (13.3-21.3)
10	42.8 (31.7-53.90)	10	25.2 (20.2-30.1)
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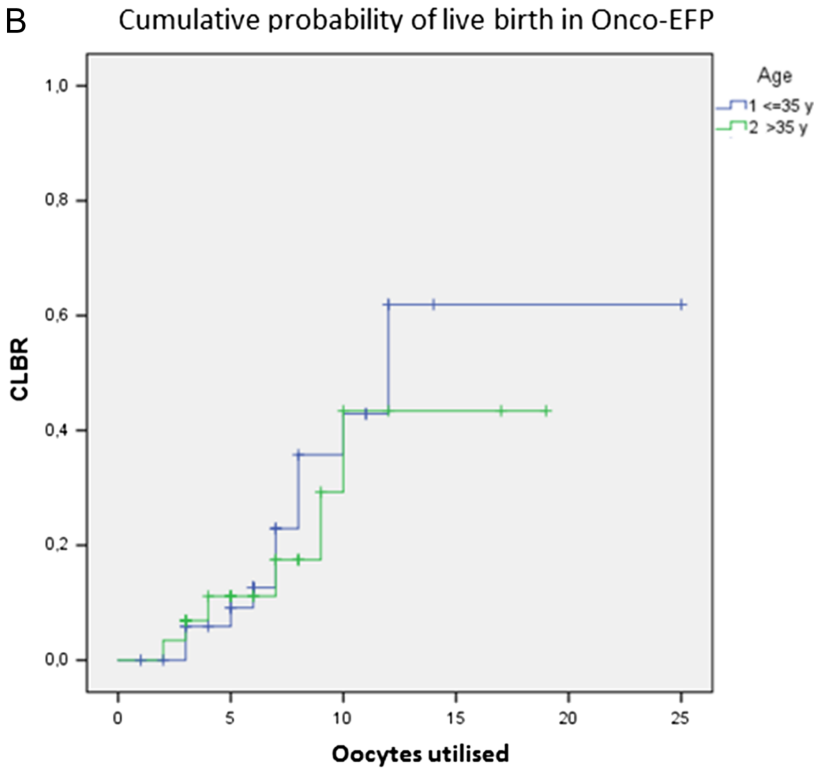
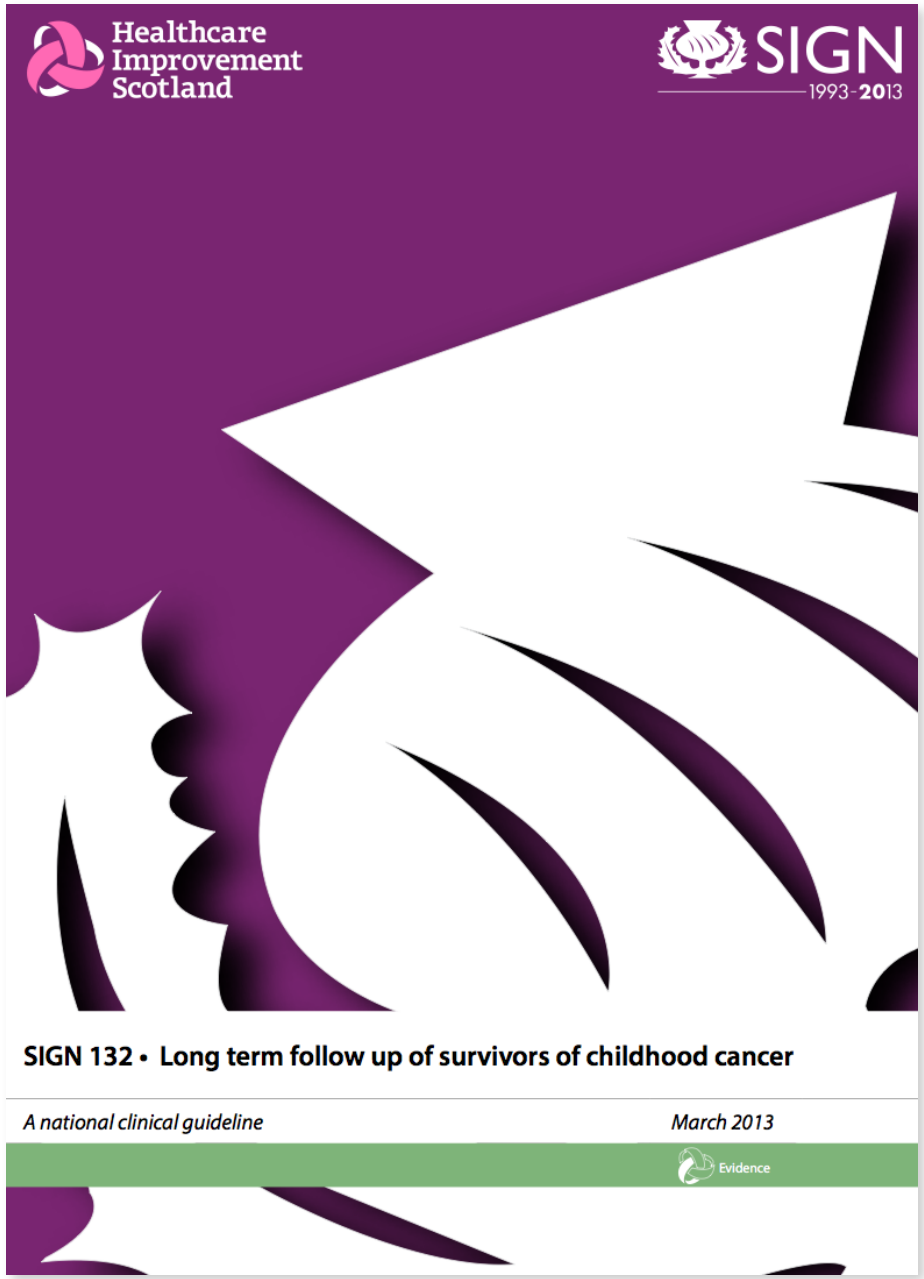
B



Age ≤35. N = 42		Age >35. N = 38	
Nºoocytes	CLBR(95%CI)	Nºoocytes	CLBR(95%CI)
5	9.1 (-0.7-19)	4	11.1 (-0.8-23.1)
8	35.8 (14.3-57.2)	9	29.3 (3.7-54.8)
10	42.9 (19.7-66.1)	10	43.4 (11.3-75.3)
12	61.9 (35.4-88.5)		

Cobo A et al 2018 Hum Reprod 33, 2222



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)

Wallace WH, Thompson L, Anderson RA
Long term follow-up of survivors of childhood cancer: summary of updated SIGN guidance. *BMJ* 2013; **346**: f1190.

thebmj

BMJ 2016;355:i6145 doi: 10.1136/bmj.i6145 (Published 30 November 2016)

EDITORIALS

Preserving fertility in girls and young women with cancer

Awareness of and access to services remains poor in the UK

Richard A Anderson *professor of clinical reproductive science*[1], Melanie C Davies *consultant gynaecologist*[2]

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 etc

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

The impact of cancer on subsequent chance of pregnancy: a population-based analysis

Richard A. Anderson[1,*], David H. Brewster[2], Rachael Wood[3], Sian Nowell[4,5], Colin Fischbacher[3], Tom W. Kelsey[6], and W. Hamish B. Wallace[7]

[1]MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, 47 Little france Crescent, Edinburgh EH16 4 TJ, UK [2]Scottish Cancer Registry, Information Services Division, NHS National Services Scotland, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [3]Information Services Division, NHS National Services Scotland, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [4]eData Research & Innovation Service (eDRIS), Information Services Division, NHS National Services Scotland, Edinburgh, 1 South Gyle Crescent, Edinburgh EH12 9EB, UK [5]Farr Institute Scotland, Nine Edinburgh Bioquarter, Little France Road, Edinburgh EH16 4UX, UK [6]School of Computer Science, University of St. Andrews, North Haugh, St. Andrews KY16 9SX, UK [7]Department of Oncology and Haematology, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF, UK

iSD SCOTLAND | NHS National Services Scotland | MRC Centre for Reproductive Health

Population-based analysis of pregnancy after cancer

1981-2012, aged 0-40
23,201 cancer survivors

38% less likely to achieve a pregnancy after diagnosis than women in the general population

28.6% vs 46.4% of women achieve a pregnancy after a cancer diagnosis

	No of women	SIR	95% CI
Cervix uteri	3498	0.34	0.31-0.37
Breast	5173	0.39	0.36-0.42
Brain, CNS	1045	0.42	0.36-0.48
Leukaemia	1077	0.48	0.42-0.54
Ovary	1129	0.63	0.57-0.69
Hodgkin lymphoma	962	0.67	0.62-0.73
Non-Hodgkin lymphoma	673	0.67	0.58-0.77
Thyroid	926	0.79	0.72-0.86
Skin	5252	0.87	0.84-0.90

ISD SCOTLAND NHS National Services Scotland

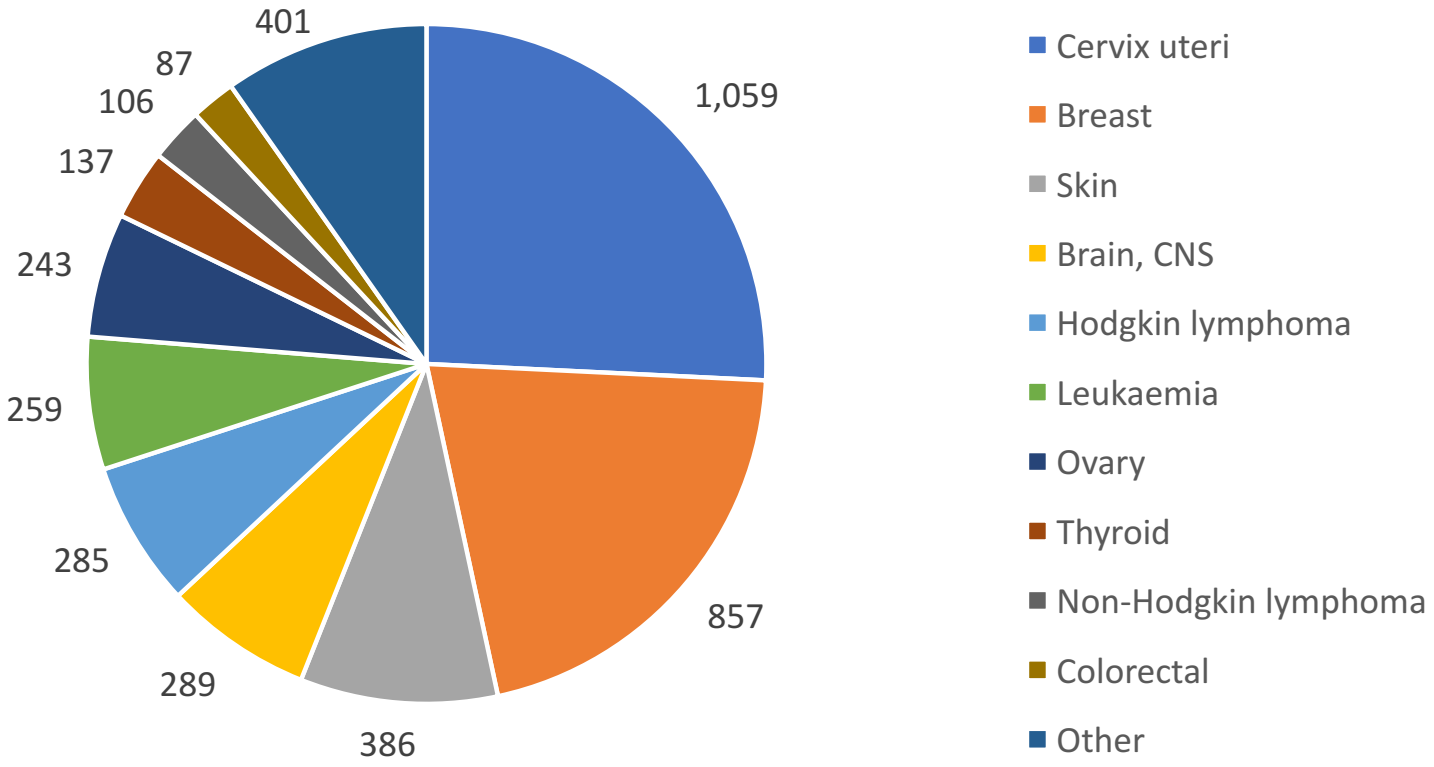
RA Anderson et al 2018 Human Reprod

Overall impact: ‘missing’ pregnancies

1981-2012, aged 0-40
23,201 cancer survivors

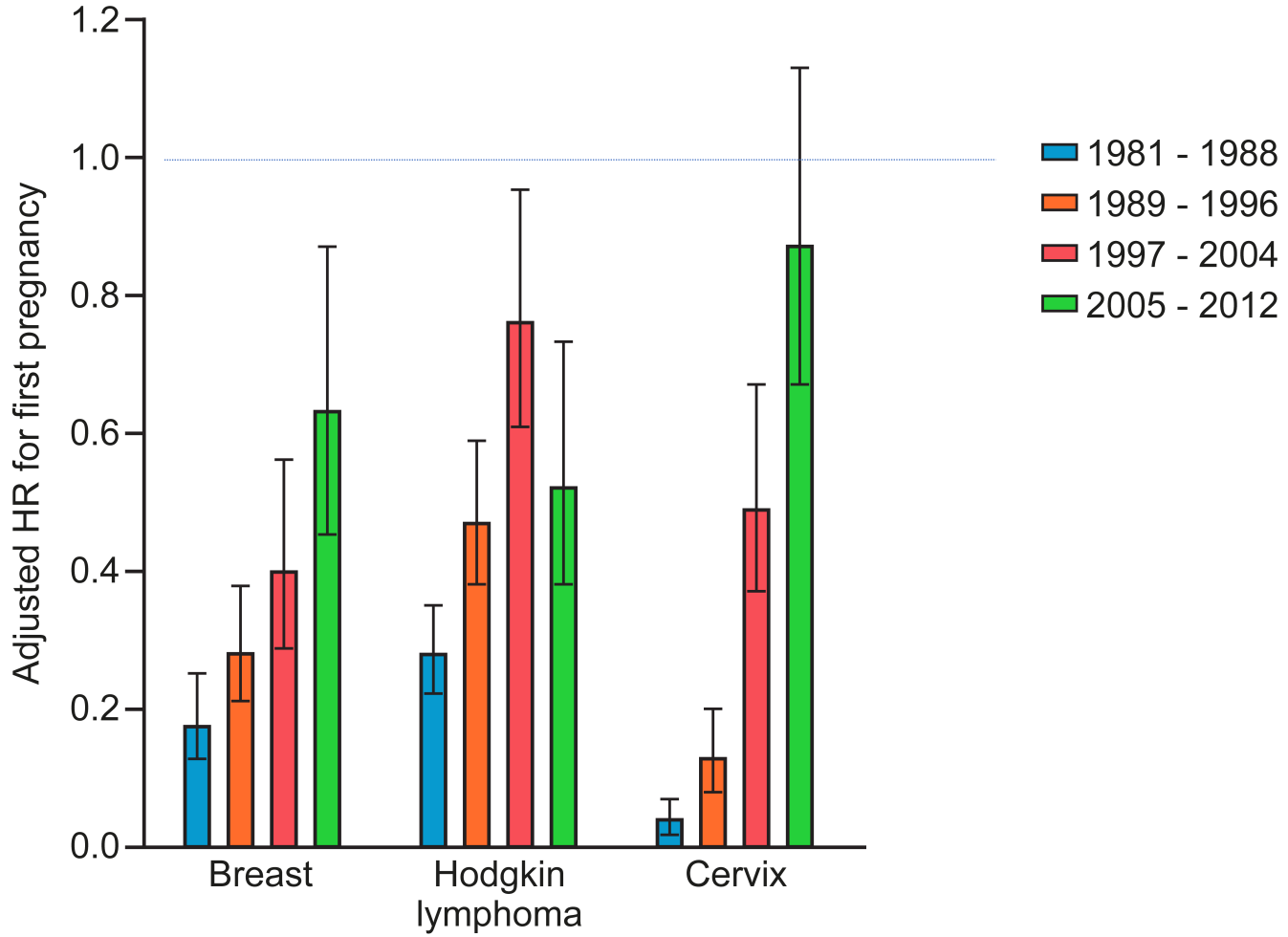
38% less likely to achieve a pregnancy after diagnosis than women in the general population

28.6% vs 46.4% of women achieve a pregnancy after a cancer diagnosis



RA Anderson et al 2018 Human Reprod

The changing risk to fertility in some cancers



RA Anderson et al 2018 Human Reprod

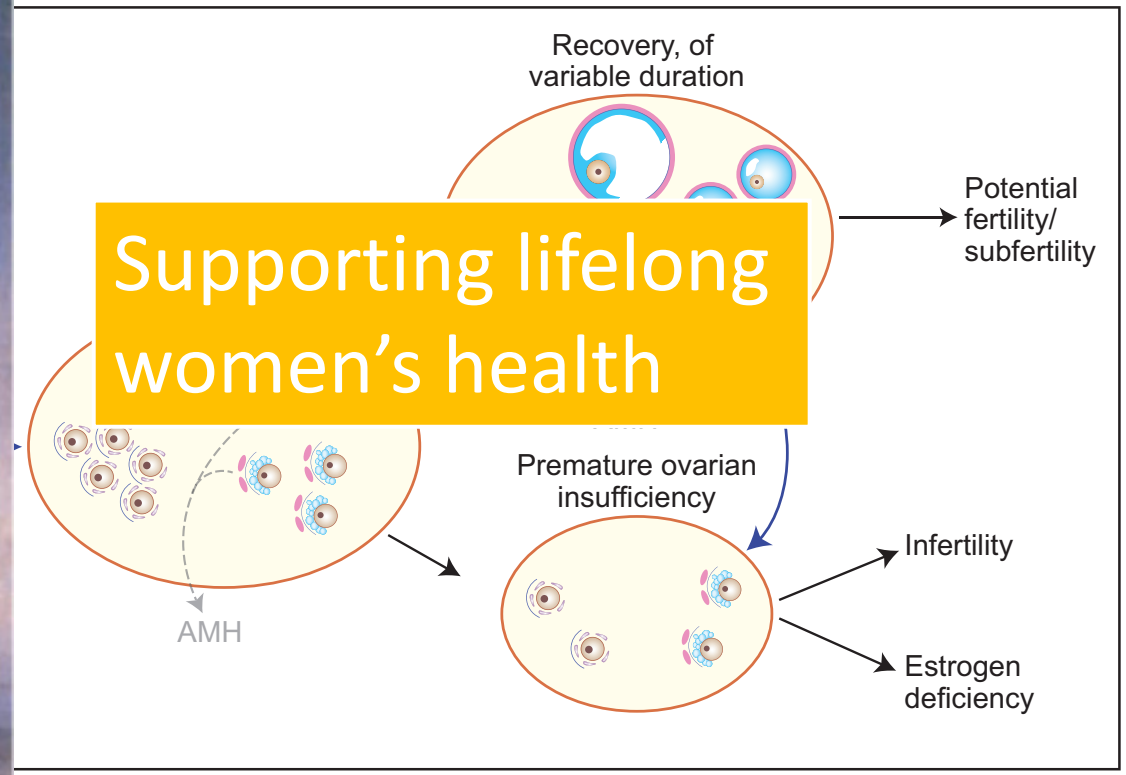
Outcome of first pregnancies after cancer

Singleton first pregnancies following cancer	Nulliparous women with cancer		Control women		Difference	95% CI	
	Number	% / rate *	Number	% / rate*		Lower	Upper
Total	2071	100	11772	100			
Miscarriage	203	9.8	1095	9.3	0.5	-0.9	1.9
Termination	231	11.2	1725	14.7	-3.5	-5.0	-2.0
Still Birth	8	0.4	53	0.5	-0.1	-0.4	0.2
Live Birth	1629	78.7	8899	75.6	3.1	1.1	5.0
Infant Death	12	7.4	43	4.8	2.5	-1.9	6.9

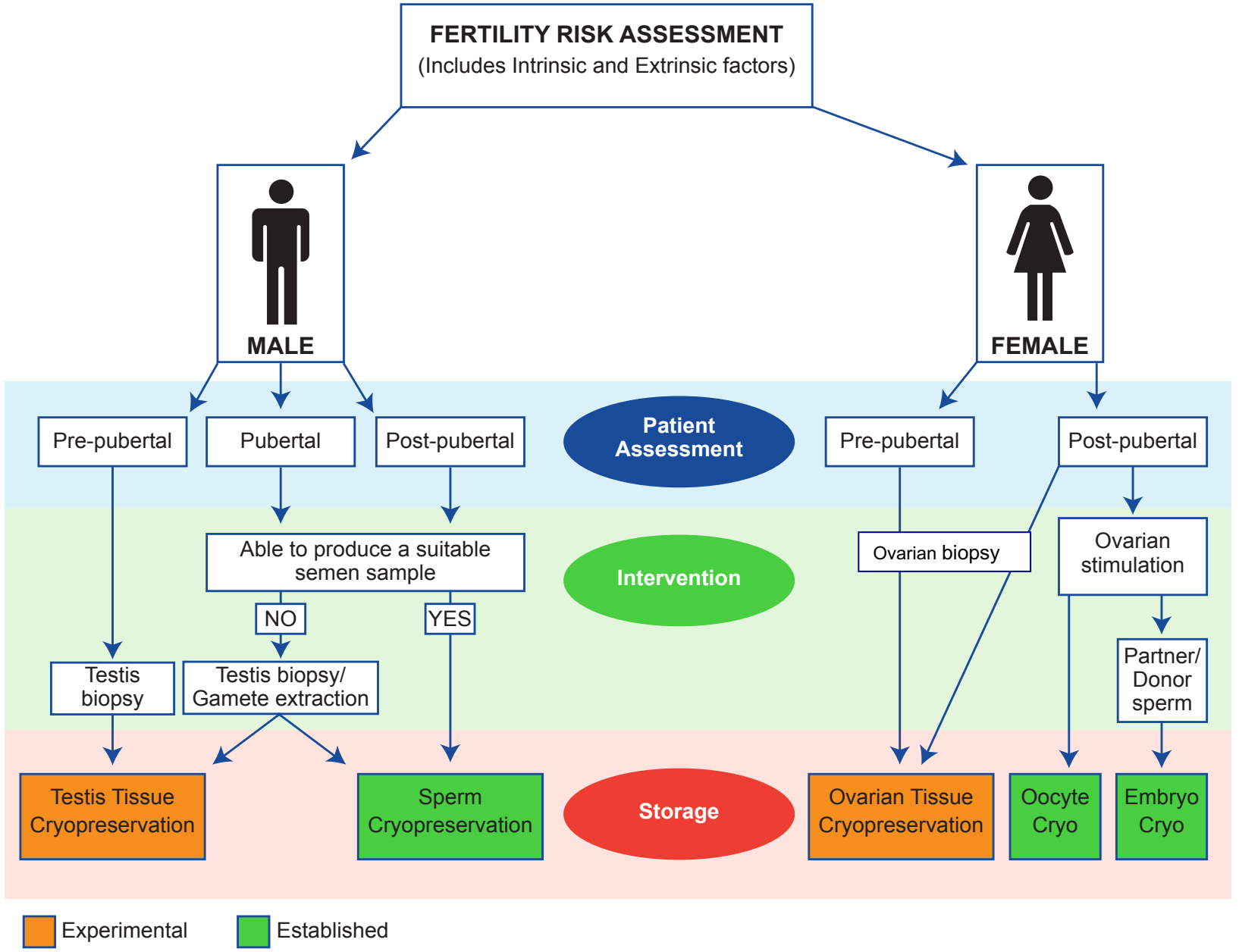
* % of all first singleton pregnancies apart from for infant deaths which is per 1000 live births

RA Anderson et al 2018 Human Reprod

Fertility and women's health: can we link short-term assessment to long term outcomes?



Jayasinghe, Wallace and Anderson 2018 Expt Rev Endo Metab



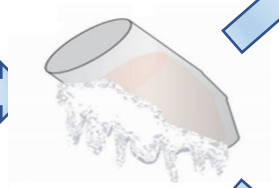
Anderson RA et al 2015 Lancet Diabetes Endocrinol

Fertility restoration using Prepubertal Testis

Pre-Treatment Biopsy

Tissue

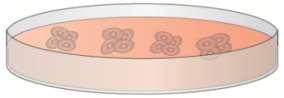
Cells



CULTURE

TRANSPLANT

Potential Clinical Options



Tissue

Cells

ICSI

Cells

(SSCs)

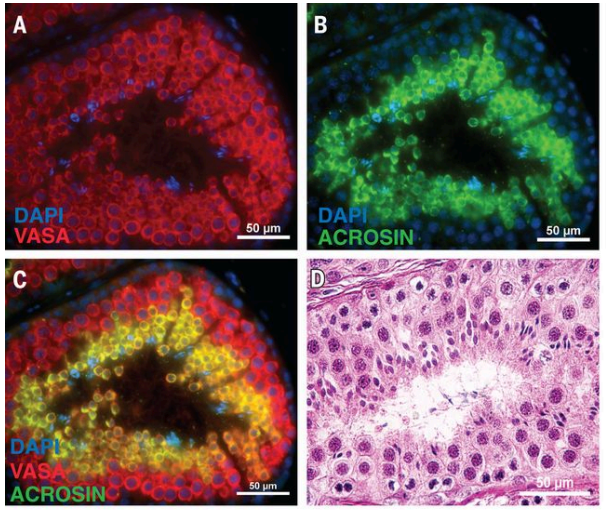
Natural Fertility

Tissue

ICSI

Led by Rod Mitchell

Sperm production and fertility after autografting in a prepubertal Rhesus monkey



Fayomi et al. Science 2019;363:1314

Establishment within NHS Scotland

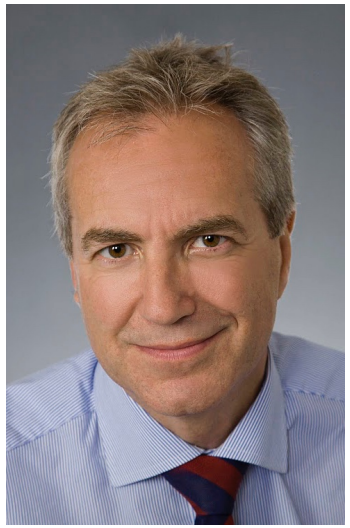
Clear national criteria for access to assisted reproduction

Development of linked criteria for fertility preservation
- women and men with cancer
- medical conditions that will compromise fertility
- transgender men and women

Not elective egg cryopreservation (‘social egg freezing’)

Key collaborators and funding

David T Baird



Hamish Wallace

CANCER RESEARCH UK

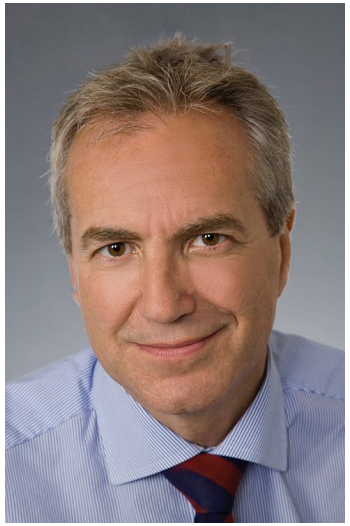
Medical Research Foundation

David Cameron and colleagues, Edinburgh Breast Unit
Bob Leonard and OPTION investigators
Peter Johnson and RATHL investigators
David Brewster and Rachael Wood, ISD, NHS Scotland
Tom Kelsey, Mathematician, St Andrews University
Roche Diagnostics for assay reagents

MRC Centre for Reproductive Health

Acknowledgements

David T Baird



Hamish Wallace

Evelyn Telfer

Rod Mitchell

- Tom Kelsey
- Marie McLaughlan
- Norah Spears

- SNBTS: George Galea/Sharon Zahra
- RHSC paed surgery: Fraser Munro
- Edinburgh breast unit: David Cameron