



The  
University  
Of  
Sheffield.

# Effects of cancer treatment on subsequent fertility

Allan Pacey  
University of Sheffield  
Sheffield Teaching Hospitals



The  
University  
Of  
Sheffield.



**British Fertility Society**

**ABA**

Association of Biomedical Andrologists



# Outline

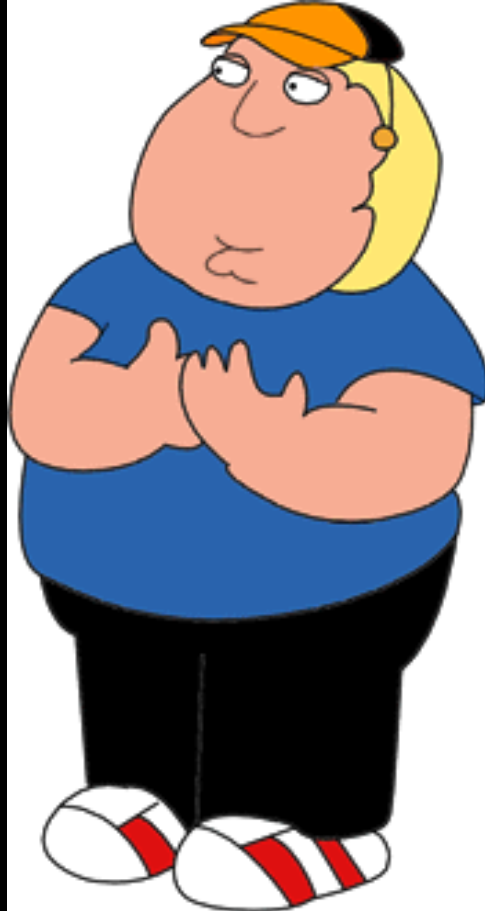


- Reproductive biology of males and females
- Cancer treatment and the reproductive system
- Fertility preservation strategies
- Natural fertility of cancer survivors
- Assisted conception in the adult survivor
- Pregnancy outcomes

Pacey (2007) Cancer Treatment Reviews 33: 646-655

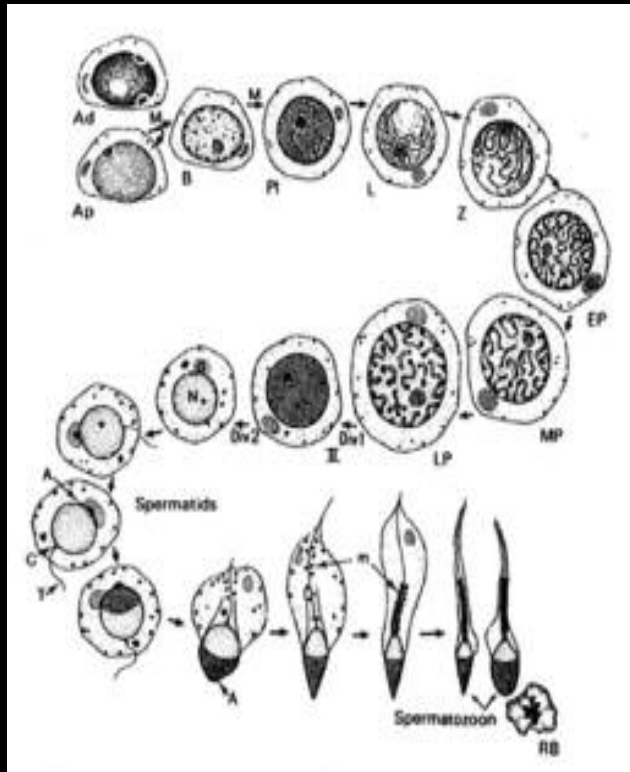
# Reproductive Biology of males and females

# Reproductive biology of males and females

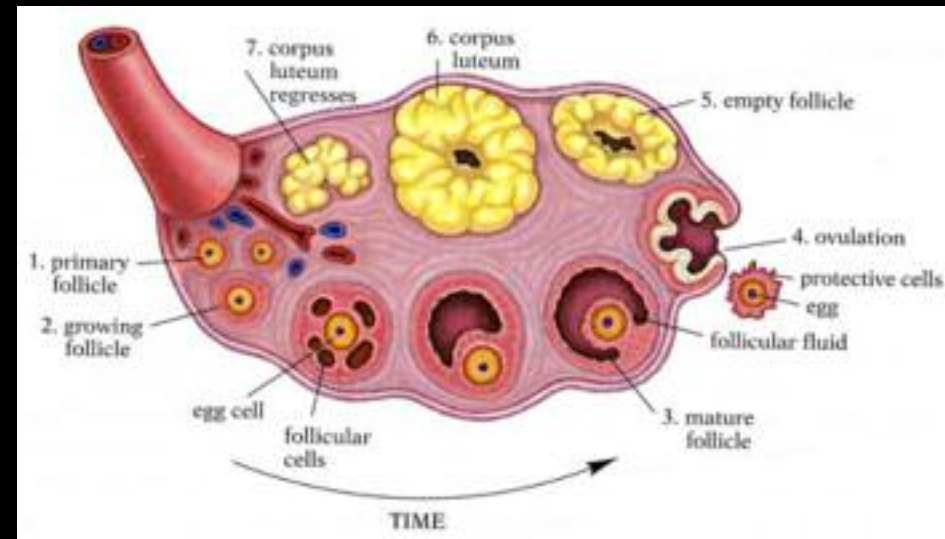


is not the same

# Reproductive biology of males and females



Men produce sperm throughout their lives



Women are born with their life supply of eggs

# Cancer treatment and the reproductive system

# Males



- Direct effect on gonad or its endocrine support
- Gonadal damage includes depletion or damage to testicular stem cells
- Irradiation of >0.1-1.2 Gy or alkylating agents
- Leydig cells are usually unaffected
- Pre-pubertal testicle is equally sensitive

Pacey (2007) Cancer Treatment Reviews 33: 646-655

# Females

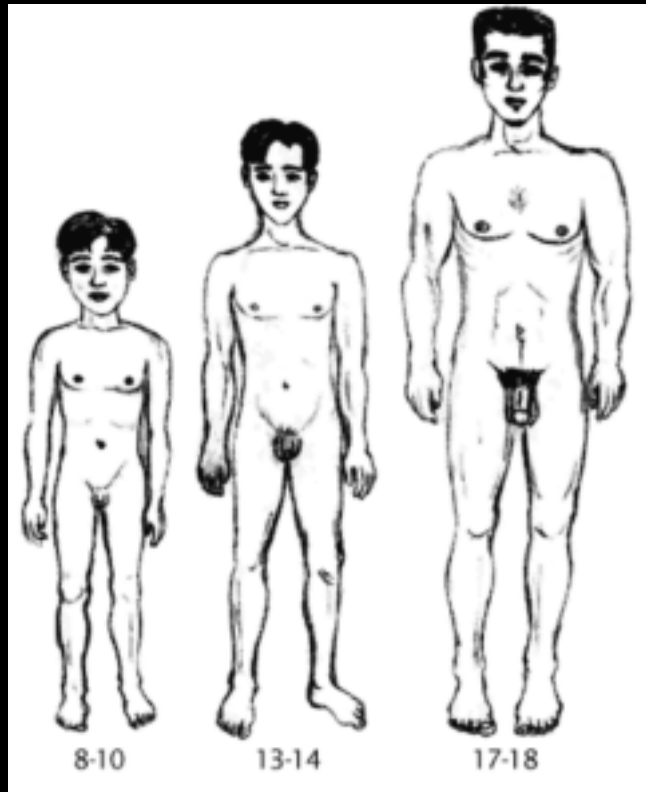


- Direct effect on gonad or its endocrine support
- Radiation and chemotherapy can deplete the size of the follicle pool
- <2 Gy can destroy 50% of follicle pool
- 5-20 Gy can lead to permanent damage regardless of age
- Impaired uterine growth and blood flow can occur in some individuals

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# Fertility preservation methods in males

# Age at Spermache



Spermache occurs at a:

- Median age of 13.4 (range 11.7-15.3 years of age).
- Median Testicular volume 11.5 ml (4.7 - 19.6ml)
- Pubic hair distribution (tanner stage) 2.5 (range 1 - 5).
- Median height of 160.4 cms (range 151.7 - 175.9).

Spermache is an early pubertal event

Nielsen *et al.*, (1986) *J Clin Endocrinol Metab.* 62: 532-535

# Initial Sample Quality

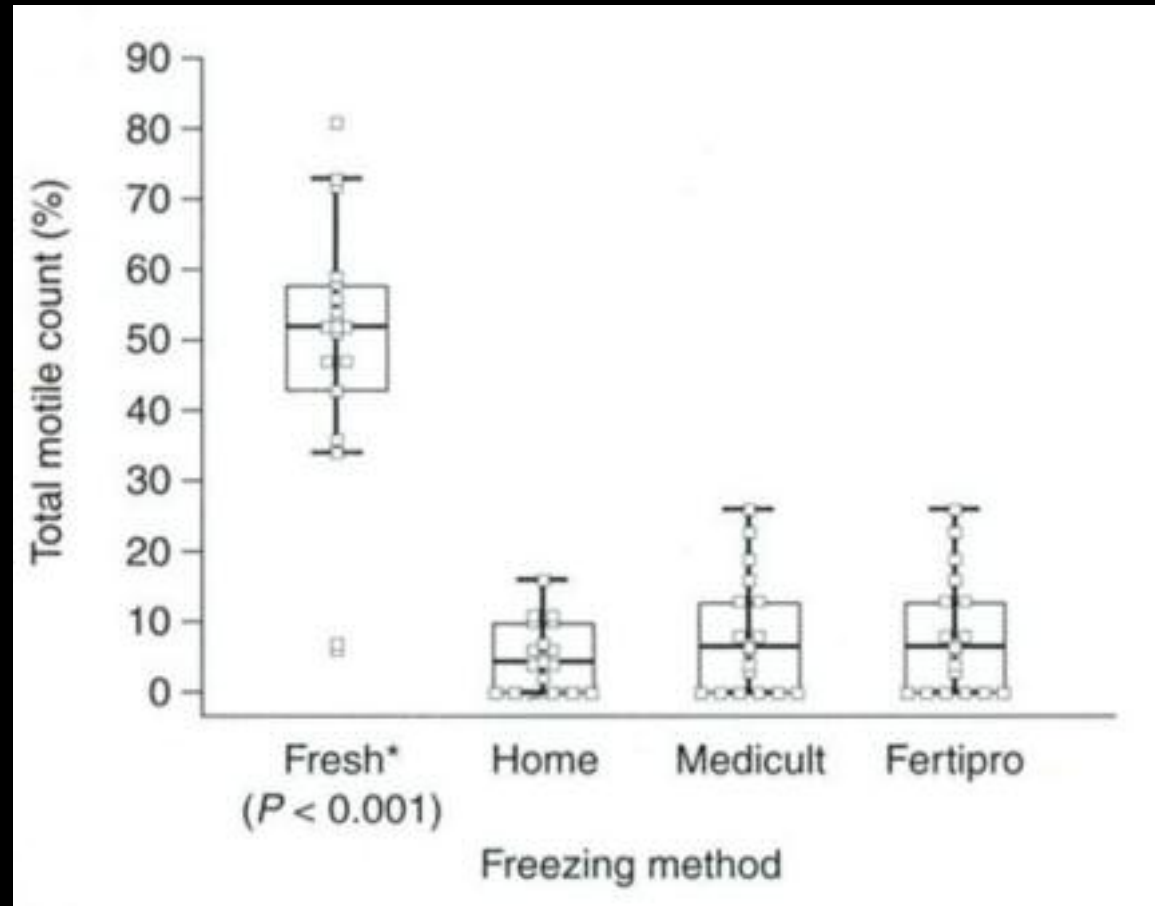
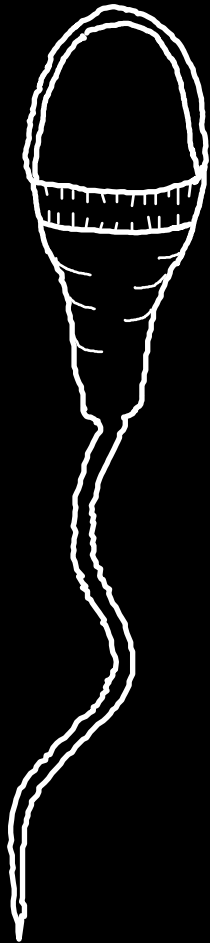
**Table I.** Age, sperm count and semen volume for disease and healthy groups

Disease/group	<i>n</i>	Age (years)		Sperm count ( $\times 10^6$ /ml)		Semen volume (ml)	
		Mean	SEM	Mean	SEM	Mean	SEM
Hodgkin's	36	16.44	0.34	55.56	7.3	1.41	0.16
Non-Hodgkin's	6	16.83	0.7	91.67	22.72	1.75	0.17
Osteosarcoma	51	16.38	0.24	59.14	6.75	1.68	0.15
Ewings sarcoma	24	16.67	0.4	49.42	9.01	2.06	0.29
ALL	7	17.43	0.48	57.43	23.15	1.02	0.42
AML	3	14.33	0.67	18	11.14	1.67	0.67
Testicular cancer	17	17.82	0.31	31.94	4.81	1.99	0.19
Leukaemia	23	16.78	0.35	38.96	8.31	1.50	0.19
Lymphoma	11	16.17	0.52	66.67	15.55	1.31	0.33
Other	27	16.96	0.29	36.41	8.88	1.26	0.19
Total cancer patients	205	16.67	0.12	50.63	3.2	1.59	0.07
Healthy donors	71	22.89	0.34	84.51	3.39	2.96	0.16

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia.

*Bahadur et al., (2002) Human Reproduction 17: 3157-3161*

# Effects of Storage



Nijs & Ombelet (2001) *Human Fertility* 4: 158-163

# Fertility preservation methods in females

# Freezing of mammalian eggs



Problems with frozen-thawed eggs:

- Hardening of the Zona Pelludica
- Damage to the meiotic spindle
- Genetic abnormalities (e.g. increased polyploidy & aneuploidy)

Whittingham (1977) *J. Reprod. Fertil.*, **49**: 89-94

# Egg Banking

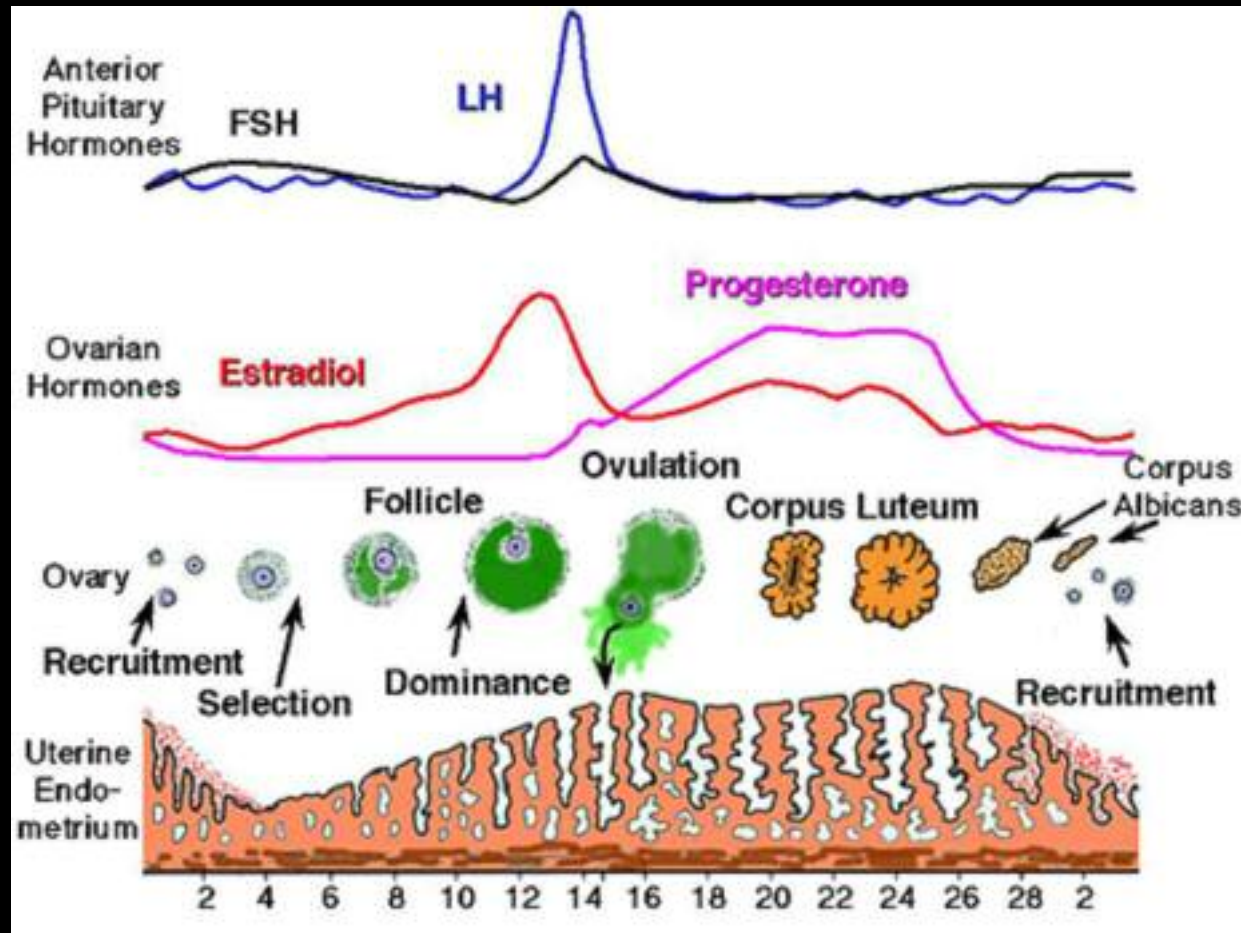
**Table 1.** Summary clinical outcome of cryopreserving human oocytes by equilibrium cooling\*

Study (ref)	Fertilized by	No. of oocytes	Pregnancies	No. of live infants
Chen, 1986 (35)	IVF	40	—	1
Van Uem et al., 1987 (36)	IVF	28	—	1
Al-Hasani et al., 1987 (37)	IVF	182	—	2
Siebzehmrübl et al., 1989 (38)	IVF	38	—	1
Tucker et al., 1996 (39)	ICSI	81	3	0
Porcu et al., 1997 (21)	ICSI	12	1	1
Tucker et al., 1998 (40)	ICSI	13	1	1
Borini et al., 1998 (41)	ICSI	129	3	—
Porcu et al., 1998 (42)	ICSI	709	9	6
Young et al., 1998 (43)	ICSI	9	1	3
Polak de Fried et al., 1998 (44)	ICSI	10	1	1
Donaldson et al., 2000 (45)	ICSI	18	2	—
Porcu et al., 2000 (46)	ICSI	1840	19	12
Winslow et al., 2001 (47)	ICSI	324	—	16
Chen et al., 2002 (48)	ICSI	8	1	—
Porcu et al., 2002 (49)	ICSI	124	—	3
Yang et al., 2002 (50)	ICSI	158	11	14
Quintans et al., 2002 (34)	ICSI	109	5	2
Fosas et al., 2003 (51)	ICSI	88	—	5
Boldt et al., 2003 (52)	ICSI	90	—	5

\*Modified from Leibo (24). IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; — = none.

Gosden (2005) *J. Natl. Cancer Inst Monogr.* 34: 60-63

# Egg Banking



Egg collection will delay cancer treatment

For those in a relationship ...



Trounsen & Mohr (1983) *Nature* 305: 707-709

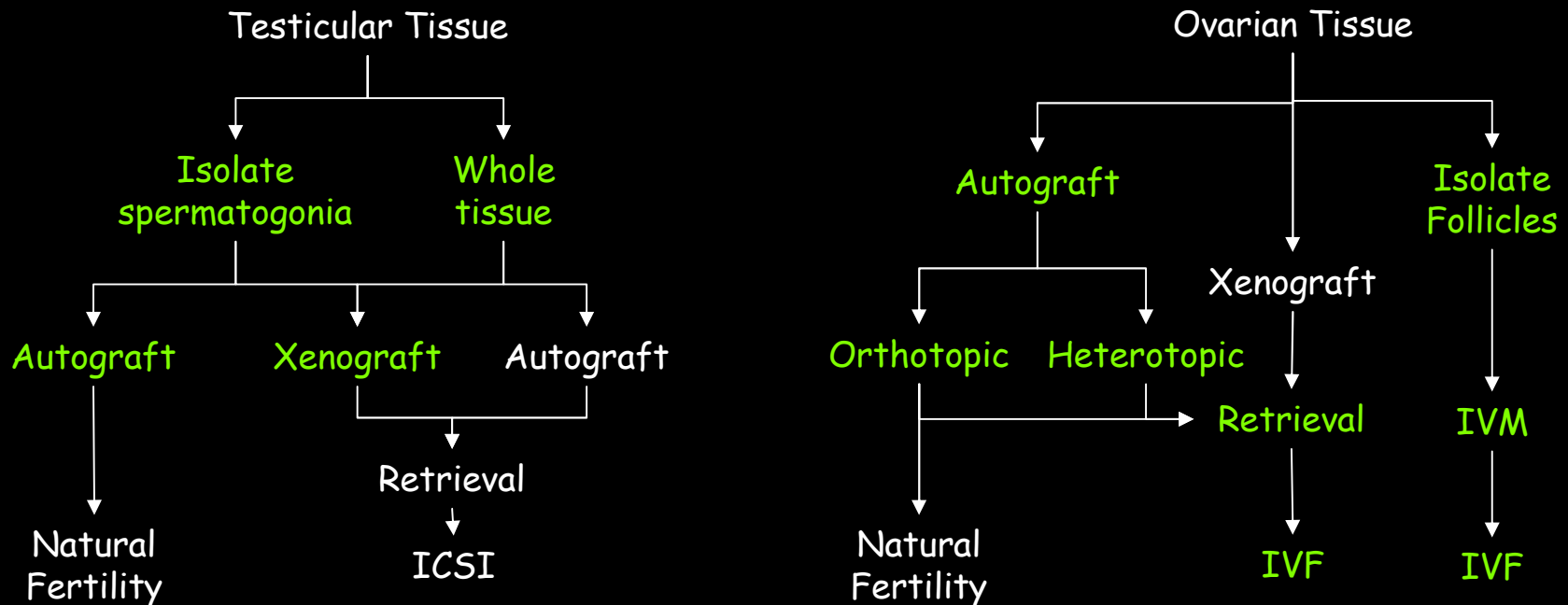
# Embryo freezing ...



- Delays cancer treatment
- Requires woman to have a partner
- Consent can be withdrawn later (e.g. Natalie Evans)
- Frozen embryo replacement is half as successful as fresh embryo replacement
- Embryo storage is 5 years only
- In some countries embryo storage is not allowed (e.g. Italy).

Fertility preservation  
methods in pre-pubertal  
individuals

# Strategies for pre-pubertal males & females



The BFS recommends that these techniques only take place as part of clinical trials

# Natural fertility of cancer survivors

# Paternity after testicular cancer



Brydøy *et al.*, (2005) *J. Natl. Cancer. Inst.*, 97: 1580-1588

# Parenthood probability in cancer patients

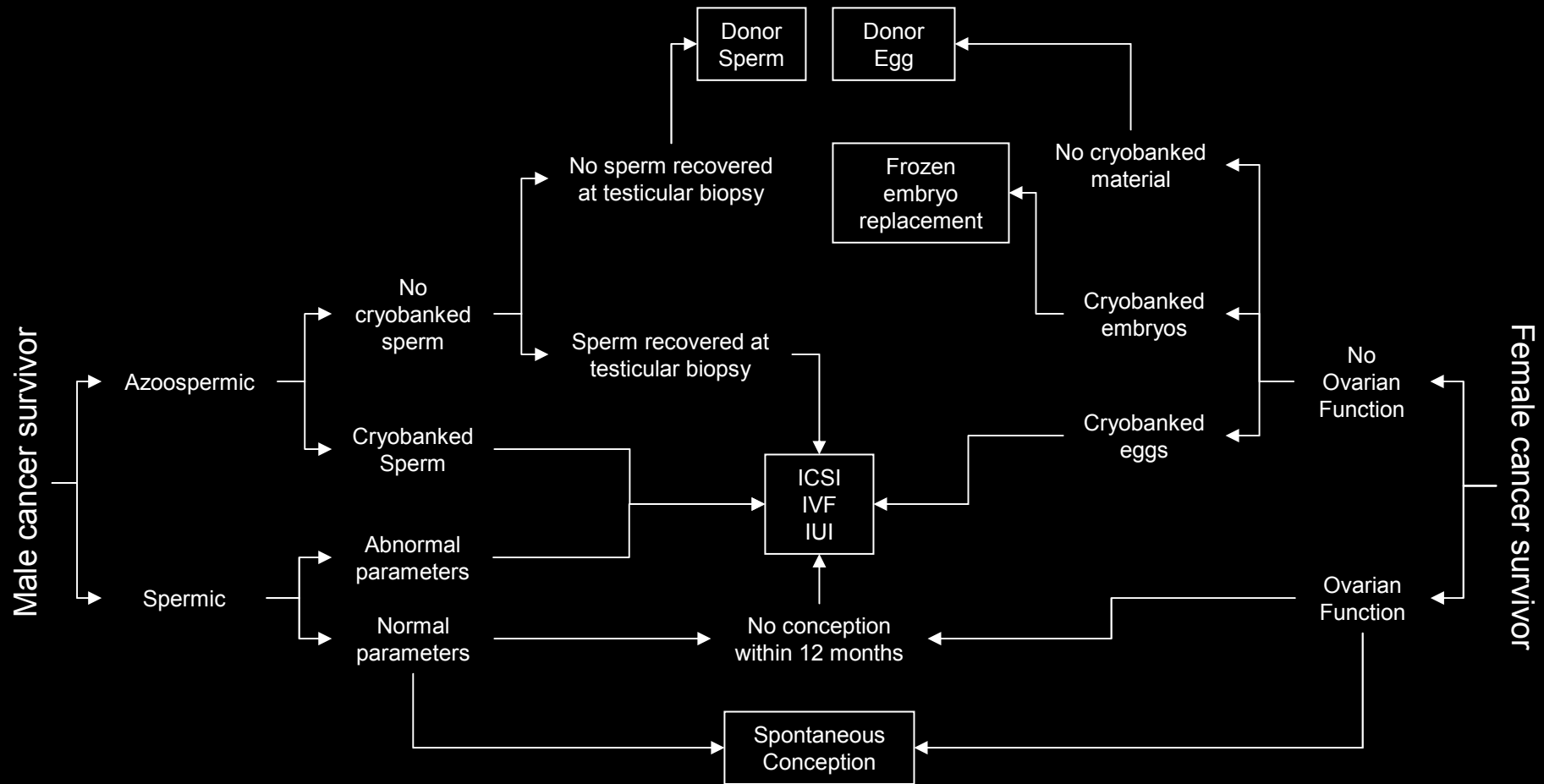
First time probability of parenthood at age 35 was:

- 63% in male cancer patients (n=463)
- 64% in the general population (n=367,068)
  
- 66% in female cancer patients (n=284)
- 79% in the general populations (n=349,576)

*Magelssen et al., (2008) Human Reproduction 23: 178-186*

Assisted conception in  
the adult survivor

# Assisted Conception Options



Pacey (2007) Cancer Treatment Reviews 33: 646-655

# Assisted Conception

Low Technology

High Technology

Natural Methods



>20 × 10<sup>6</sup> sperm/ml  
>50% motile  
>14% normal forms

Normal  
Female  
Biology

IUI



>5 × 10<sup>6</sup> motile sperm  
Post preparation

Patent Fallopian Tubes  
Possible ovulatory problems

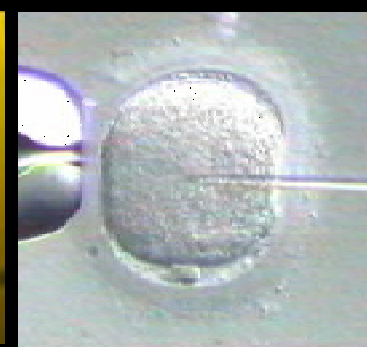
IVF



>1 × 10<sup>6</sup> motile sperm  
Post preparation

Blocked or Damaged Fallopian Tubes  
Ovulatory problems

ICSI



>1 viable sperm  
post preparation

ICSI

# Success after long-term storage

Exclusive: Parents of the deep-freeze boy talk to the Mail

## THE BABY AGED 23



Daniel, the boy who made history

THIS is the miracle 'deep freeze' baby conceived using sperm frozen for 21 years. Daniel White, identified for the first time today, made medical history when he was born two years ago. Until now, Daniel and his family have remained anonymous. But now his parents Joan and Trevor White have told the Daily Mail the remarkable story of Daniel's birth – and how Mr White had his sperm frozen before undergoing treatment for testicular cancer which he knew would make him sterile.

**FULL STORY – PAGES 2 TO 4**

Horne *et al.*, (2004) *Human Reproduction* 19: 1448-1449

# Success after long-term storage

## Successful sperm storage for 28 years

Joseph Feldschuh, M.D.,<sup>a</sup> James Brassel, M.D.,<sup>a</sup> Nancy Durso, M.D.,<sup>b</sup> and Allen Levine, M.D.<sup>c</sup>

<sup>a</sup> Idant Laboratories, New York, New York; <sup>b</sup> Mid-Atlantic Fertility Center, Bethesda, Maryland; and <sup>c</sup> Orange OB/GYN Association, New York, New York

**Objective:** To report on two instances of successful long-term cryopreservation resulting in live births.

**Design:** Case report.

**Setting:** The patient stored his sperm at a private sperm banking facility, and his partner underwent artificial insemination at an obstetrics/gynecology practice for one pregnancy and at a fertility center for the other.

**Patient(s):** One man who stored his sperm before treatment for cancer.

**Intervention(s):** Storage of sperm under liquid nitrogen in a carousel canister system. Intrauterine insemination in which the semen was thawed, washed with human tubal fluid (HTF), and inseminated.

**Main Outcome Measure(s):** Successful pregnancy resulting in live birth.

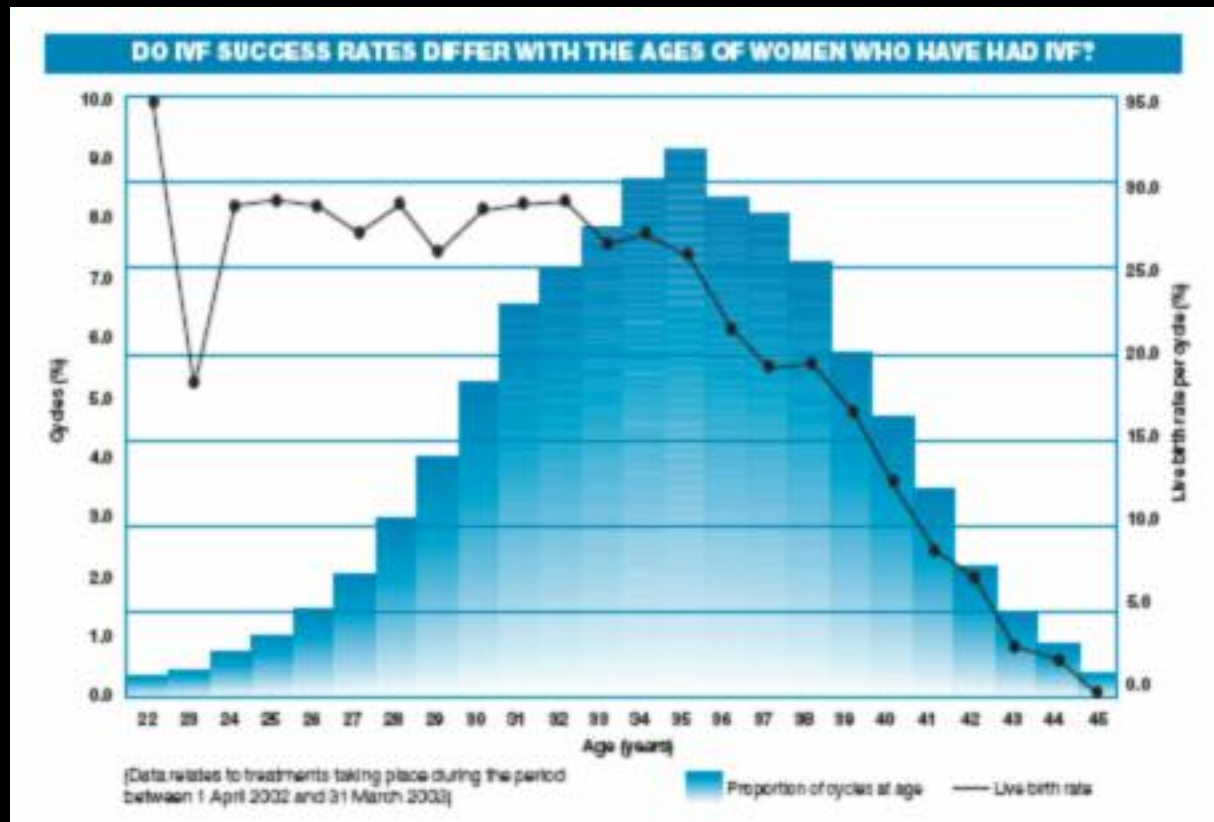
**Result(s):** Artificial insemination with semen cryopreserved for 21 and 28 years resulted in two live births.

**Conclusion(s):** This case report describes the to-date longest known successful cryopreservation of sperm, with two live births resulting from IUI. Successful long-term semen storage can be very beneficial for men facing impaired fertility or sterility early in life, so that they have sufficient time to make appropriate family planning decisions. (*Fertil Steril*® 2005;84:1017.e3–4. ©2005 by American Society for Reproductive Medicine.)

**Key Words:** Semen storage, cryopreservation, intrauterine insemination

Feldschuh *et al.*, (2005) *Fertility and Sterility* 84: 1017

# Female Age and Success at IVF



HFEA (2005) The Patient's Guide

Pregnancy outcomes

# Parenthood probability in cancer patients

First time probability of parenthood at age 35 was:

- 63% in male cancer patients (n=463)
- 64% in the general population (n=367,068)
  
- 66% in female cancer patients (n=284)
- 79% in the general populations (n=349,576)

Risk of low birthweight, pre-term delivery and perinatal mortality in infants born to female cancer patients was 2.3 times increased (95% CI = 1.1-5.0)

*Magelssen et al., (2008) Human Reproduction 23: 178-186*

# Incidence of genetic disease

	Potentially mutagenic (n=408)	Low or non mutagenic (n=1,695)	Controls (n=4,544)
Cytogenetic syndrome	0 (0%)	4 (0.2%)	6 (0.1%)
Single gene disorder	1 (0.2%)	13 (0.8%)	10 (0.2%)
Simple malformation	12 (2.9%)	44 (2.6%)	127 (2.8%)
Total	13 (3.2%)	61 (3.6%)	142 (3.1%)

Meistrich and Byrne (2002) *Am. J. Hum. Genet.*, 70: 1069-1071

# Conclusions

- Cancer treatment can affect the reproductive system in complex ways
- Sperm banking and its use in ART is now routine
- Egg freezing is possible but currently has low rates of success. Embryo freezing is the only current option for women
- Strategies for fertility preservation in pre-pubertal individuals (of either sex) remains experimental
- Fertility outcomes for cancer survivors are generally very good

Thank You!