Dr Richard Fisher

Reproductive Medicine
Co-founder, Fertility Associates

Everything You Wanted to Know About Fertility But Were Too Afraid To Ask - Pre-Conference Workshop

Thursday, 20 June 2013 Start 2:00pm Duration: 120mins Sigma

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

Fertility Associates –
Leaders in Fertility

What is infertility?

NICE

Failure to conceive after regular unprotected intercourse for 2 years in the absence of known reproductive pathology.

RCOG press 2004

What is infertility?

WHO

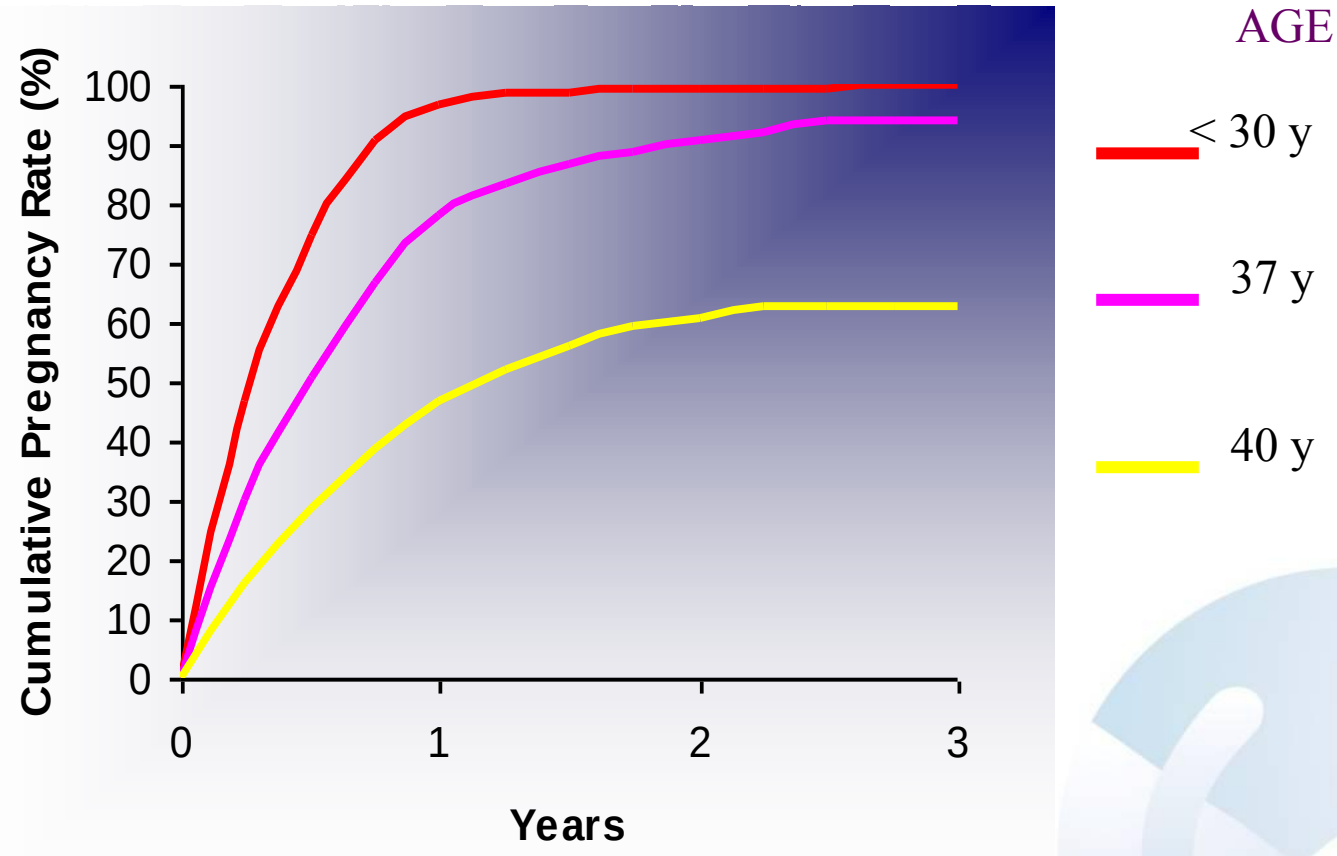
Failure to conceive a pregnancy after 1 years contraceptive free intercourse (under 34 yrs)

Failure to conceive a pregnancy after 6 months contraceptive free intercourse if female is over 36

(Cooper – Human Reprod. Update 16)

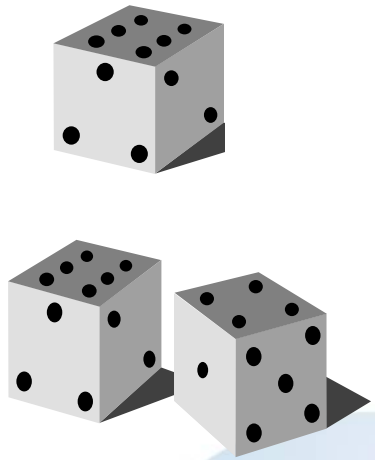
What is infertility?

An emotional experience which sometimes requires a physical solution


Cumulative Pregnancy Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
Years
AGE
< 30 y
37 y
40 y

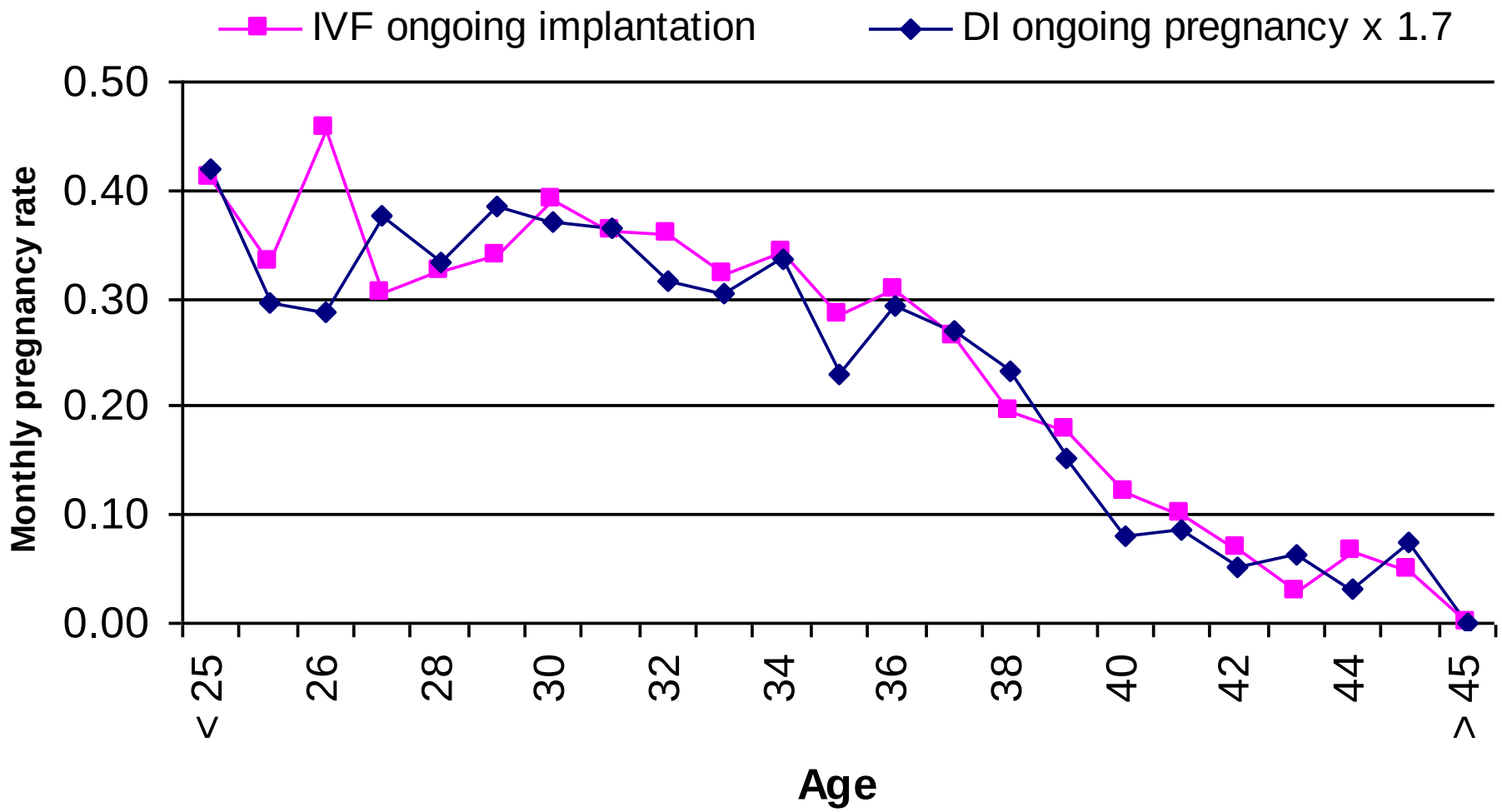
Monthly fecundity by age

Years	%
25	25
30	20
35	16
37	11
40	6
42	4
44	2



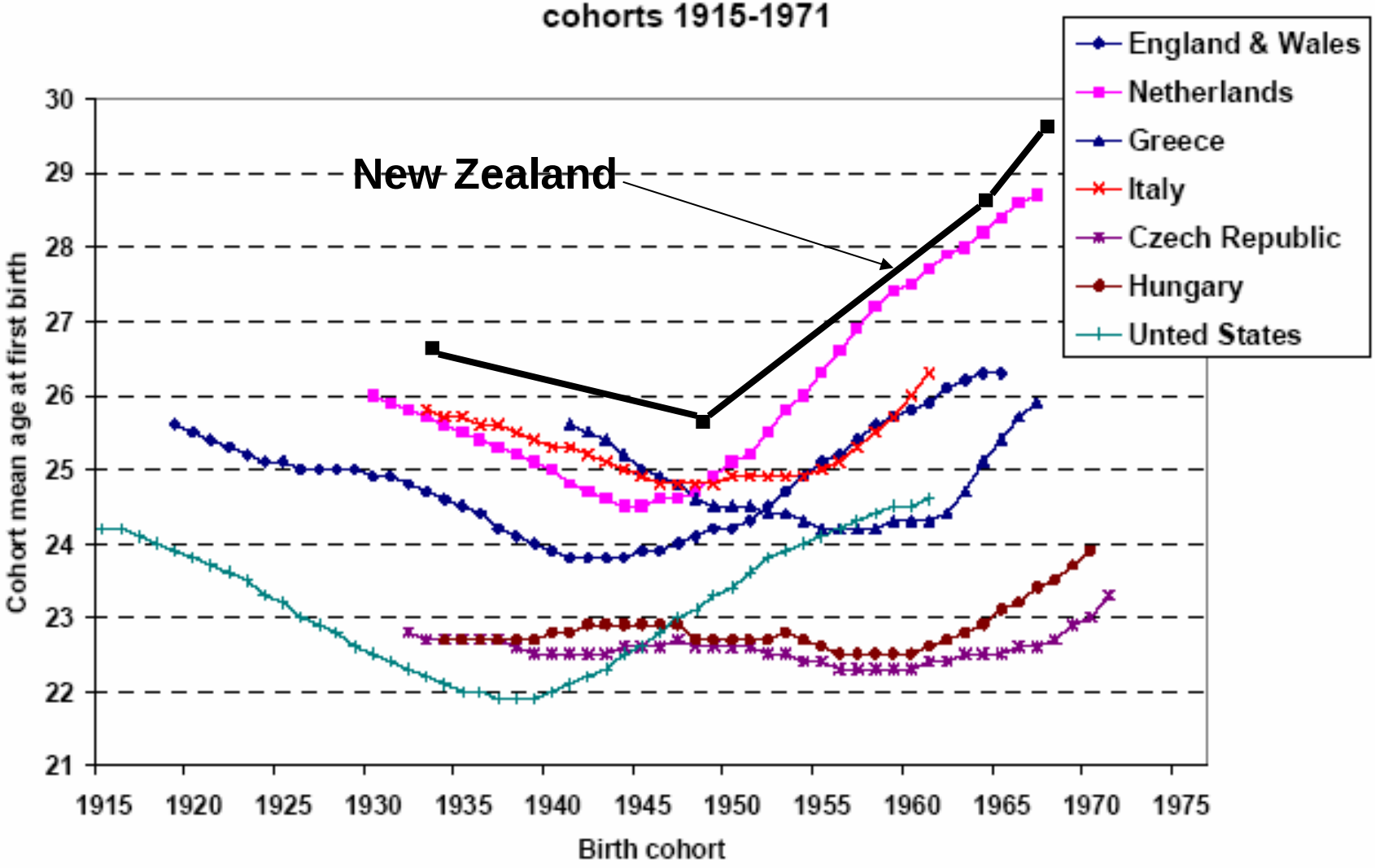
Source: Fertility Associates

Decline in fertility with age



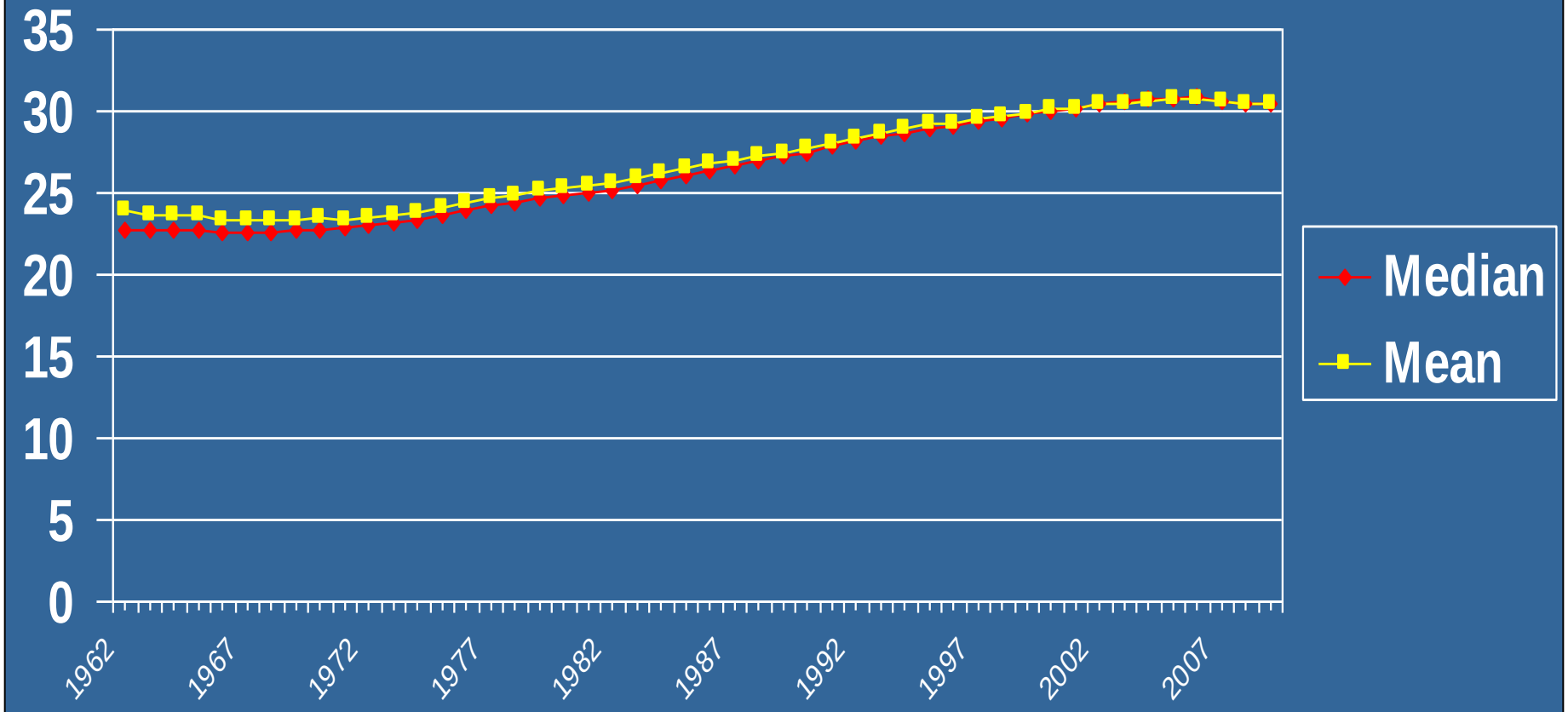
Source: Fertility Associates

Figure 4 - Cohort mean age at first birth, selected countries, birth cohorts 1915-1971

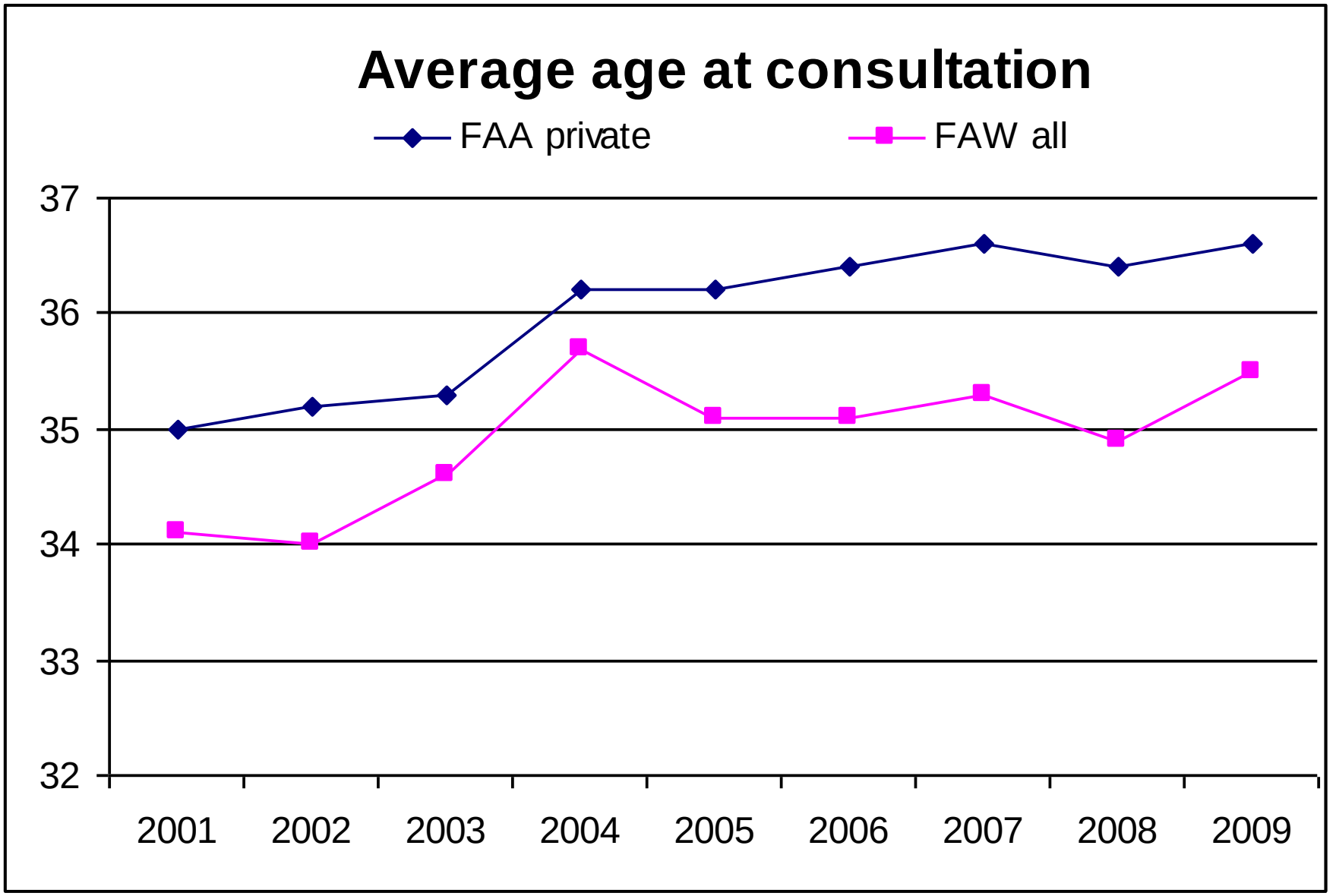


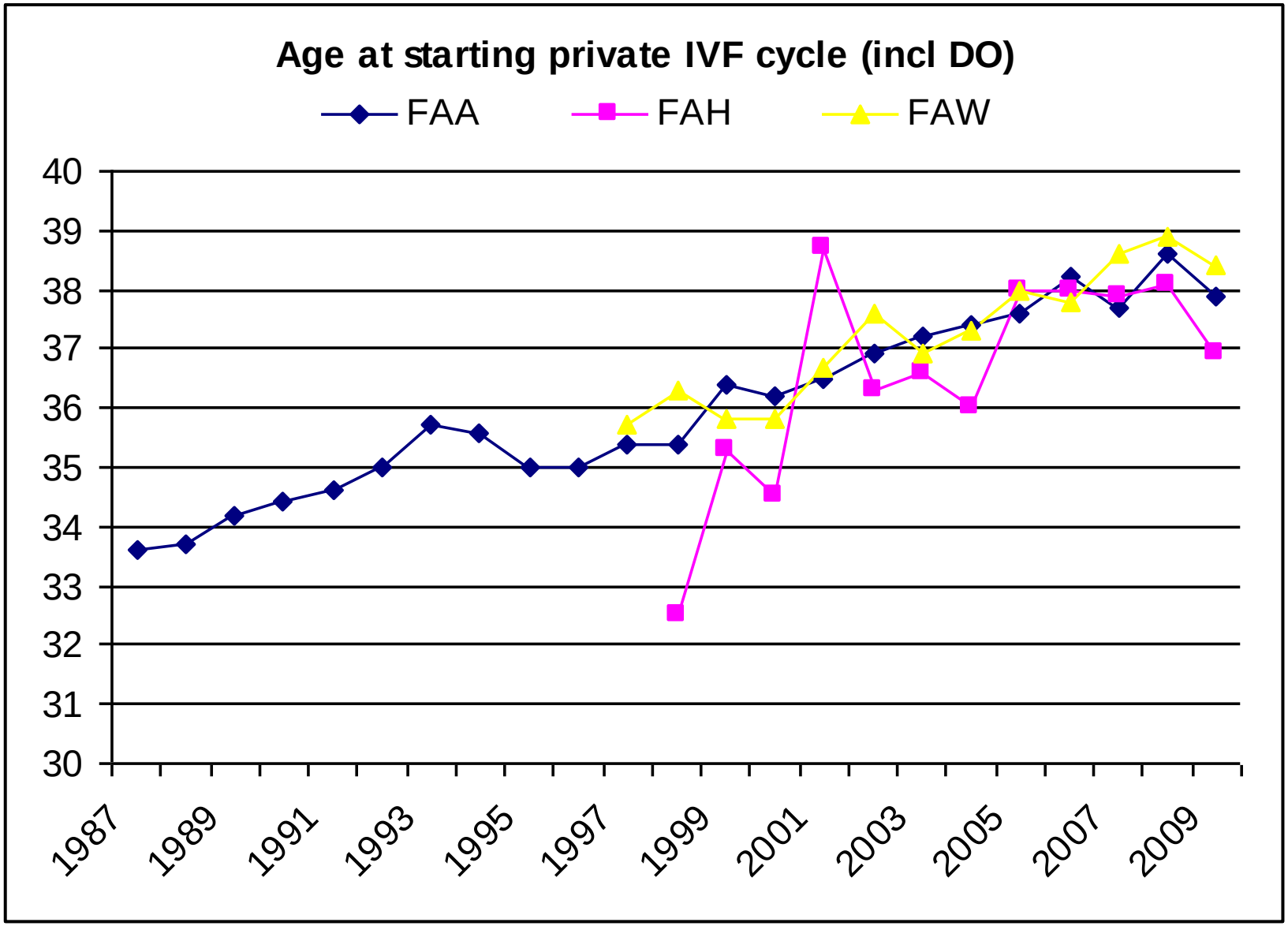
Source: Max Planck Institute

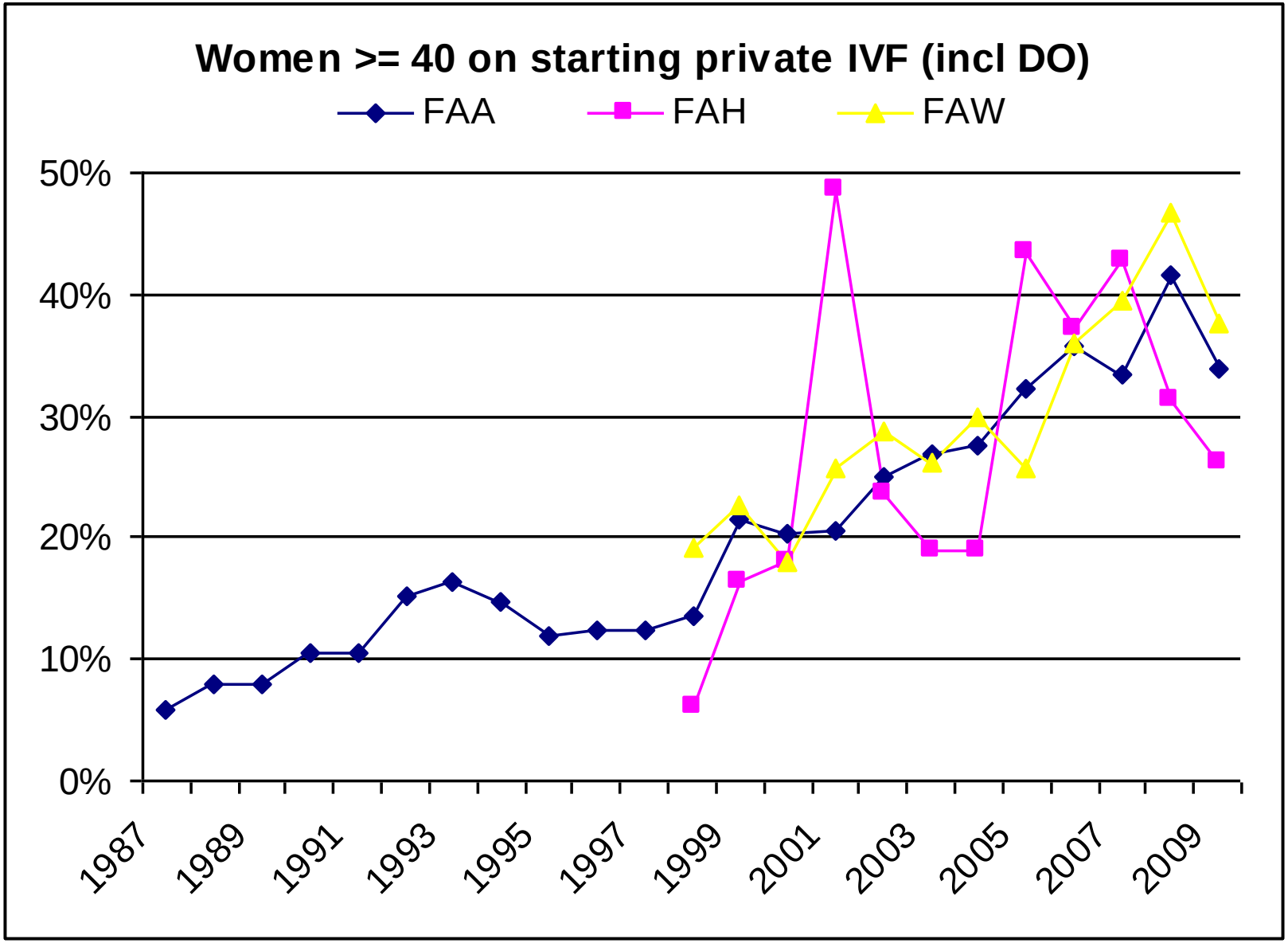
Average age of mother at first birth in New Zealand

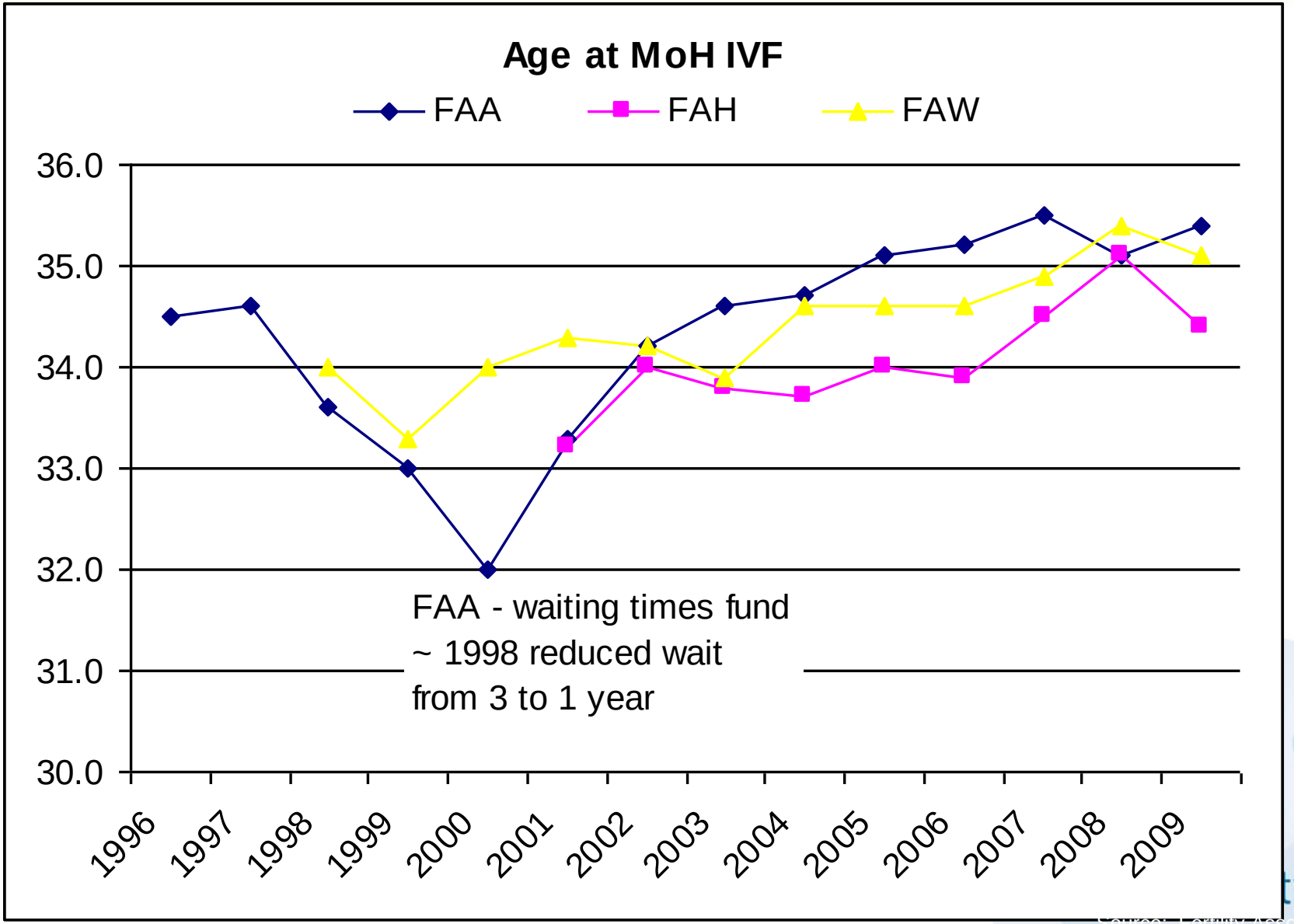


Source: Statistics New Zealand 2009


Average age at consultation
FAA private
FAW all
37
36
35
34
33
32
2001
2002
2003
2004
2005
2006
2007
2008
2009


Age at starting private IVF cycle (incl DO)
FAA
FAH
FAW
40
39
38
37
36
35
34
33
32
31
30
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009


Women >= 40 on starting private IVF (incl DO)
FAA
FAH
FAW
50%
40%
30%
20%
10%
0%
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009



Source: Fertility Associates

When?

Social model of infertility

Community

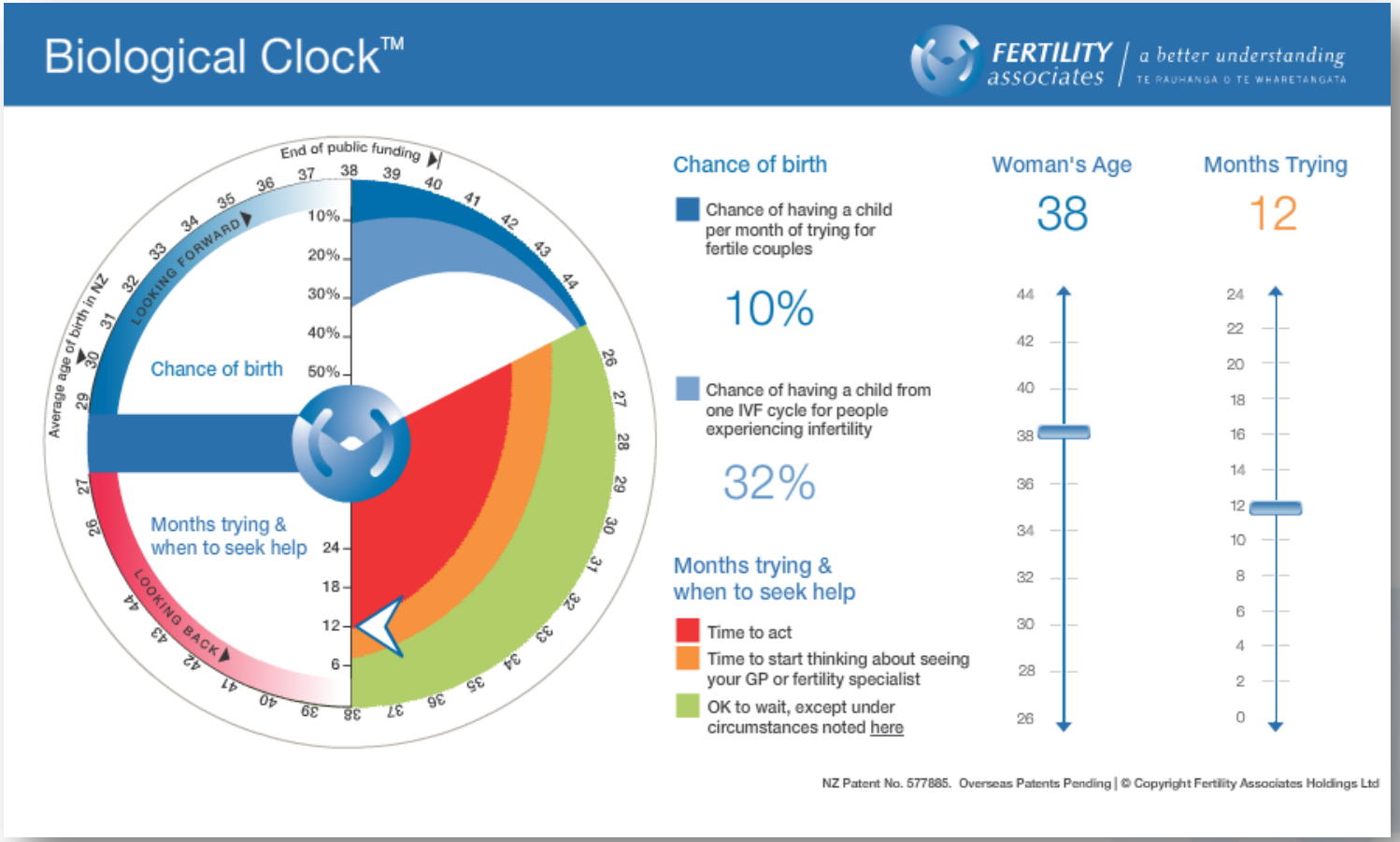
Time

Gender

Social model of infertility

Is normal acceptable?

When should I seek advice?



What?

Depends on

- Diagnosis
- Time
- Age
- Resources

Diagnosis

- Sperm
- Ovulation
- Fallopian tubes
- Female pelvis
- Age

Time

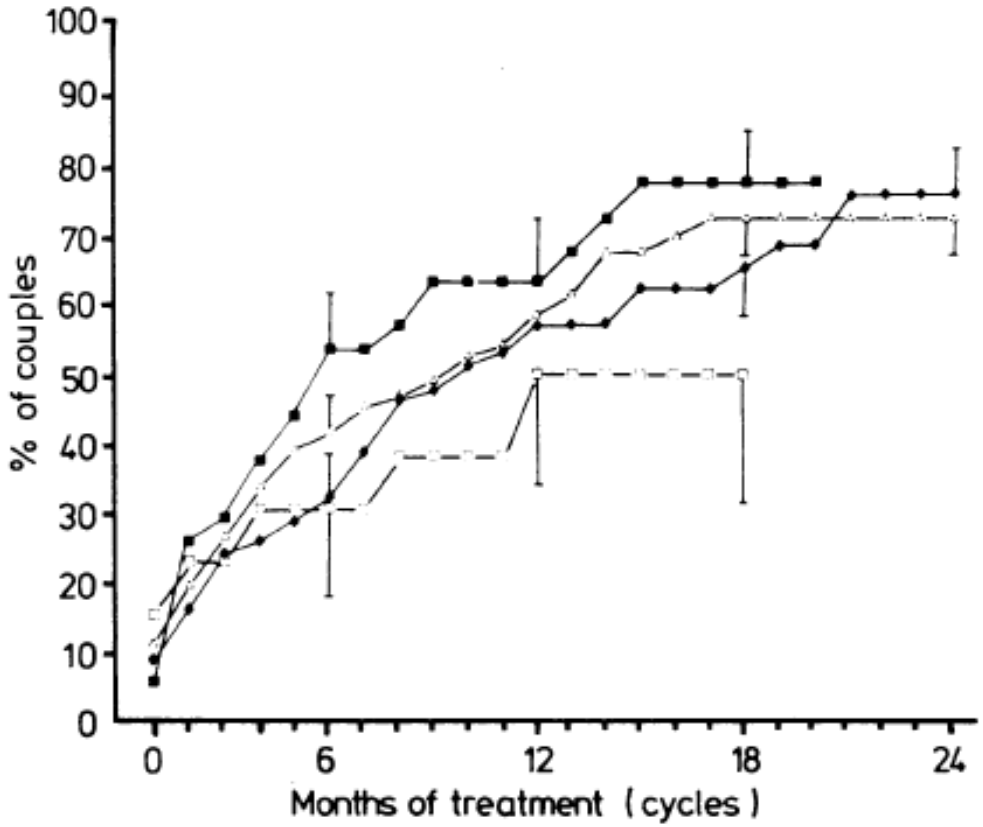


FIG 2—Cumulative rates of conception from first attendance at clinic in couples with unexplained infertility related to age of woman. Rates for each age group shown as: ■——■ <25 years; △——△ 25-29 years; ◆——◆ 30-34 years; □——□ ≥ 35 years. Standard error of proportions are given at six, 12, 18, and 24 months.

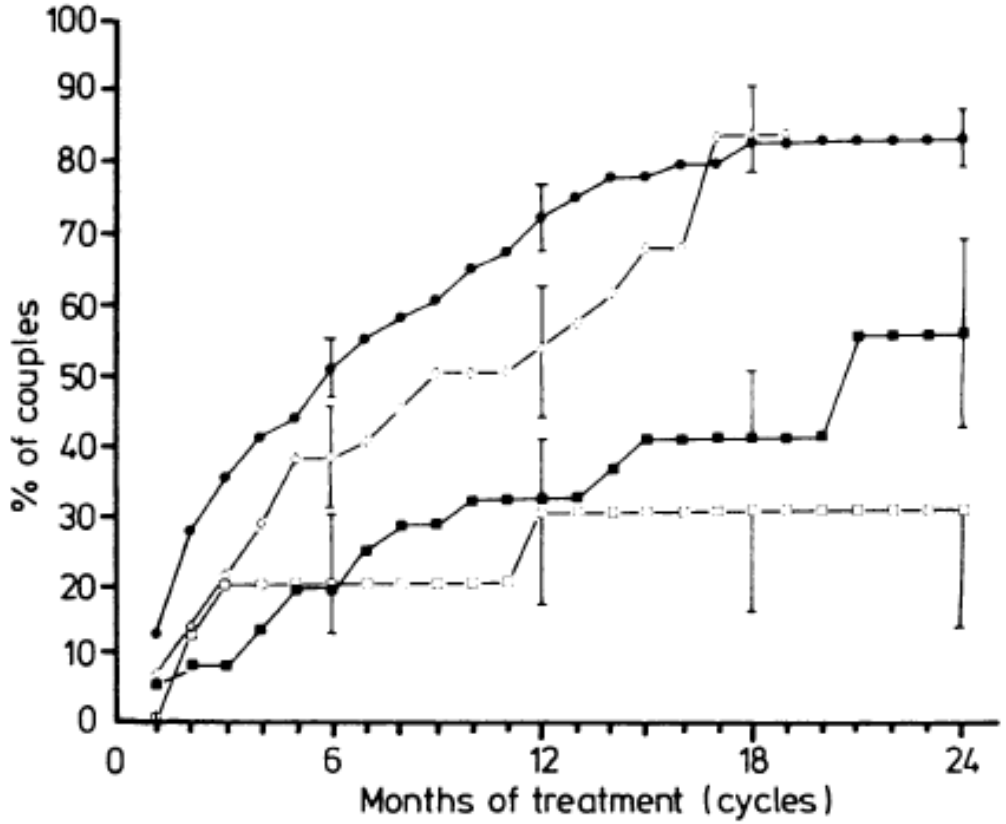
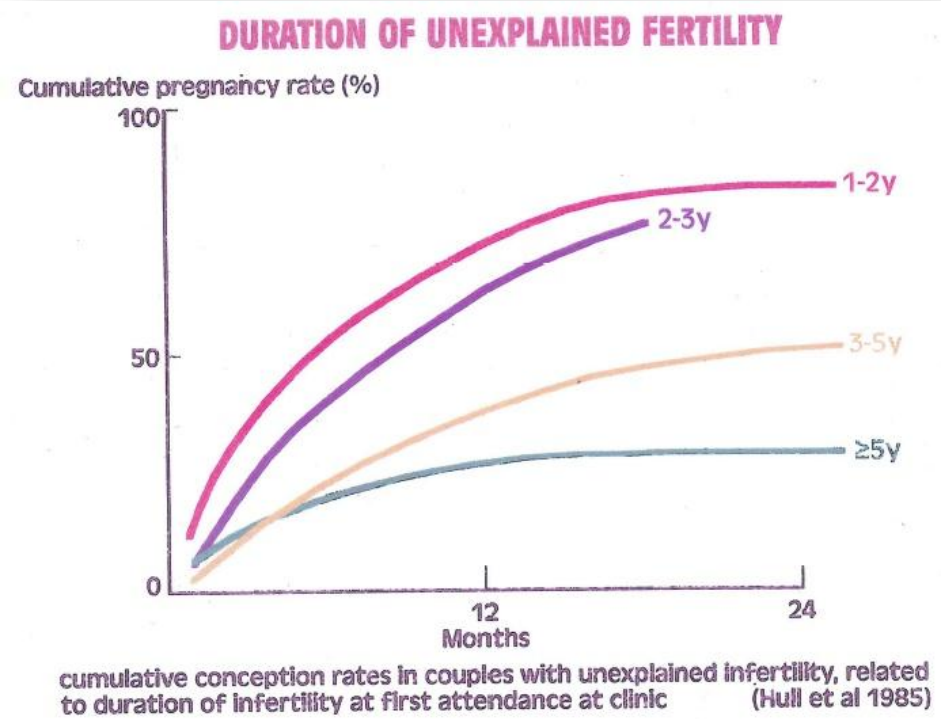


FIG 3—Cumulative rates of conception in couples with unexplained infertility related to duration of infertility at first attendance at clinic. Rates shown as: ●——● 1-2 years; ◇——◇ 2-3 years; ■——■ 3-5 years; □——□ ⩾5 years. Standard error of proportions are given at six, 12, 18, and 24 months.

- Unexplained subfertility
- Spontaneous chance of conception



cumulative conception rates in couples with unexplained infertility, related to duration of infertility at first attendance at clinic (Hull et al 1985)

- C.F. clomiphene, IUI

What then?

- Time alone
- Management of pelvic abnormalities
  - Tubal disease
  - Endometriosis
  - Fibroids
  - Uterine abnormalities

- Ovulation disorders
  - Clomiphene
  - Gonadotrophin ovulation induction
  - IVF

- Male factor
  - Now 50% of all couples for IVF
  - IUI sometimes an option
  - ICSI has revolutionised IVF for males
  - DI for couples now unusual
  - Vasectomy | reversal

AMH

- Anti Mullerian Hormone
- Produced in the gonads alone
- In female rises from zero at birth to modest levels at puberty and see slow and steady decline thereafter
- Can be measured at any time of cycle and while on oral contraceptives

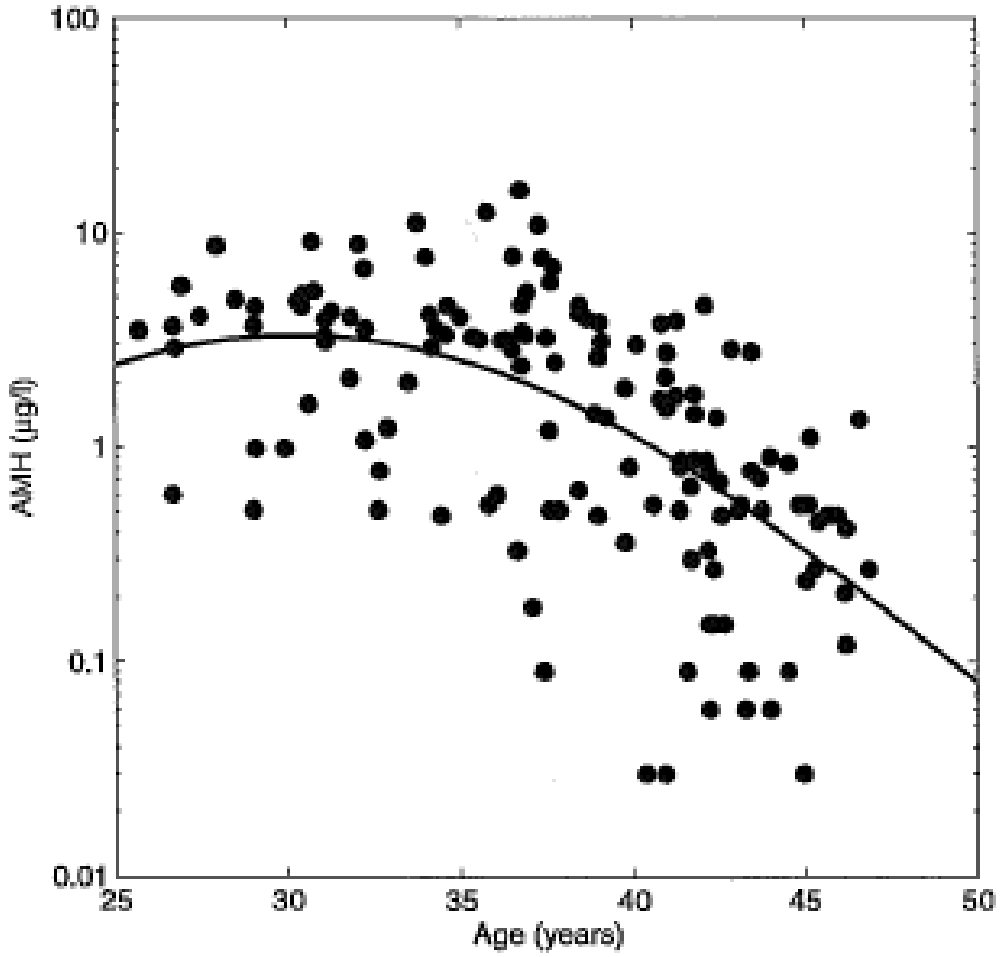
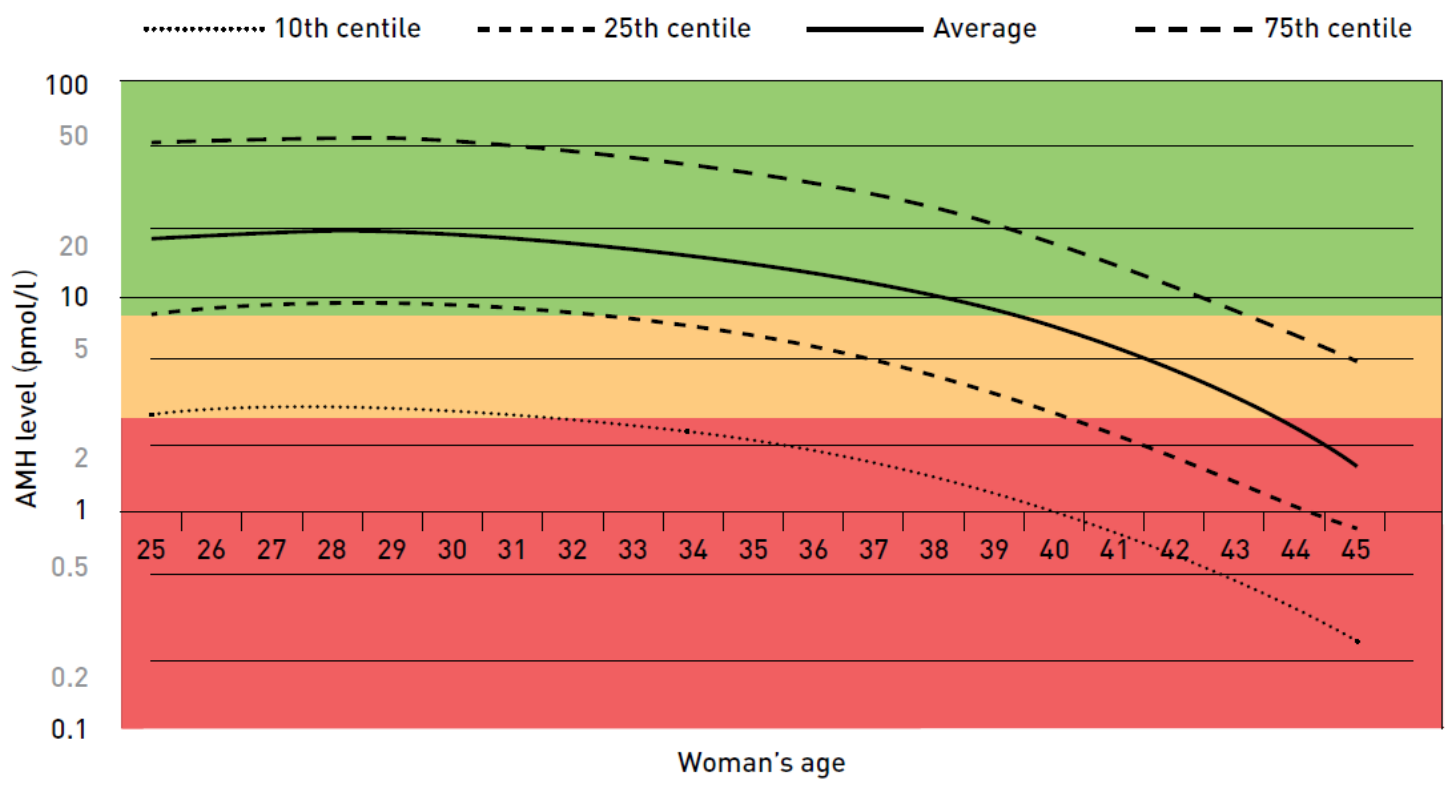


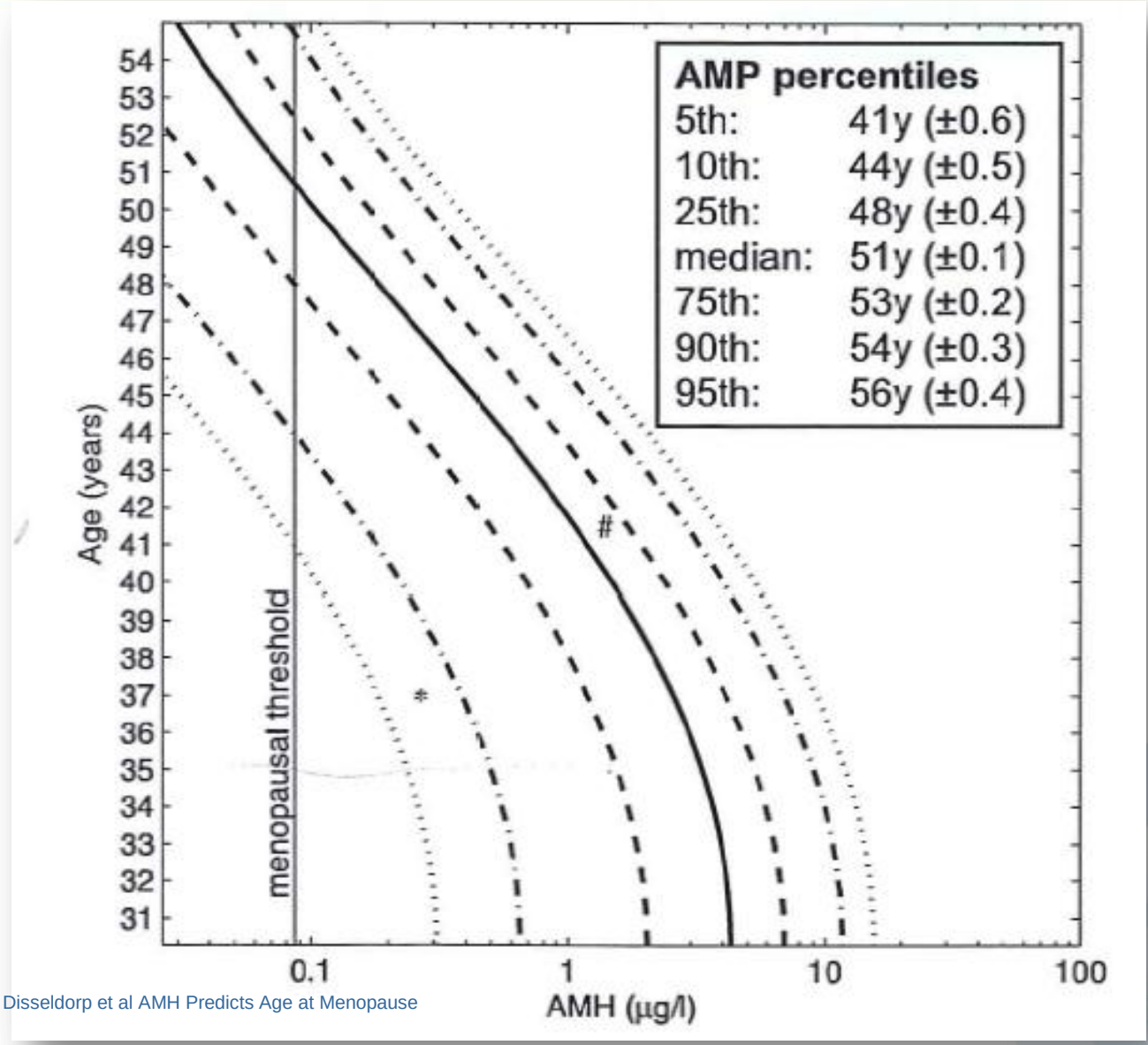
FIG. 1. Age-dependent AMH levels (●) plotted on a logarithmic scale to show more homogeneous variation (n = 144). The *solid line* indicates the smoothed estimate of mean AMH level as a function of age.

AMH

- Useful to assist in estimating likely age at menopause and consequently ovarian reserve
- Changes before FSH starts to rise
- Helpful in managing patients likely to hypo or hyperstimulate in response to gonadotrophin
- Current evidence doesn't support its use in determining clinical outcomes in treatment



Green zone	Above the 25th centile for younger, fertile women	Very likely normal ovarian reserve – age is the best predictor of your future fertility	80% chance of 6 or more eggs in IVF
Orange zone	Between the 25th and 10th centiles for younger, fertile women	Some women in this range will have reduced ovarian reserve	50% chance of 6 or more eggs in IVF
Red zone	Below the 10th centile for younger, fertile women	Very likely reduced ovarian reserve	20% chance of 6 or more eggs in IVF

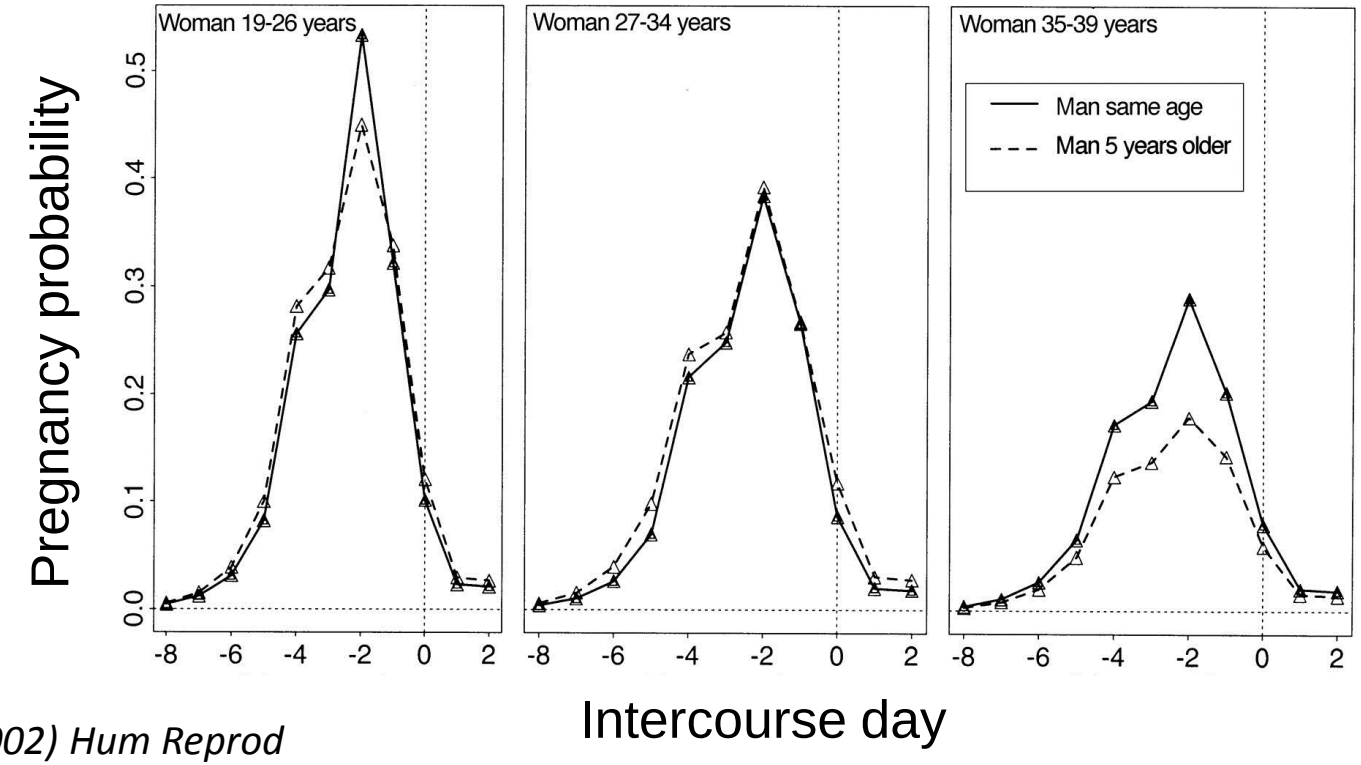


Source: van Disseldorp et al AMH Predicts Age at Menopause

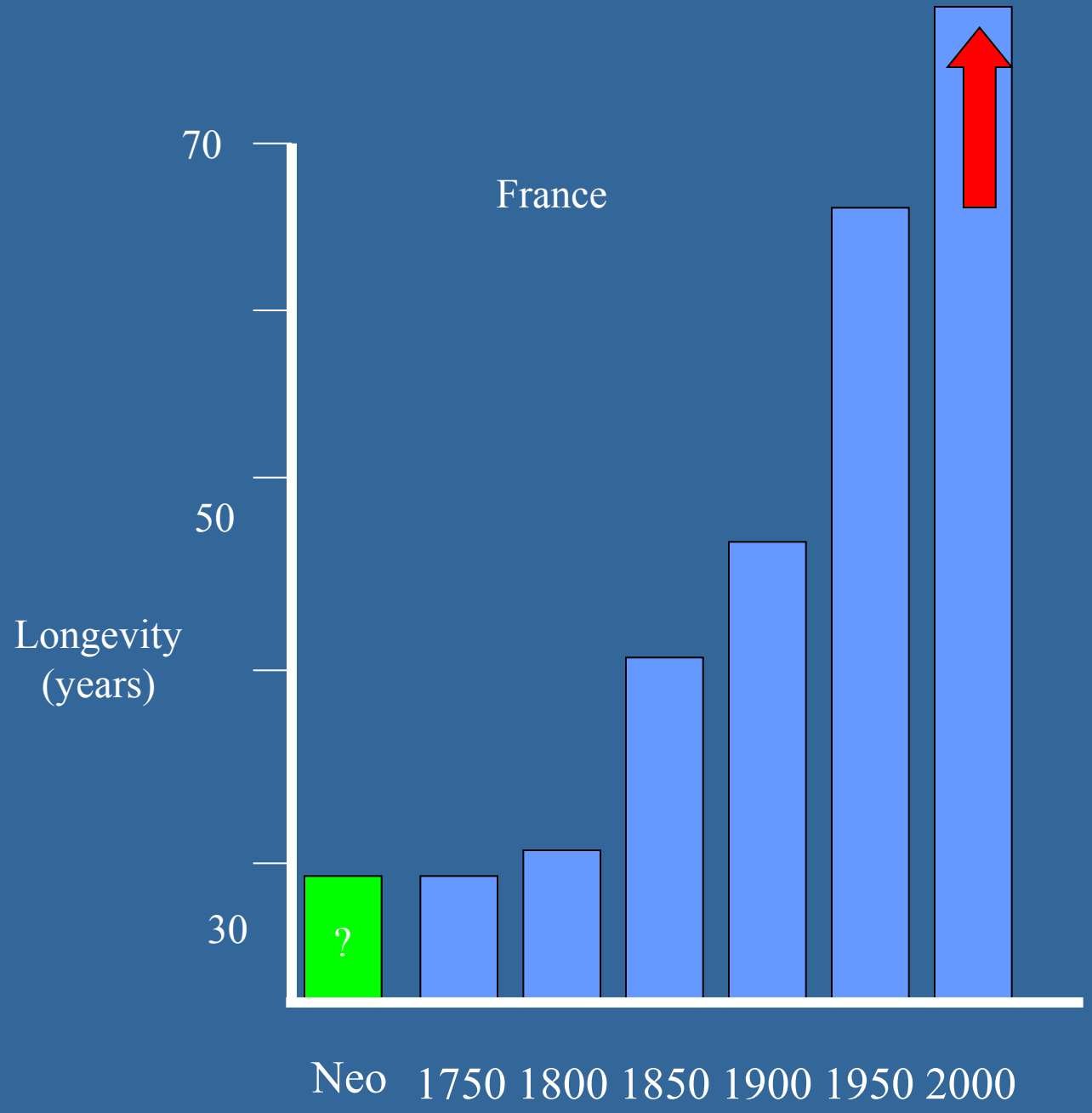
Fertility declines with age

Reproductive ageing

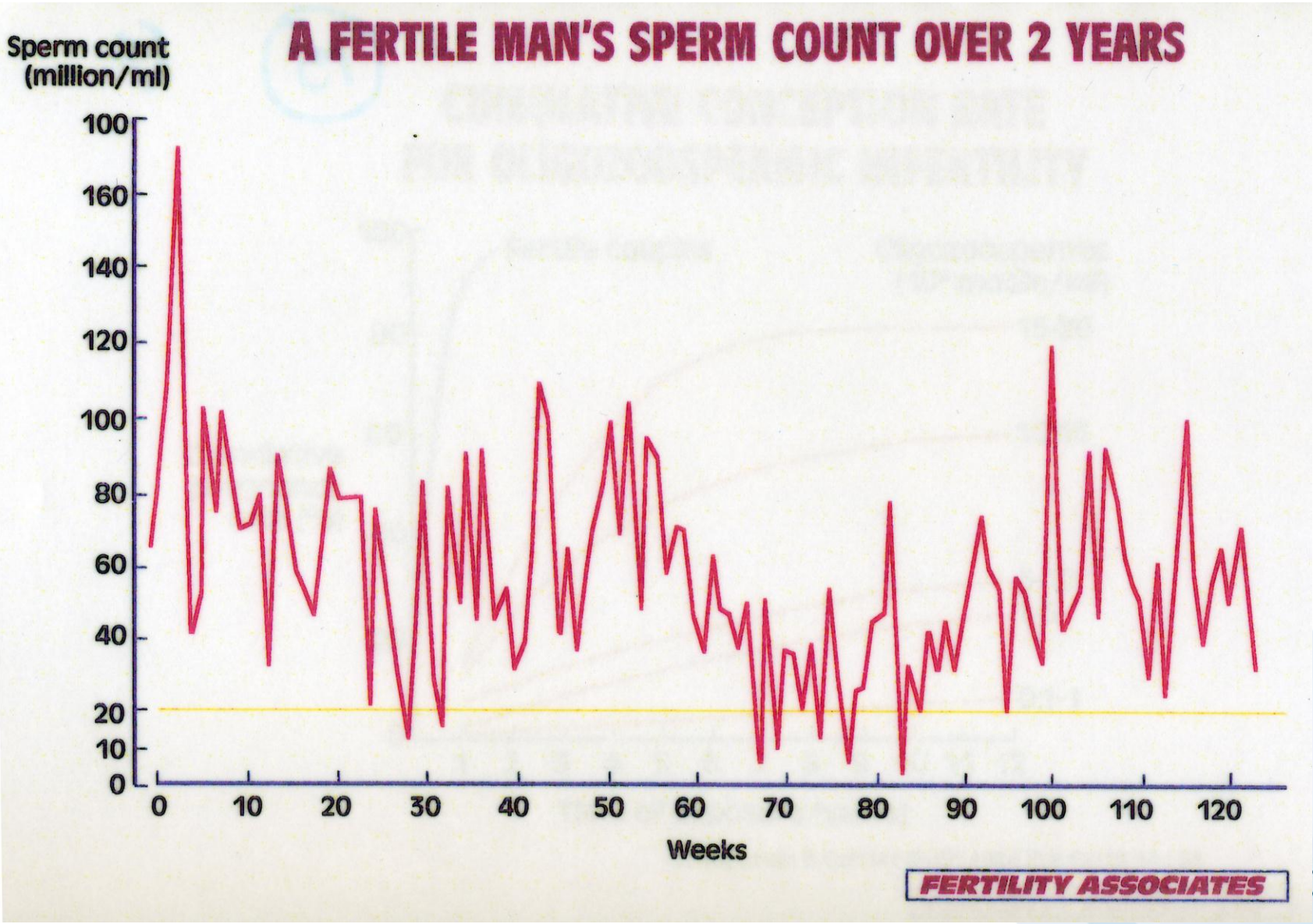
Woman's age (years): 19–26 27–34 35–39



Dunson et al. (2002) Hum Reprod


70
50
30
Longevity
(years)
France
?
Neo
1750
1800
1850
1900
1950
2000

But what about men?


A FERTILE MAN'S SPERM COUNT OVER 2 YEARS
Sperm count (million/ml)
100
160
140
120
100
80
60
40
20
10
0
0
10
20
30
40
50
60
70
80
90
100
110
120
Weeks
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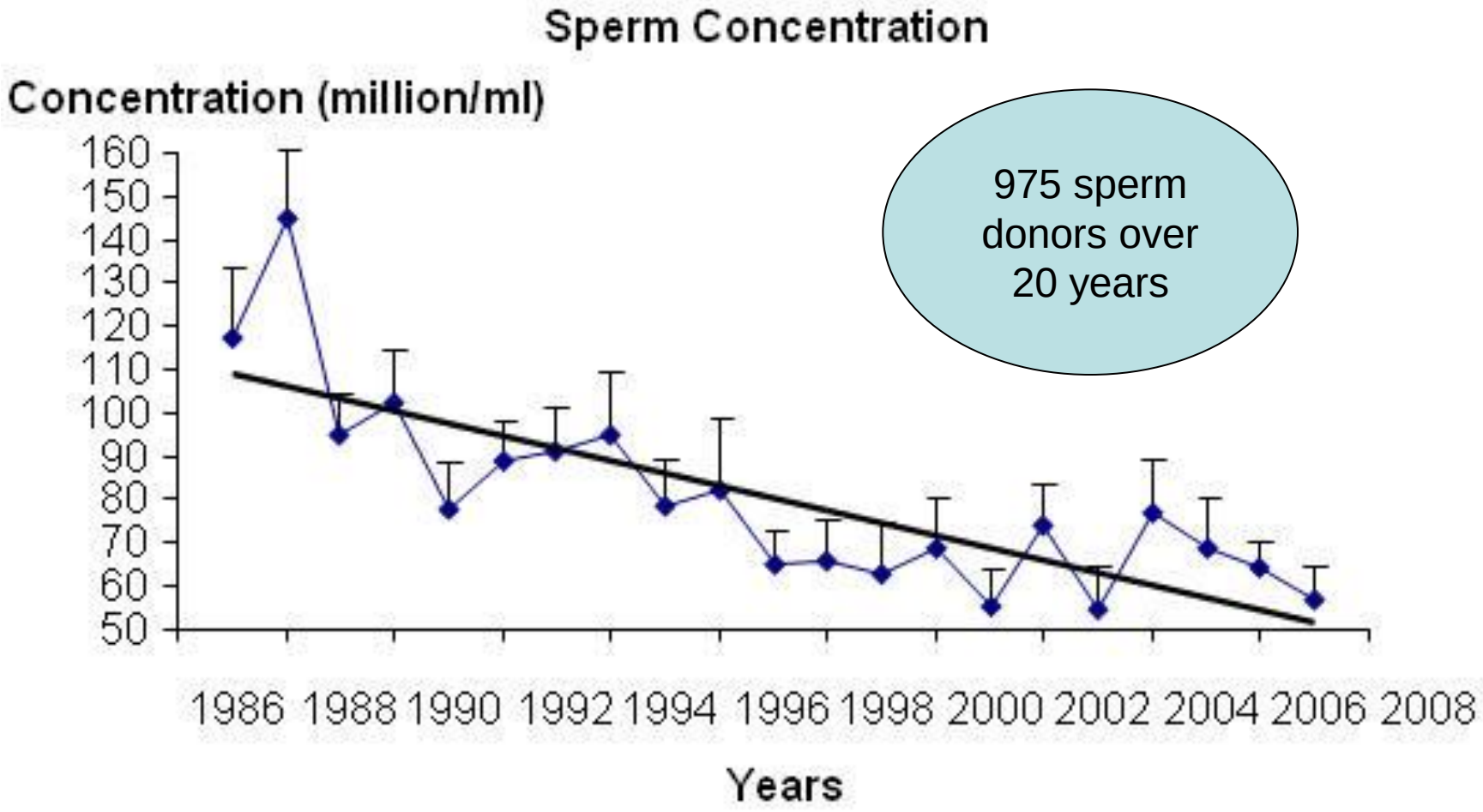
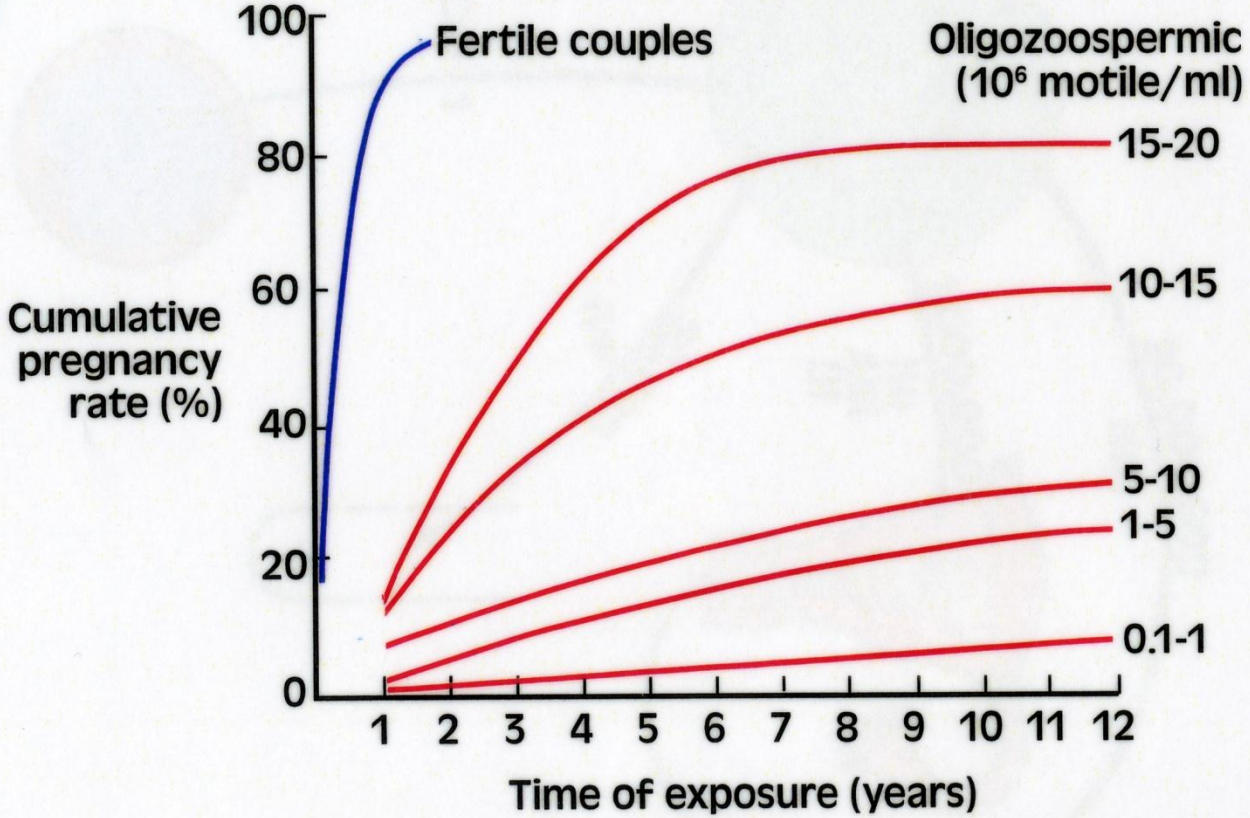


Rebecca Shine, Mary Birdsall, John Peek

Diagnosis

- Tertiary lab semen analysis
- Motility
- Morphology
- Sperm antibodies
- Sperm D.N.A damage

CUMULATIVE CONCEPTION RATE FOR OLIGOZOOSPERMIC INFERTILITY



Schoysman & Gerris (1983) Aeta Eur Fertil 14 : 51

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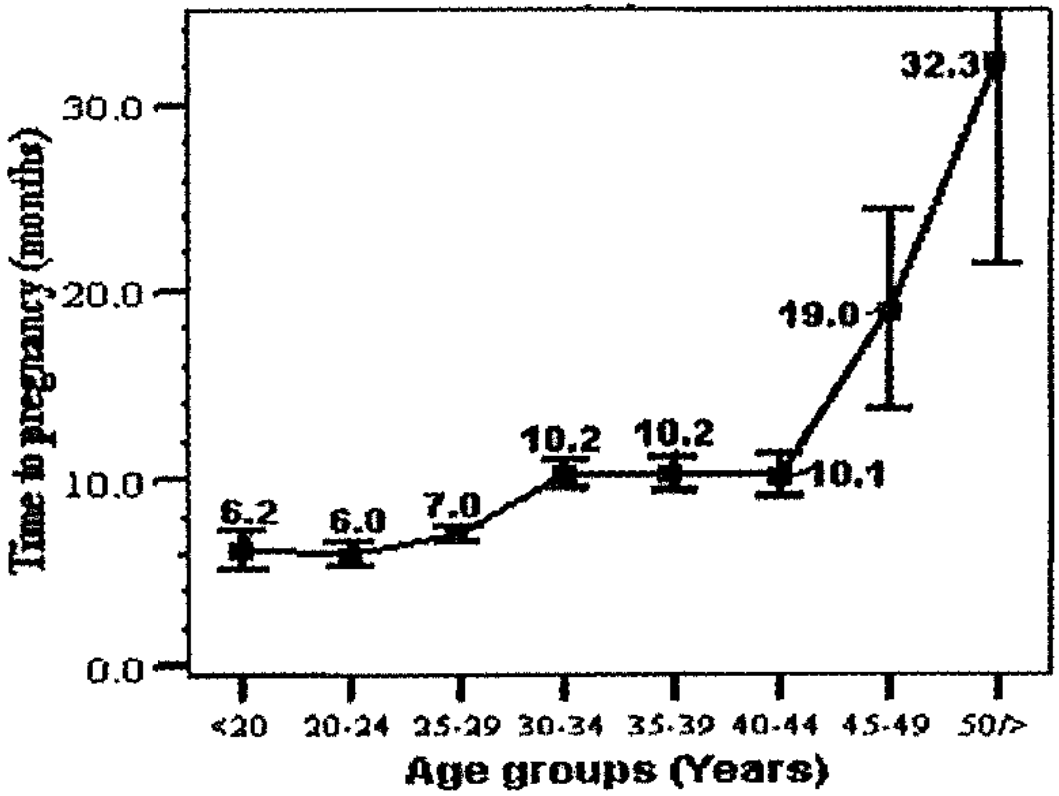
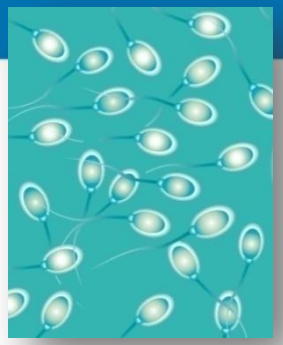
Paternal age effects on time to pregnancy



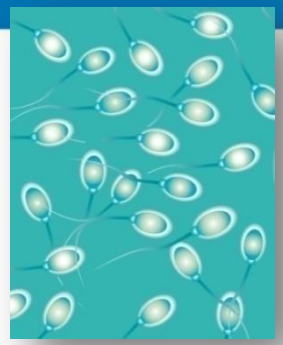
Sartorius & Nieschlag, 2010

Some Facts about Ageing, Men and Sperm



Conception rate adjusted for female age

Years	Rate
< 25	1.00
30-34	0.62
35-39	0.50
> 40	0.51



Some Facts about Ageing, Men and Sperm

Effect of Weight on Infertility (Nguyen 2007)

Independent of sexual frequency, age, smoking

Normal weight	:	1.0
Overweight	:	1.2
Obese	:	1.36

Effect of Temperature on Infertility (U.S.C. study)

- Infertile men spend >30 mins / week in a hot tub
- Total motile sperm increased 490% at 3-6 months after stopping

Some Facts about Ageing, Men and Sperm

- As men age the testes get smaller and softer, sperm morphology and motility tend to decline
- DNA fragmentation increases
- IVF pregnancy rate decreases as DNA fragmentation increases
- Paternal age >50 leads to doubling the chance of fetal death
- Paternal age >40 leads to increased rate of miscarriage independent of maternal age

Some Facts about Ageing, Men and Sperm

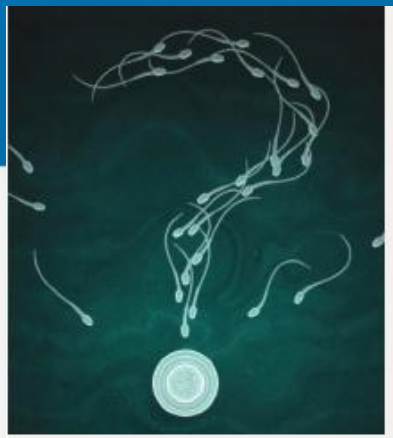
Paternal age is a robust risk factor for the incidence of:

- Schizophrenia in offspring
  - At 45+ odds ratio 3.0 = 1:46 chance (Malaspina 2001)
  - Specific for schizophrenia
- Increase in autism
  - Compared with 30 years
  - >40 3 x the risk
  - >50 5 x the risk
- Increase in achondroplasia

Changes in sperm

- DNA fragmentation
  - Age
  - ROS – heat
  - Chemo and radiation
  - Environmental toxins
  - Higher in ejaculate than testicular sperm
- Tests
  - TUNEL
  - SCSA
  - HALO

Changes in sperm



Measuring sperm DNA damage using the SCSA test

The SCSA test tends to be more accurate than other sperm tests as it measures thousands of sperm at once.

Traditionally the diagnosis of a male contribution to infertility has been based on the number ('sperm concentration'), movement ('motility') and shape ('morphology') of sperm as seen down a microscope.

There is increasing evidence sperm DNA damage may also contribute to male infertility. Most sperm DNA damage is caused in one way or another by 'Reactive Oxygen Species' (ROS). It may be associated with increased age, defective DNA packaging inside the sperm head, increased scrotal temperature, having a varicocele, genital tract infection, smoking, a diet with low levels of antioxidants, or exposure to environmental contaminants and toxins.

The body's main defence against ROS damage is to maintain an optimal antioxidant environment for sperm maturation and storage before ejaculation. This is one of the reasons why Fertility Associates promotes a healthy lifestyle, healthy eating and considering the use of antioxidant supplements.

Sperm DNA damage can be measured by a variety of tests. We now offer the SCSA (Sperm Chromatin Structure Assay) test, which uses computer flow cytometry to measure DNA damage in individual sperm. Because it measures thousands of sperm at once, it tends to be more accurate than other tests.

Your doctor will discuss whether a SCSA test for sperm DNA damage may be useful for you, taking into consideration your medical and fertility history, lifestyle and the outcome of other investigations and treatments.

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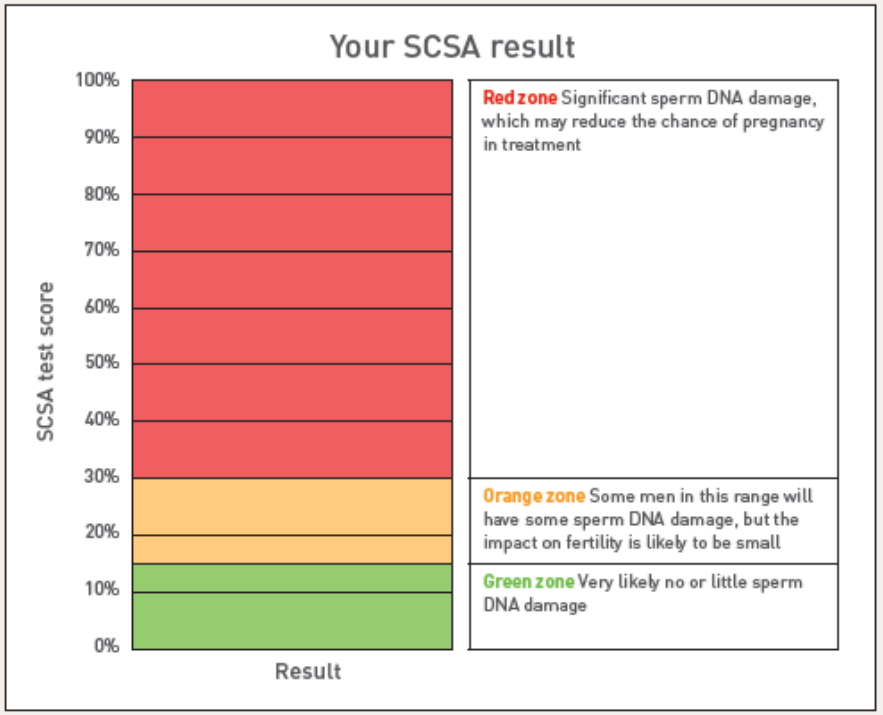
The SCSA test involves booking a semen sample at a Fertility Associates clinic – our semen analysis form covers booking the test, the preferred period of abstinence and other instructions. The tests are done once a week in Wellington, so results are available within two weeks of providing the sample. Your doctor will tell you the result in person, by telephone or by sending you a letter.

Like most fertility tests, a sperm DNA fragmentation test does not give a black and white answer. The higher the test result, the more sperm DNA damage, and the more likely that the damage may affect your chance of pregnancy. We divide the results into green, orange and red zones in the graph to indicate the likely impact of your SCSA test result.



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Contact us: www.fertilityassociates.co.nz • Phone 0800 10 28 28

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- **North Shore** Level 1, Suite 107, 119 Apollo Drive, Albany P 09 475 0310 E fas@fertilityassociates.co.nz
- **Hamilton** Level 2, 62 Tristram Street, Hamilton P 07 839 2603 E fah@fertilityassociates.co.nz
- **Wellington** Level 2, 205 Victoria Street, Te Aro P 04 384 8401 E faw@fertilityassociates.co.nz
- **Christchurch** Level 1, Hiatt Chambers, 249 Papanui Road P 03 375 4000 E fac@fertilityassociates.co.nz

We also hold clinics in Whangarei, East Auckland, West Auckland, Tauranga, Gisborne, New Plymouth, Hawke's Bay, Palmerston North, Lower Hutt, Nelson and Queenstown. Please call us or check our website for further details.

Sperm retrieval for IVF

- Very few men in whom sperm are unobtainable
- PESA, TESA, TESE, biopsy, microsurgical biopsy
- Even in Klinefelter's Syndrome

What then?

- Intrauterine insemination
  - Simple
  - Stimulated
- IVF
- Donor gametes
  - Eggs
  - Sperm

Clomiphene alone

FA study: 15% / month

IUI 5 years 2007-11: live births

	< 38		≥ 38	
Clomiphene stimulation alone	30/265	15%	8/104	7%
	21%	multiple	0	multiple
Clomiphene but high oestrogen	20/190	11%	9/153	6%
	5%	multiple	0	multiple
Clomiphene with FSH	217/1188	18%	54/714	8%
	18%	multiple	13%	multiple

Anovulation

- Cycle length
- Family history
- Social/adolescent history
- Weight
- Signs of androgenisation

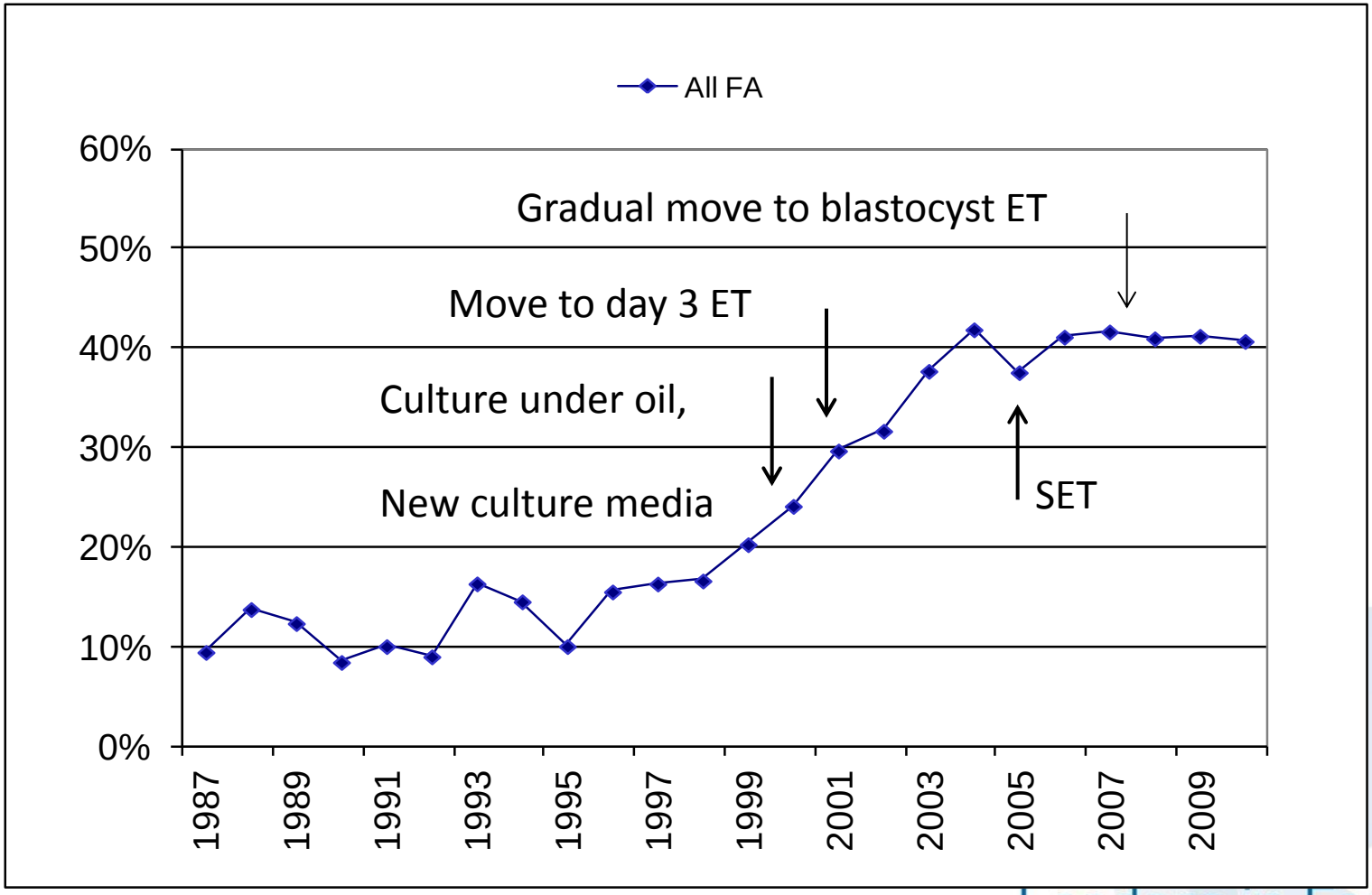
Who should do IVF?

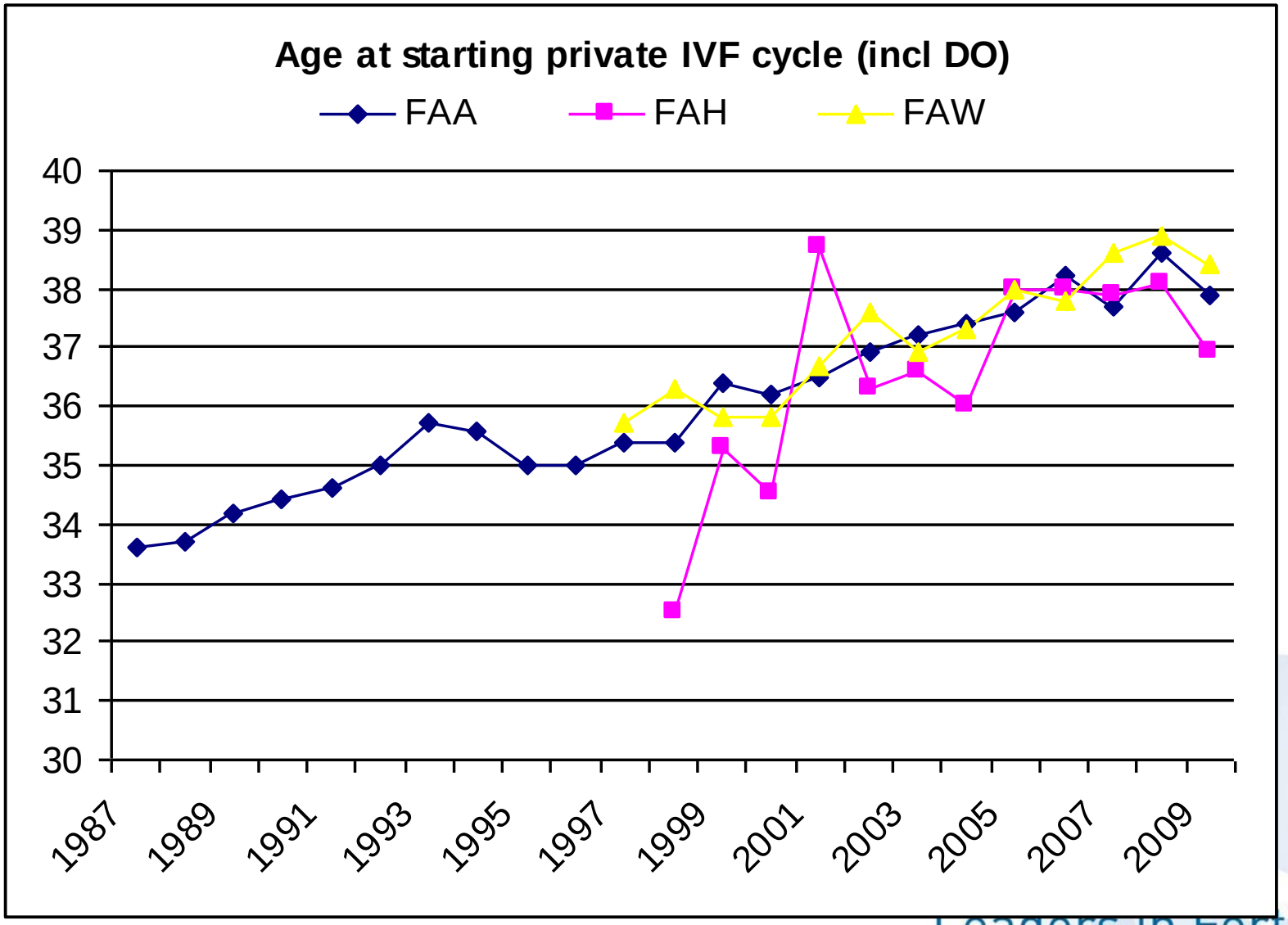
Depends on what the question is

IVF in 2013

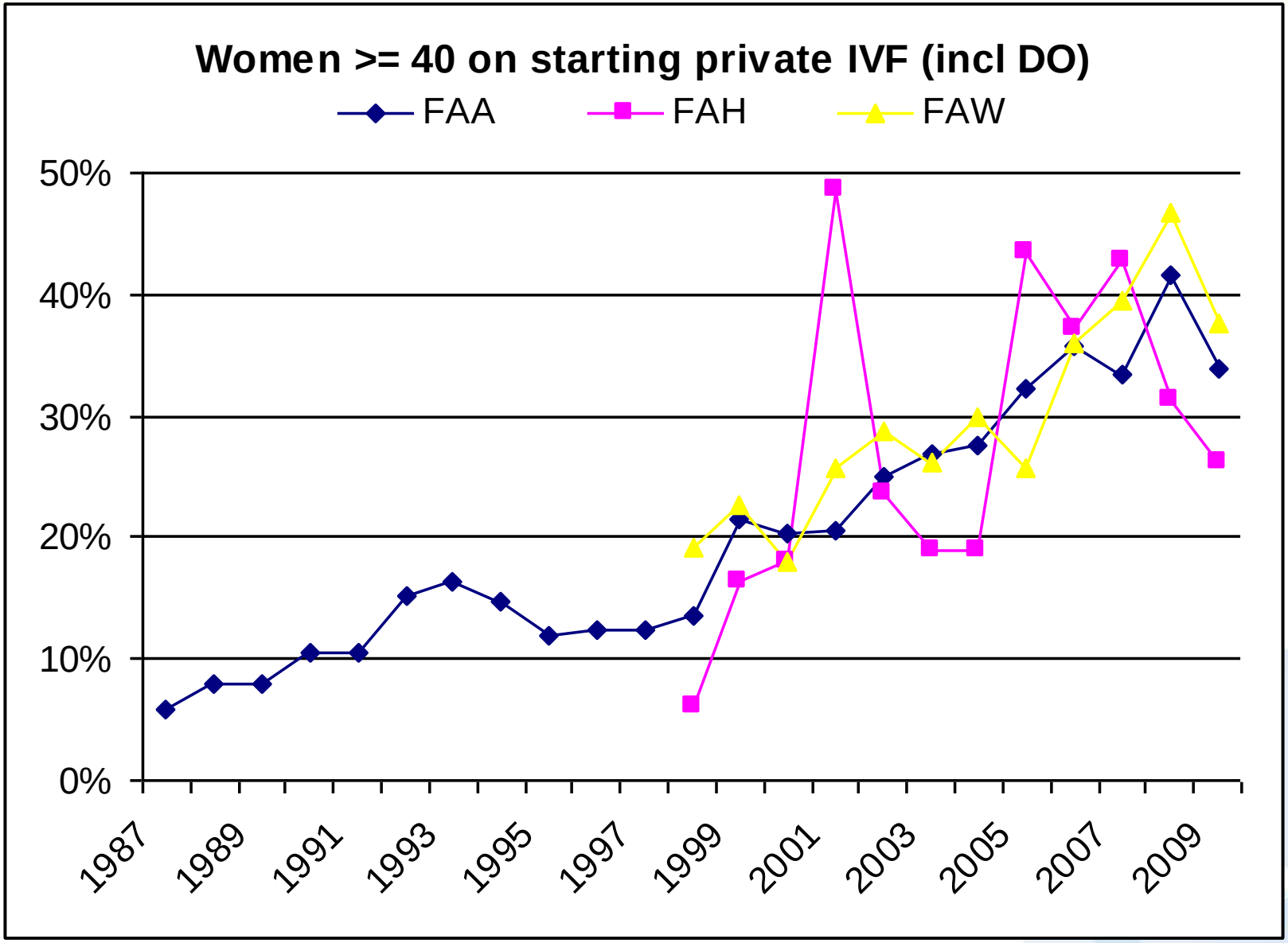
- All causes, both male and female
- Blood tests
- Drugs to block ovulation
- Ultrasound egg retrieval & embryo replacement
- Common to be in 40’s
- Single women and lesbian couples increasingly represented
- Fertility preservation now an option

Fresh implantation rates, women aged =< 37



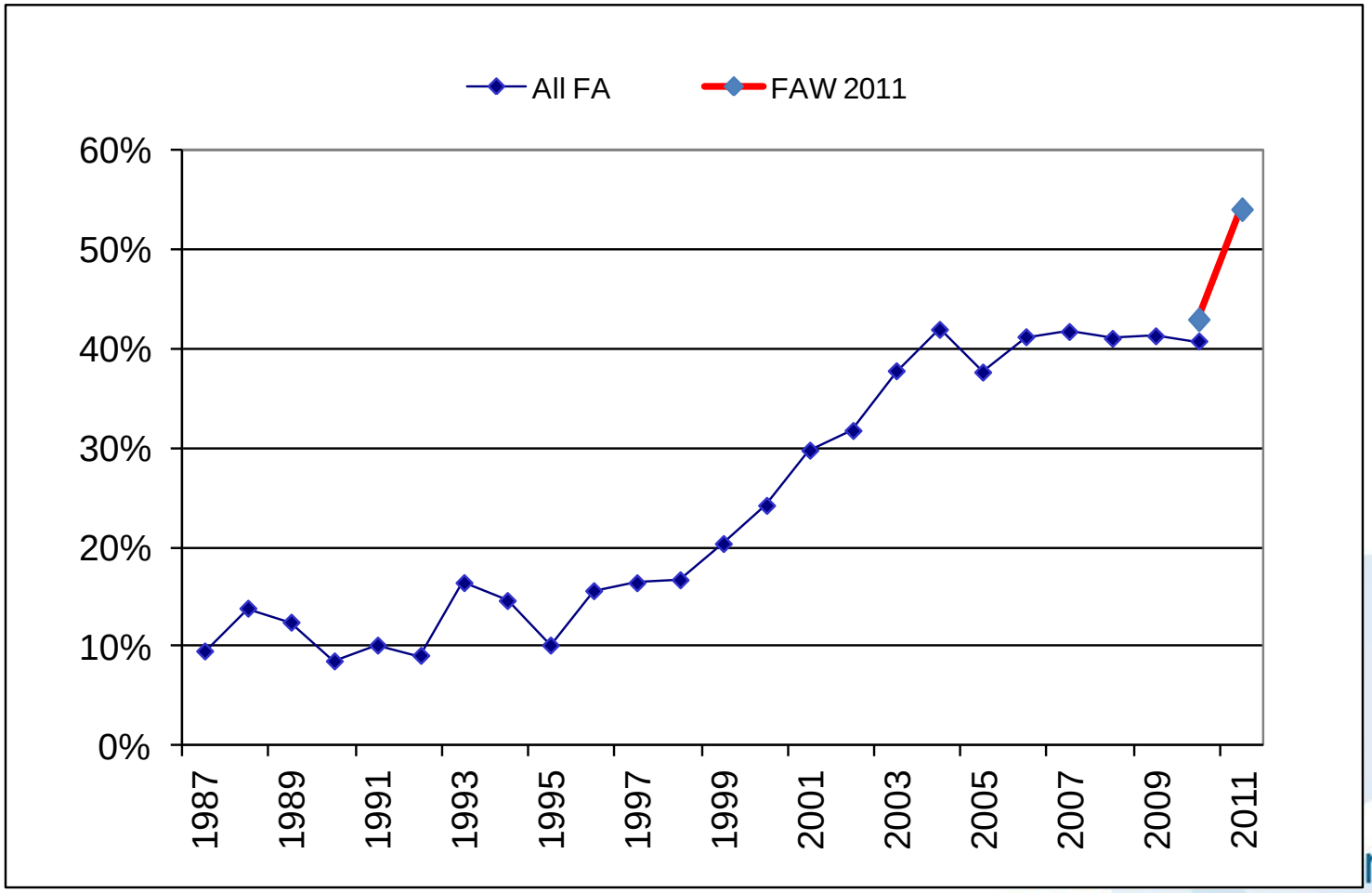


Source: Fertility Associates

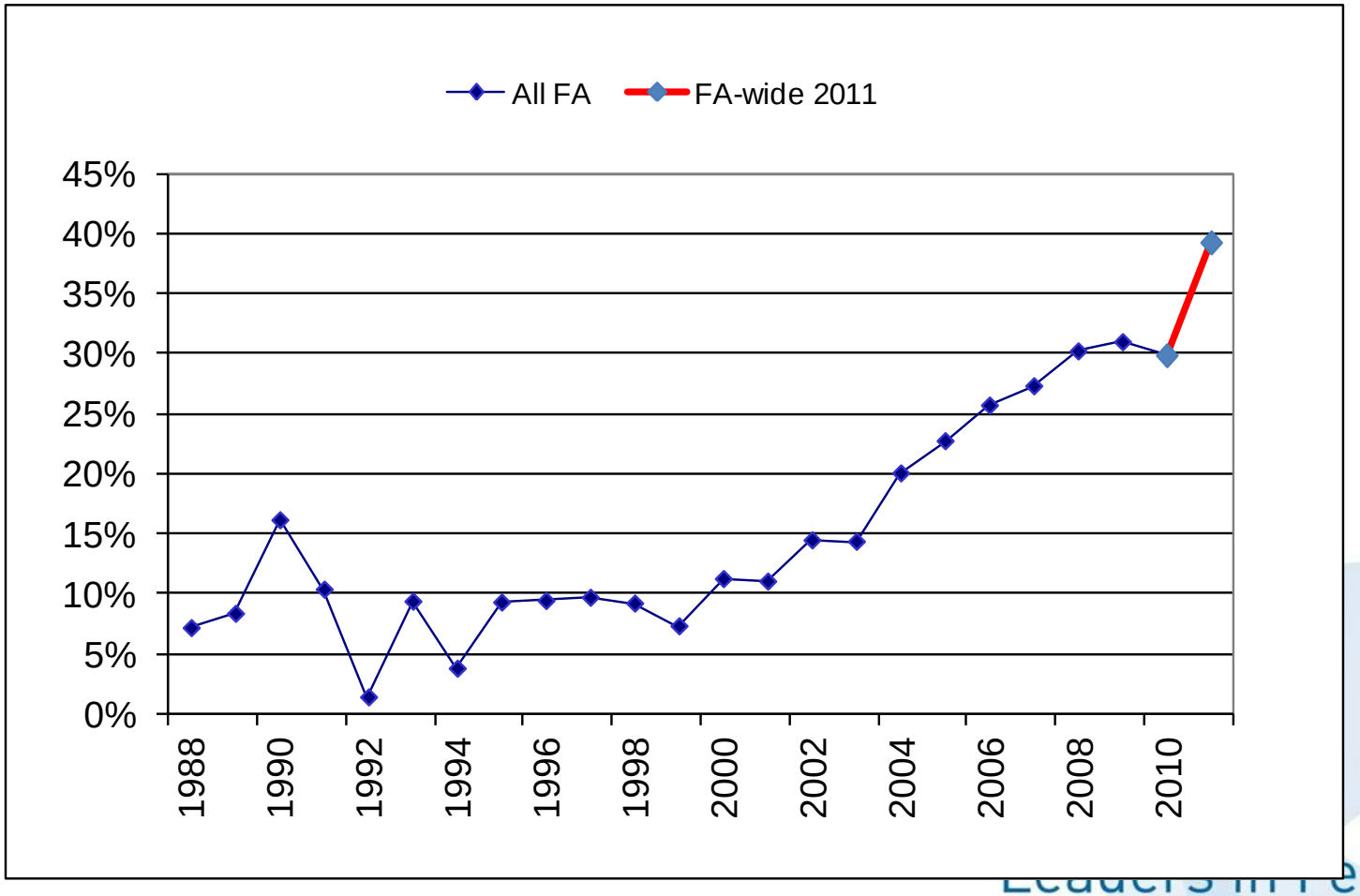


Source: Fertility Associates

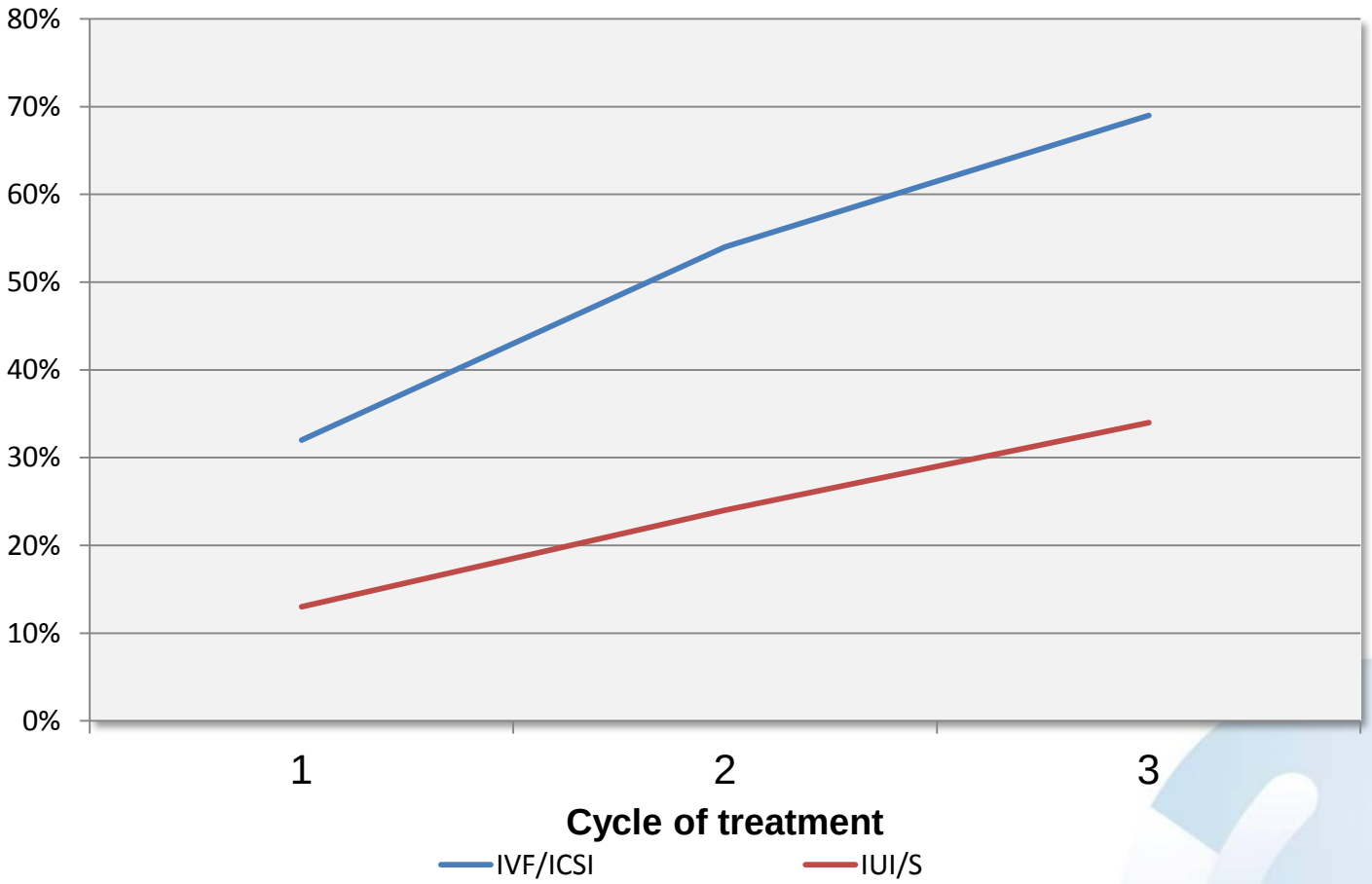
Fresh implantation rates, women aged =< 37 – FAW breaking through the 'glass ceiling'

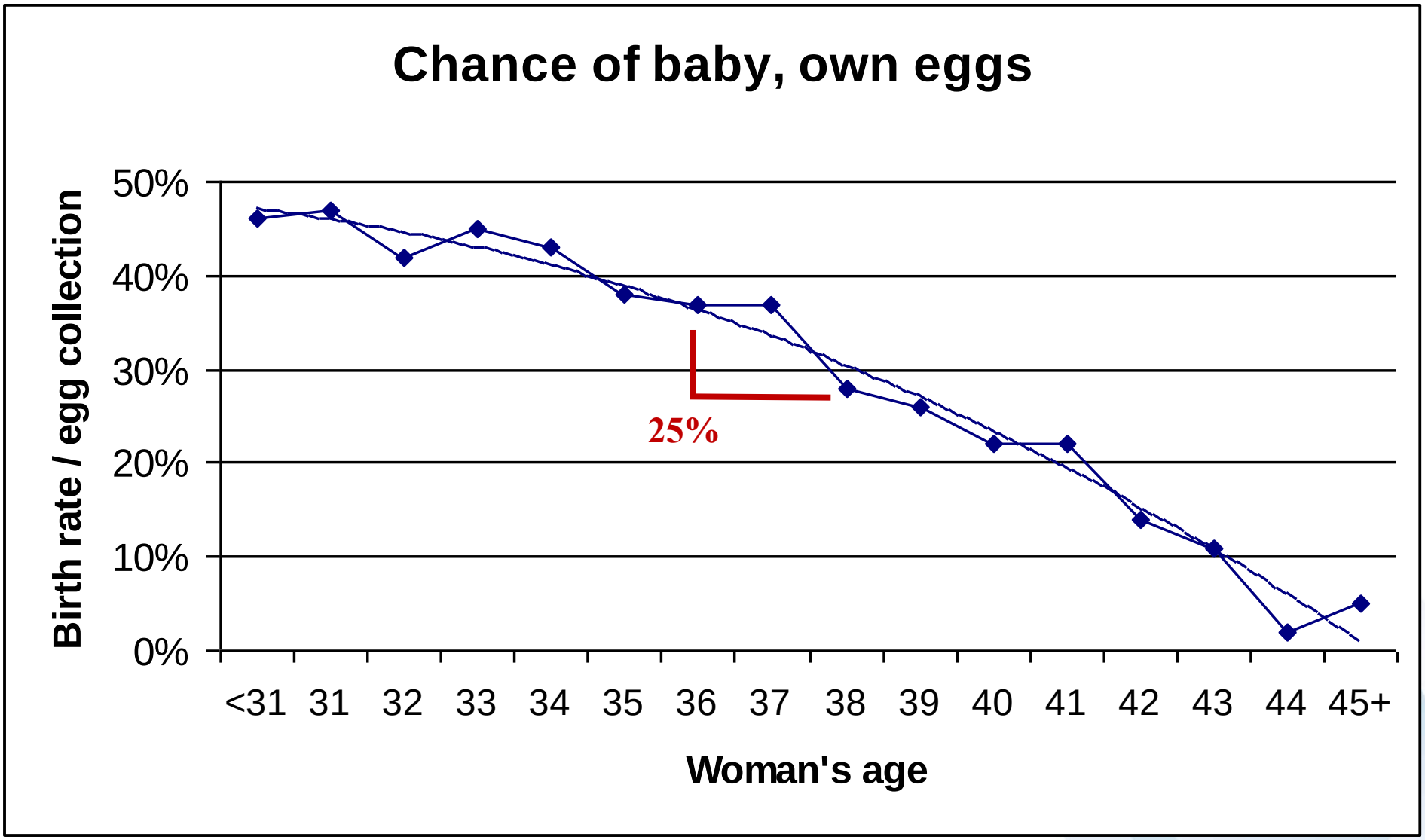


Thaw implantation rates, women aged =< 37
- Impact of having mainly frozen blastocysts in 2011

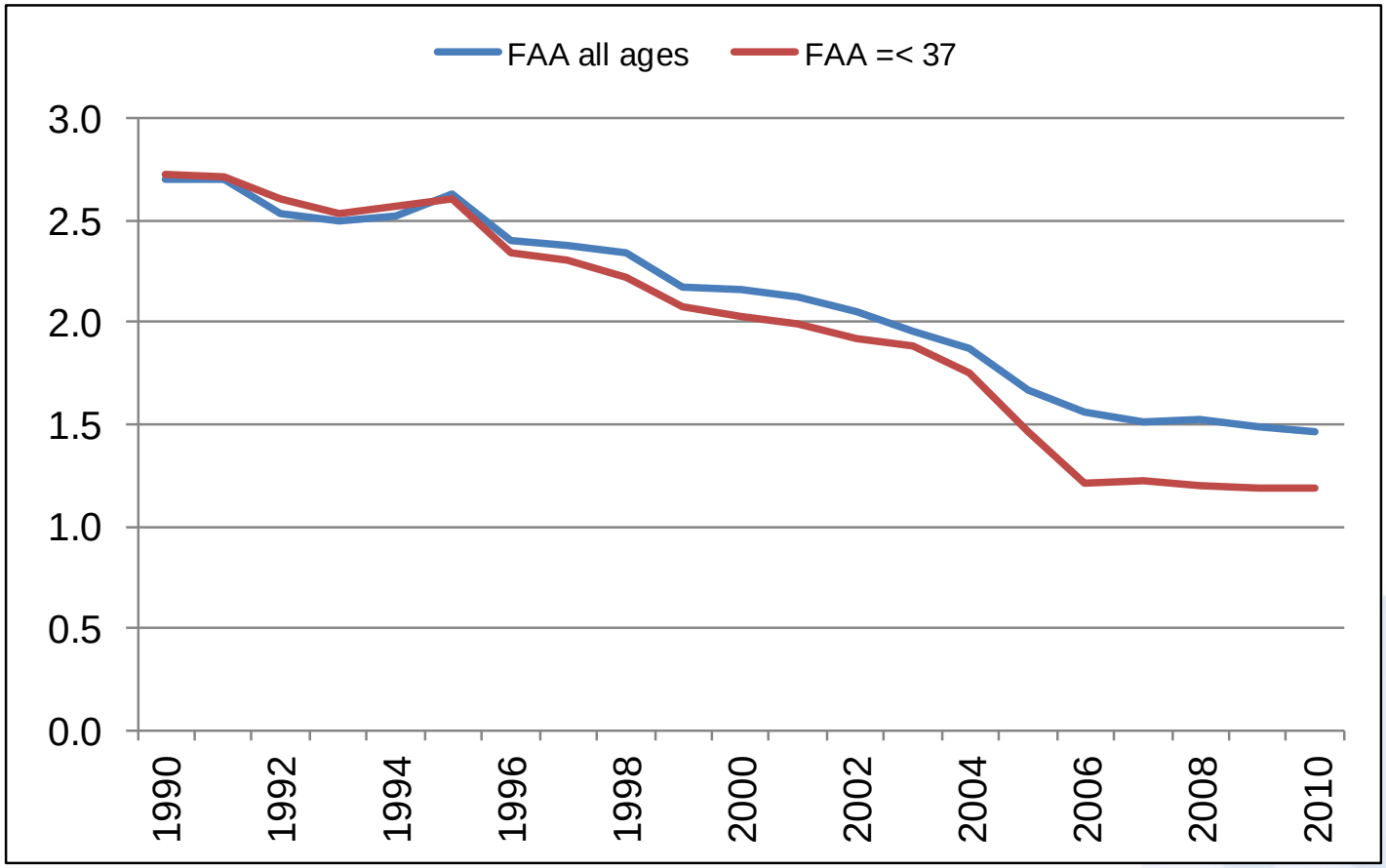


Estimate cumulative birth rate, women 37y

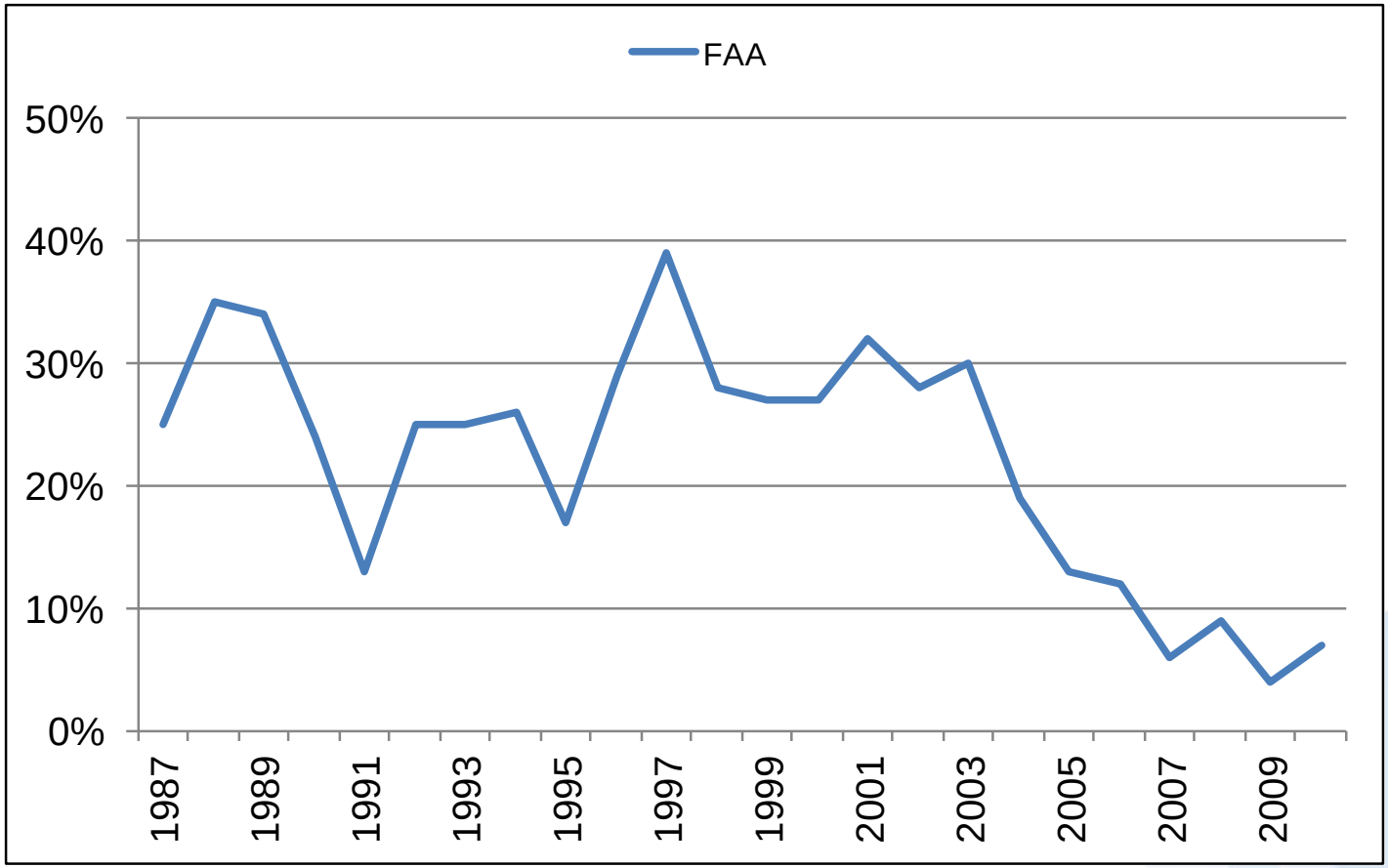



Chance of baby, own eggs
Birth rate / egg collection
50%
40%
30%
20%
10%
0%
25%
<31
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45+
Woman's age

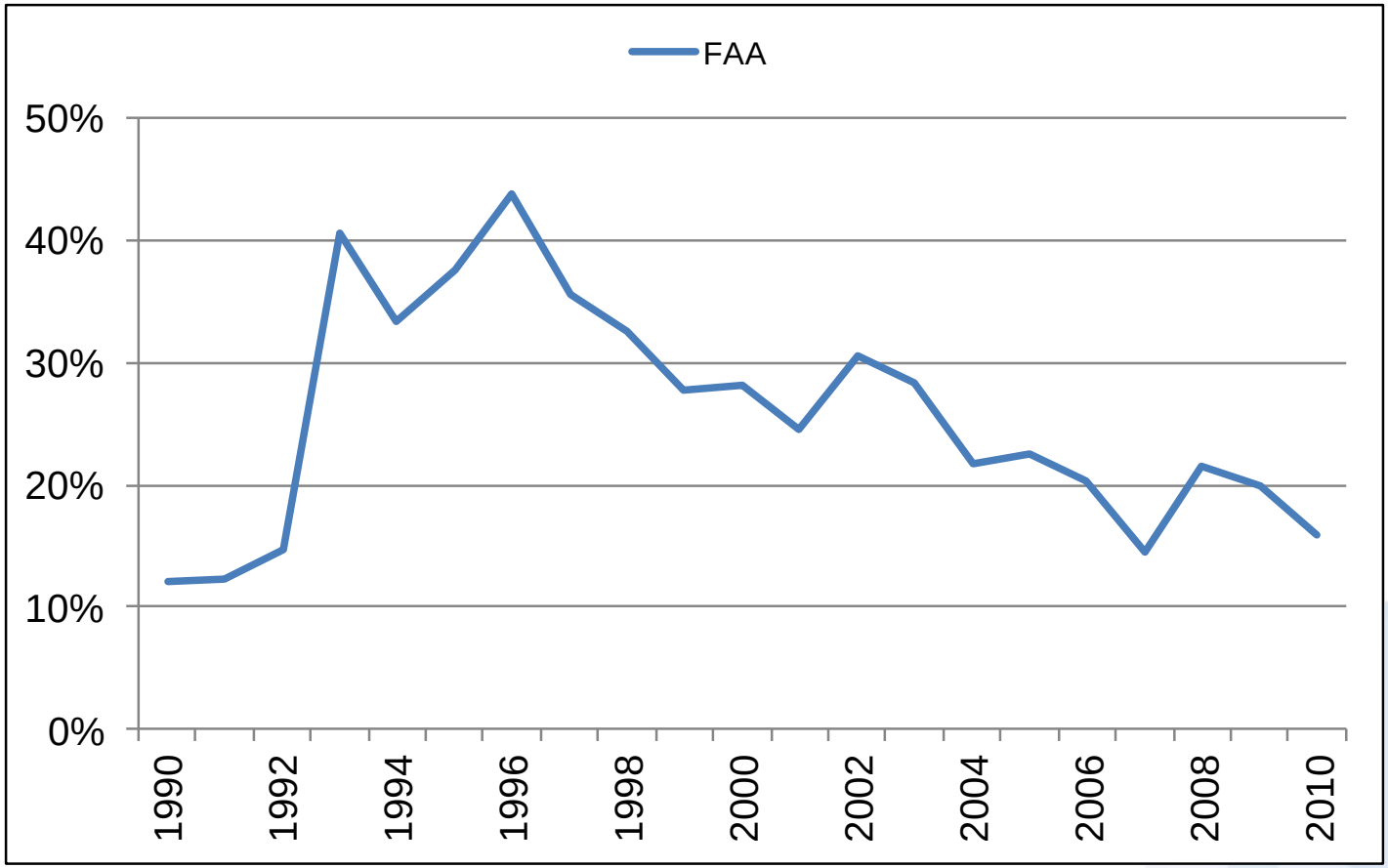
Average number of embryos transferred



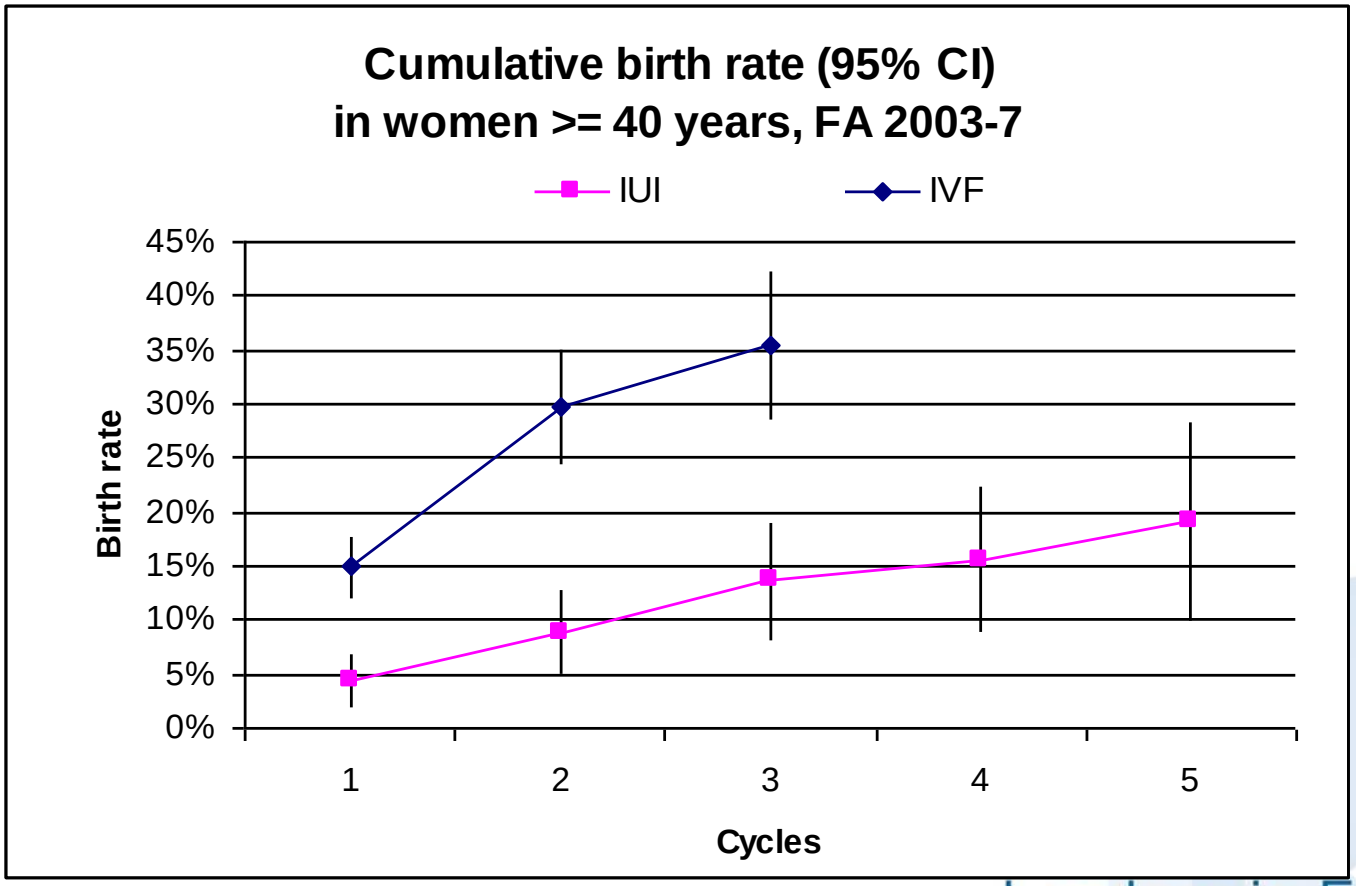
Multiple IVF birth rate fresh IVF



Proportion of all embryos frozen



Age alone ? even an indication



Adjuvant “treatments”

- Aspirin
- Aspirin / Heparin
- Colorado protocol
- Bondi protocol
- Immunotherapy
  - IVIG
  - Intralipid
- Acupuncture
- Lipiodol
- H.S.G
- Endometrial injury
- DHEA
- Viagra

Public access

Consultation 2° level

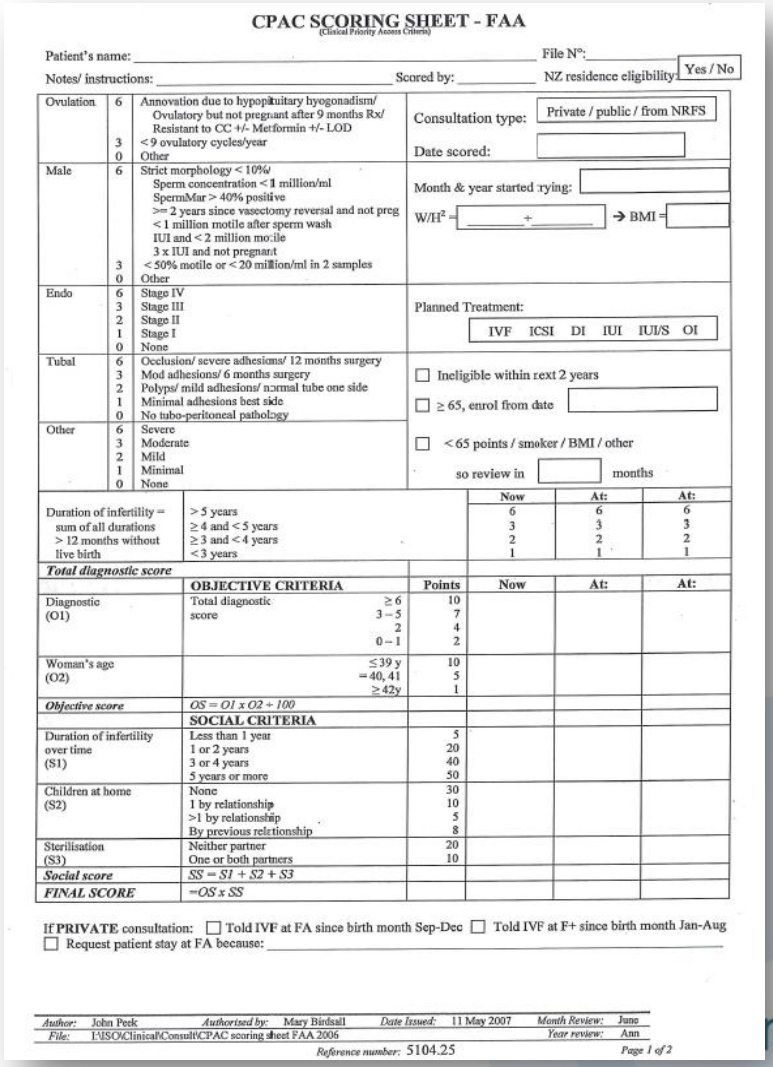
- PRELIMINARY INVESTIGATIONS
  - History and examination of both partners
  - Rubella, VDRL, Hepatitis B antigen, blood group antibodies in the woman
  - Length of menstrual cycles, and Progesterone 5-9 days before menses
  - FSH day 2-4 cycle
  - Prolactin, LH and thyroid function if irregular cycles
  - Semen analysis; repeated in 4-6 weeks if not totally normal
  - Laparoscopy or hysterosalpingogram unless anovulation, or severe male factor
  - Pelvic ultrasound scan if menstrual or ovulation disorder

- REFERRAL GUIDELINES
  - Duration of infertility > 18 months OR any abnormality on examination or investigation
  - BMI < 35
  - Woman $\leq$ 39
  - EARLY REFERRAL, if
    - Woman's age $\geq$ 35
    - Female history of pelvic surgery, STD, PID, severe cyclic pain
    - Male history of genital pathology, urogenital surgery, STD

Public Access

- 3º level
  - IVF / IUI / Ovulation induction /

    DI / DO



CPAC SCORING SHEET - FAA
(Clinical Priority Access Criteria)

Patient's name: _____ File N°: _____

Notes/ instructions: _____ Scored by: _____ NZ residence eligibility: Yes / No

Ovulation	6	Annovation due to hypopituitary hyogonadism/ Ovulatory but not pregnant after 9 months Rx/ Resistant to CC +/- Metformin +/- LOD	Consultation type: Private / public / from NRFS
	3	< 9 ovulatory cycles/year	Date scored:
	0	Other	
Male	6	Strict morphology < 10%/ Sperm concentration < 1 million/ml SpermMar > 40% positive >= 2 years since vasectomy reversal and not preg < 1 million motile after sperm wash IUI and < 2 million motile 3 x IUI and not pregnant	Month & year started trying: W/H² = ___ ÷ ___ → BMI =
	3	< 50% motile or < 20 million/ml in 2 samples	
	0	Other	
Endo	6	Stage IV	Planned Treatment: IVF ICSI DI IUI IUI/S OI
	3	Stage III	
	2	Stage II	
	1	Stage I	
	0	None	
Tubal	6	Occlusion/ severe adhesions/ 12 months surgery	☐ Ineligible within next 2 years
	3	Mod adhesions/ 6 months surgery	☐ ≥ 65, enrol from date
	2	Polyps/ mild adhesions/ normal tube one side	
	1	Minimal adhesions best side	
	0	No tubo-peritoneal pathology	
Other	6	Severe	☐ < 65 points / smoker / BMI / other
	3	Moderate	so review in ___ months
	2	Mild	
	1	Minimal	
	0	None	

		Now	At:	At:
Duration of infertility = sum of all durations > 12 months without live birth	> 5 years	6	6	6
	≥ 4 and < 5 years	3	3	3
	≥ 3 and < 4 years	2	2	2
	< 3 years	1	1	1
Total diagnostic score				

	OBJECTIVE CRITERIA	**Points**	**Now**	**At:**	**At:**
Diagnostic (O1)	Total diagnostic score ≥ 6	10			
	3 – 5	7			
	2	4			
	0 – 1	2			
Woman's age (O2)	≤ 39 y	10			
	= 40, 41	5			
	≥ 42y	1			
Objective score	*OS = O1 x O2 ÷ 100*				
	SOCIAL CRITERIA				
Duration of infertility over time (S1)	Less than 1 year	5			
	1 or 2 years	20			
	3 or 4 years	40			
	5 years or more	50			
Children at home (S2)	None	30			
	1 by relationship	10			
	>1 by relationship	5			
	By previous relationship	8			
Sterilisation (S3)	Neither partner	20			
	One or both partners	10			
Social score	*SS = S1 + S2 + S3*				
FINAL SCORE	*=OS x SS*				

If **PRIVATE** consultation: ☐ Told IVF at FA since birth month Sep-Dec ☐ Told IVF at F+ since birth month Jan-Aug
☐ Request patient stay at FA because: _____

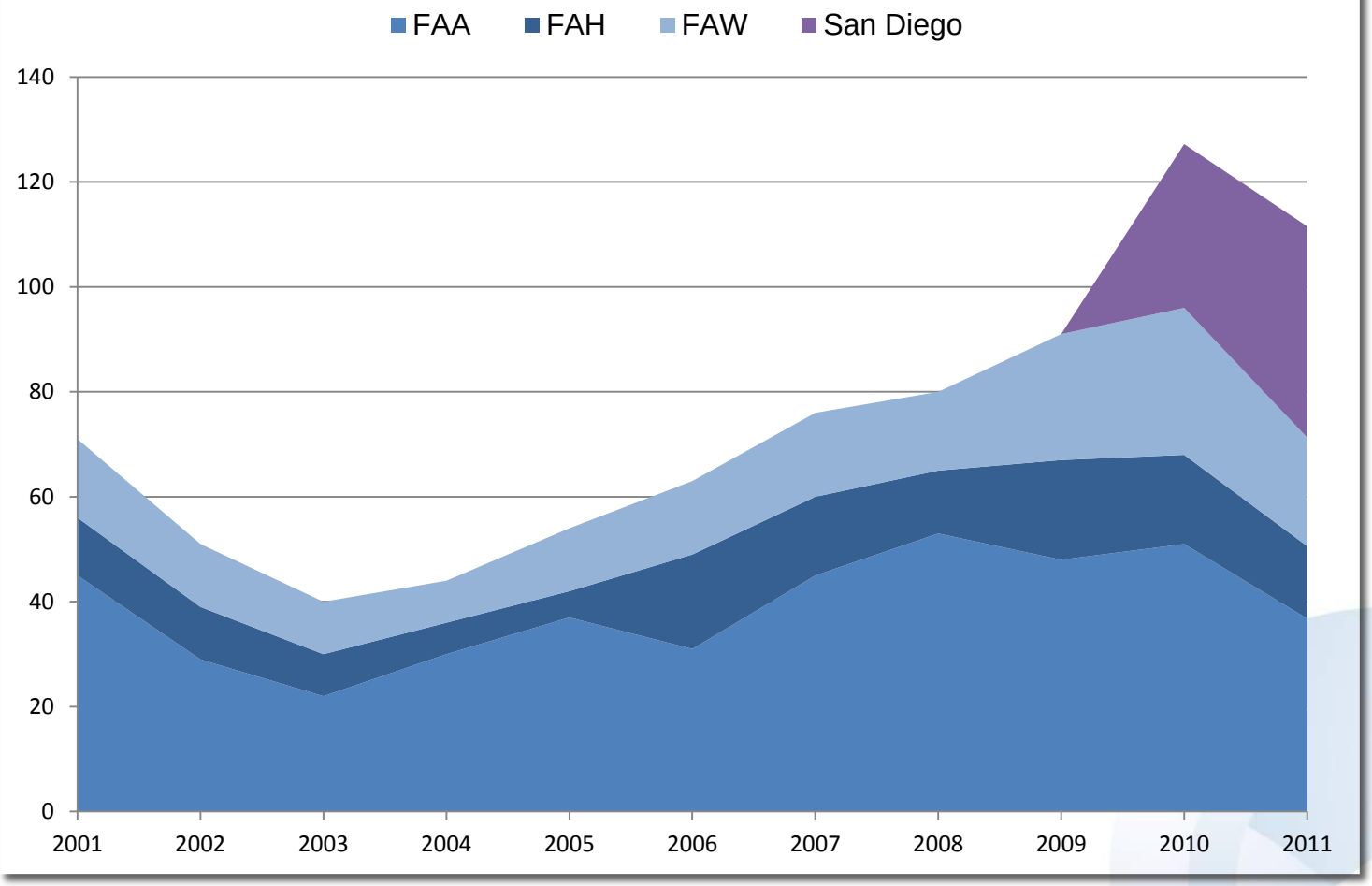
Author: John Peck *Authorised by:* Mary Birdsall *Date Issued:* 11 May 2007 *Month Review:* June
File: I:\ISO\Clinical\Consult\CPAC scoring sheet FAA 2006 *Year review:* Ann
Reference number: 5104.25 *Page 1 of 2*

Public Access

- Referral from GP

  Northern Regional Fertility Service
  PO Box 24 587
  Royal Oak
  Auckland 1345

Donor egg cycles



Dilemmas

- Age
- Weight
- Marital status
- Cancer care
- Fertility preservation
- Cross border reproductive care
- Embryo disposal
- Embryo research

Oocyte freezing

- Prior to chemo/radiotherapy
- Religious reasons
- Legislative restriction
- Strategy for cumulative outcomes
- “Social”

Oocyte freezing

A. Cobo - Vitrification

- 486 cycles
- 2721 oocytes
- 84% survived thawing
- 128 deliveries, 29% / transfer

If >8 oocytes then pregnancy rate (46.4%)

Leaders in Fertility

Case history:

6/12 trying

Age 35

Irregular cycles, 35-56 days

BMI 25

- What differential diagnosis?
- What tests to confirm?
- What treatment likely?

Case history:

Age 32

3 miscarriages in 1st trimester

- What history matters?
- What tests?
- What treatment?

Case history:

8/12 trying

Age 25

Regular cycles

- What history?
- What tests?
- What treatment?

Case history:

9/12 trying

Age 39

Partner had vas reversal, normal semen analysis

Regular cycles

Previous pregnancy terminated in prior relationship

- What history?
- What tests?
- What treatment?

Ageing is bad for you and for your gametes

Ageing is a terminal disease

Think probability and time when considering referral

Young sperm is good sperm

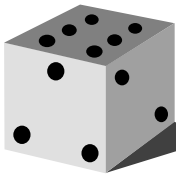
Fresh sperm is good sperm

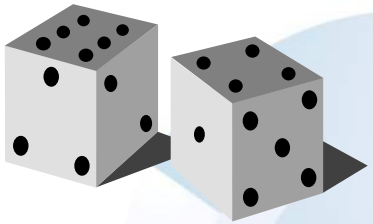
Bonk early and often

Leaders in Fertility

Monthly fecundity by age

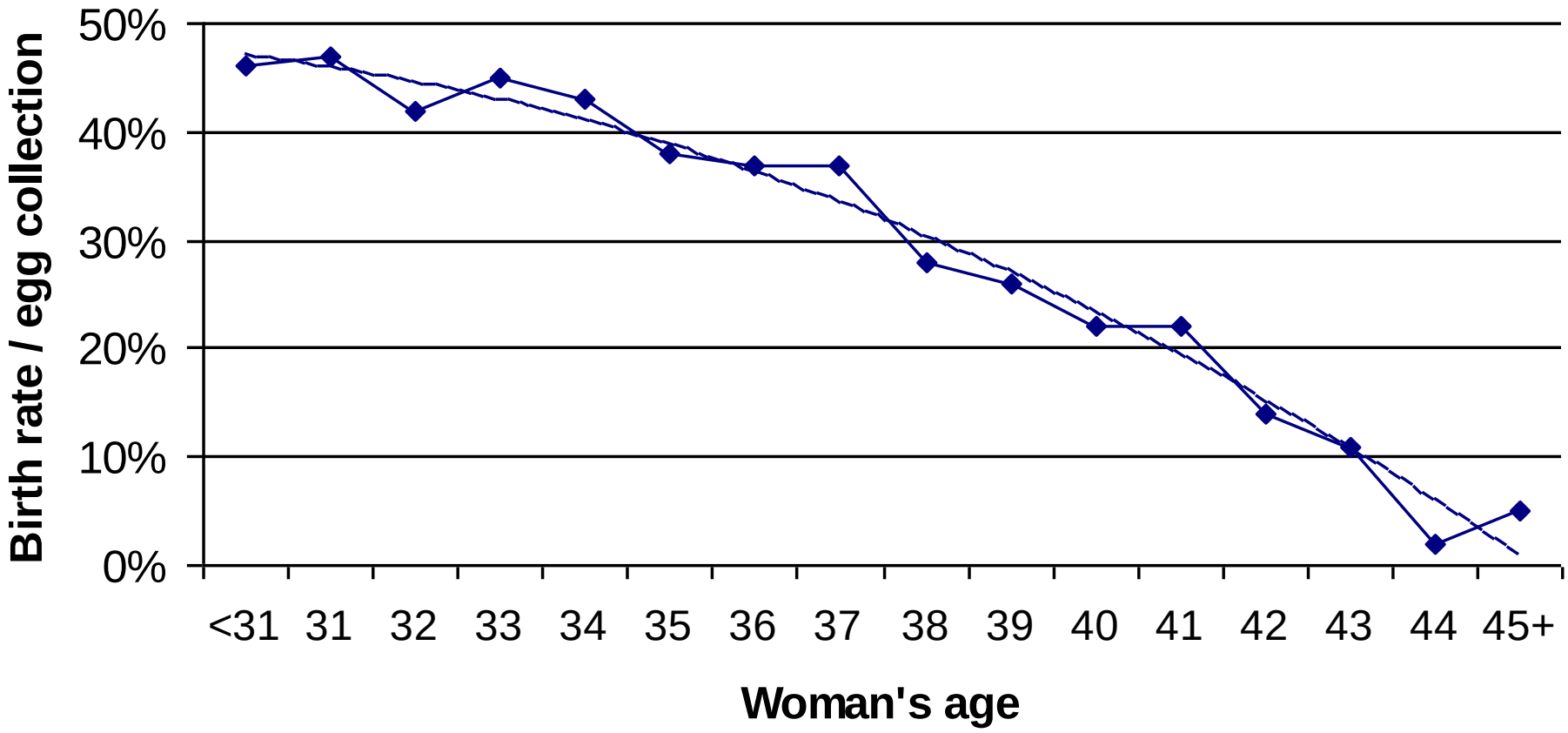
Years	%
25	25
30	20
35	16
37	11
40	6
42	4
44	2





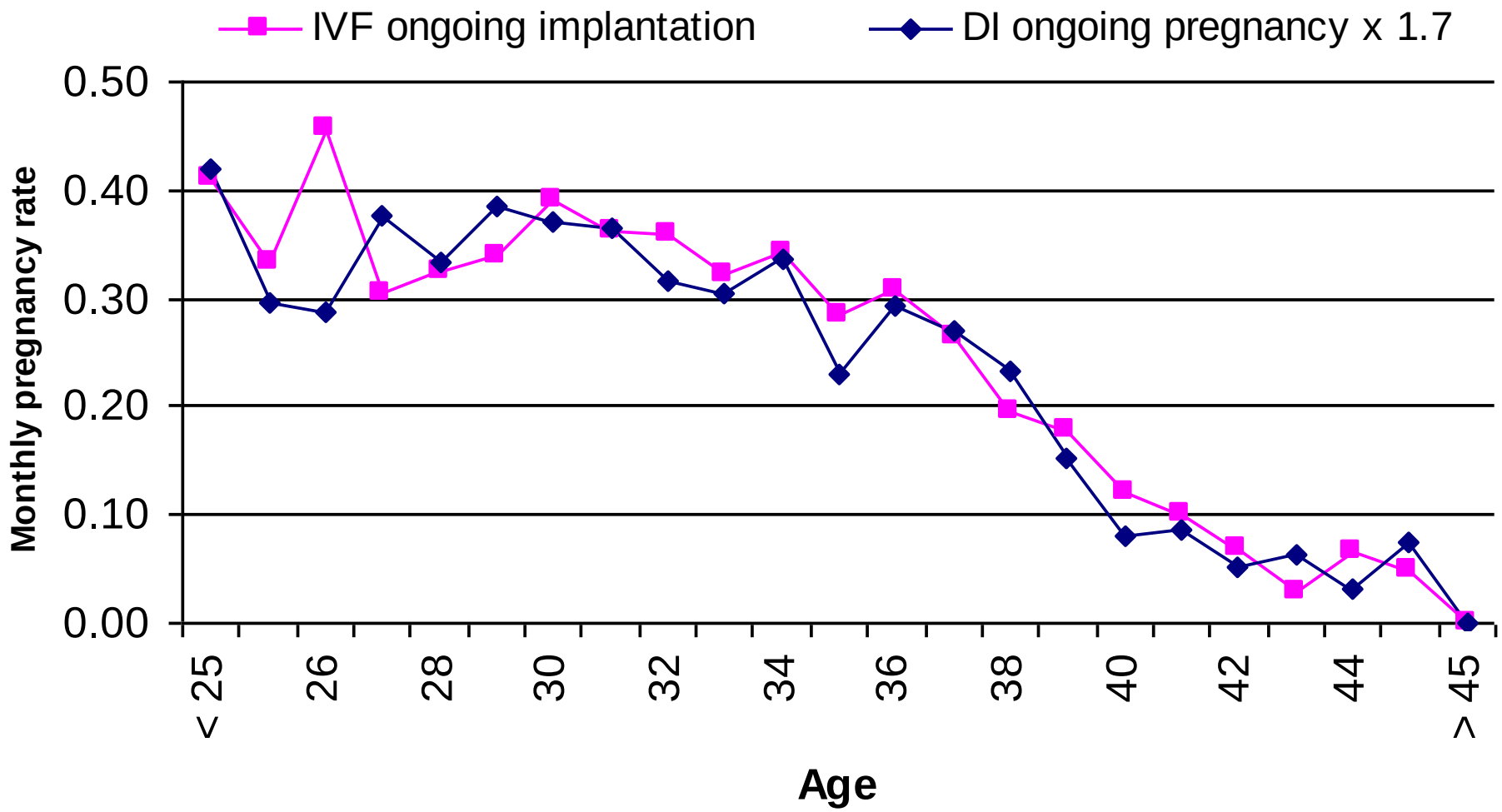
Source: Fertility Associates

Chance of baby, own eggs



Source: Fertility Associates

Decline in fertility with age



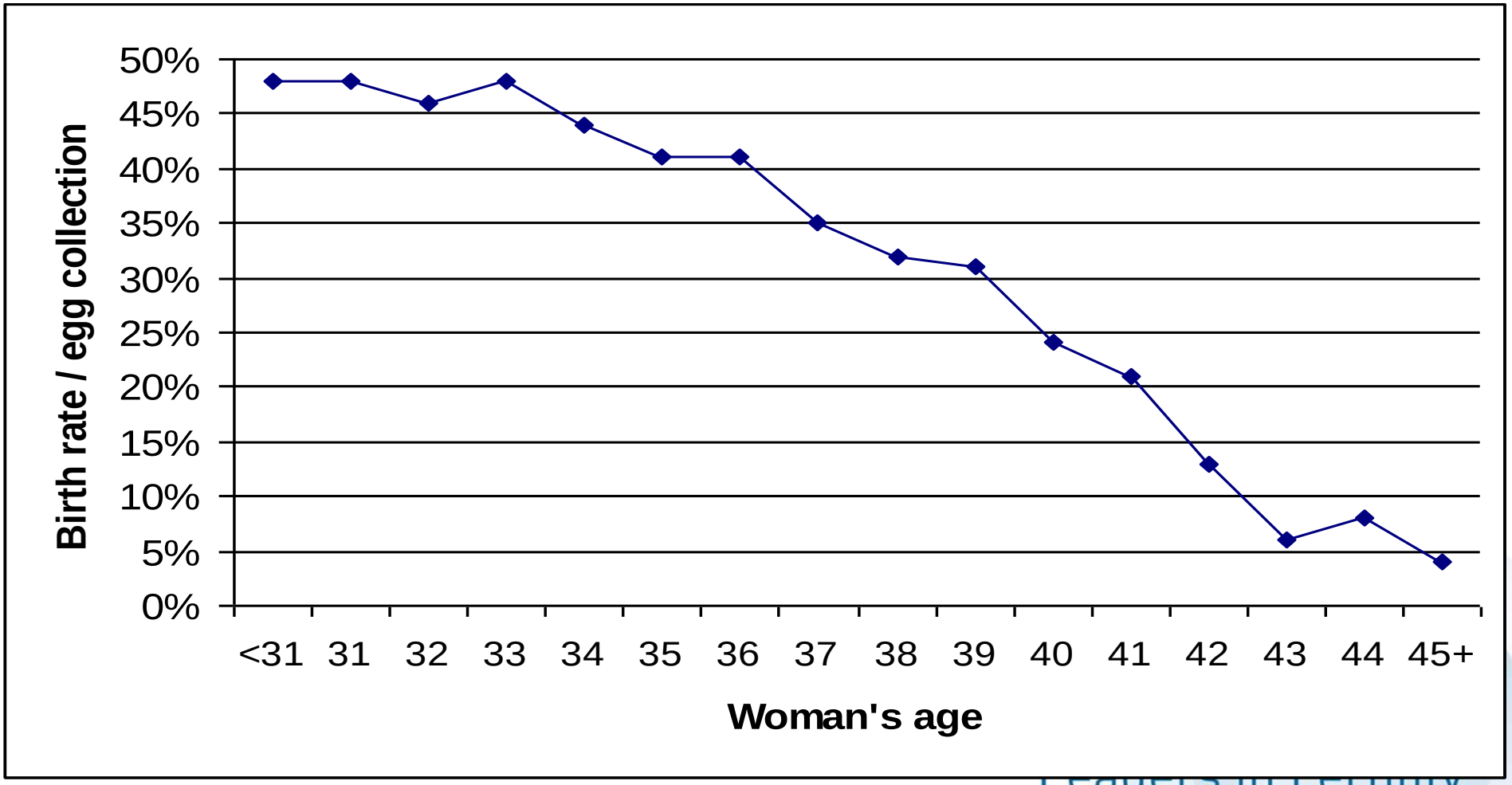
Source: Fertility Associates

A new species?

IVF-lings…

- Girls born lighter
- Taller when compared to MPH
- There is a trend towards a lower BMI in the IVF groups
- Lower fasting triglycerides and LDL levels
- Higher HDL levels
- Trend to lower fasting insulin levels
- Trend towards higher IGF I levels

IVF success rates



Source: Fertility Associates

Effect of age on outcome

Social consequences of reproductive ageing

- Altered family relationships
- Grandparents
- Have dependents at both end of life scale
- Increased requirements for state social support

The problem is a social one requiring a social solution

A new species?

IVF-lings…

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- Higher HDL levels
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Nutrition in fertility

- Clearly a factor in growth and development
- A factor in incidence of congenital abnormality
- Likely to be important in epigenetic influences
- Perhaps important in ‘ideal’ development

Blastocyst culture

- A method for selection
- ‘Best’ embryos transferred
- Fewer transfers and same # of babies

Freezing things

- Embryos
- Eggs
- Sperm

Oocyte freezing – who might benefit?

- Prior to chemotherapy (not the only option)
- Prior to surgical management of endometriosis
- Mosaic Turners Syndrome
- Family history of early menopause (with early evidence)
- ‘Social’

Sperm freezing - who might benefit?

- Prior to chemotherapy
- Prior to vasectomy
- In men with family history of declining sperm counts
- ‘Social’

The future

- Sex for fun
- Insemination for conception
- IVF using frozen eggs for ‘insurance’

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

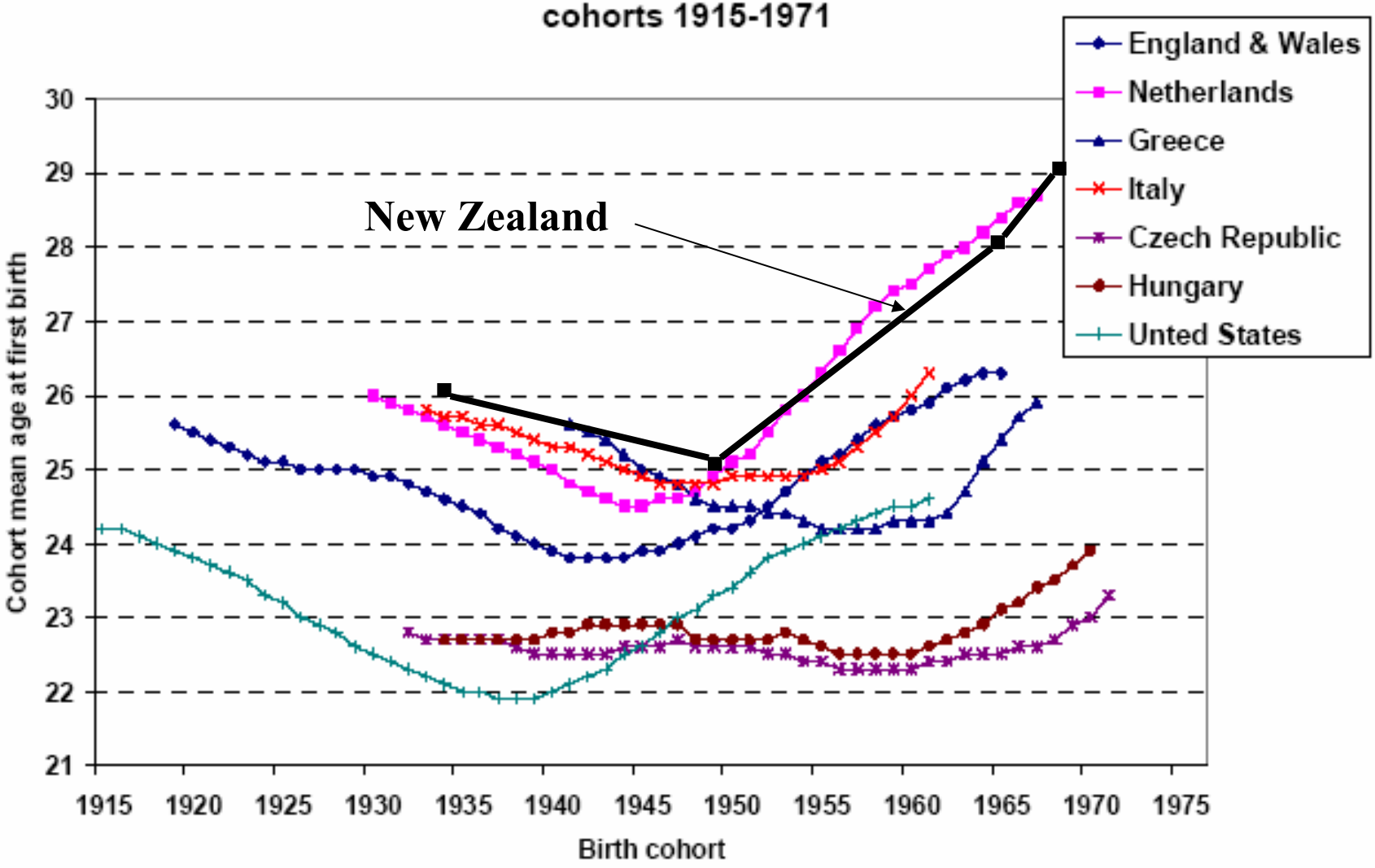
The expanding role of IVF

Dr Richard Fisher

Leaders in Fertility

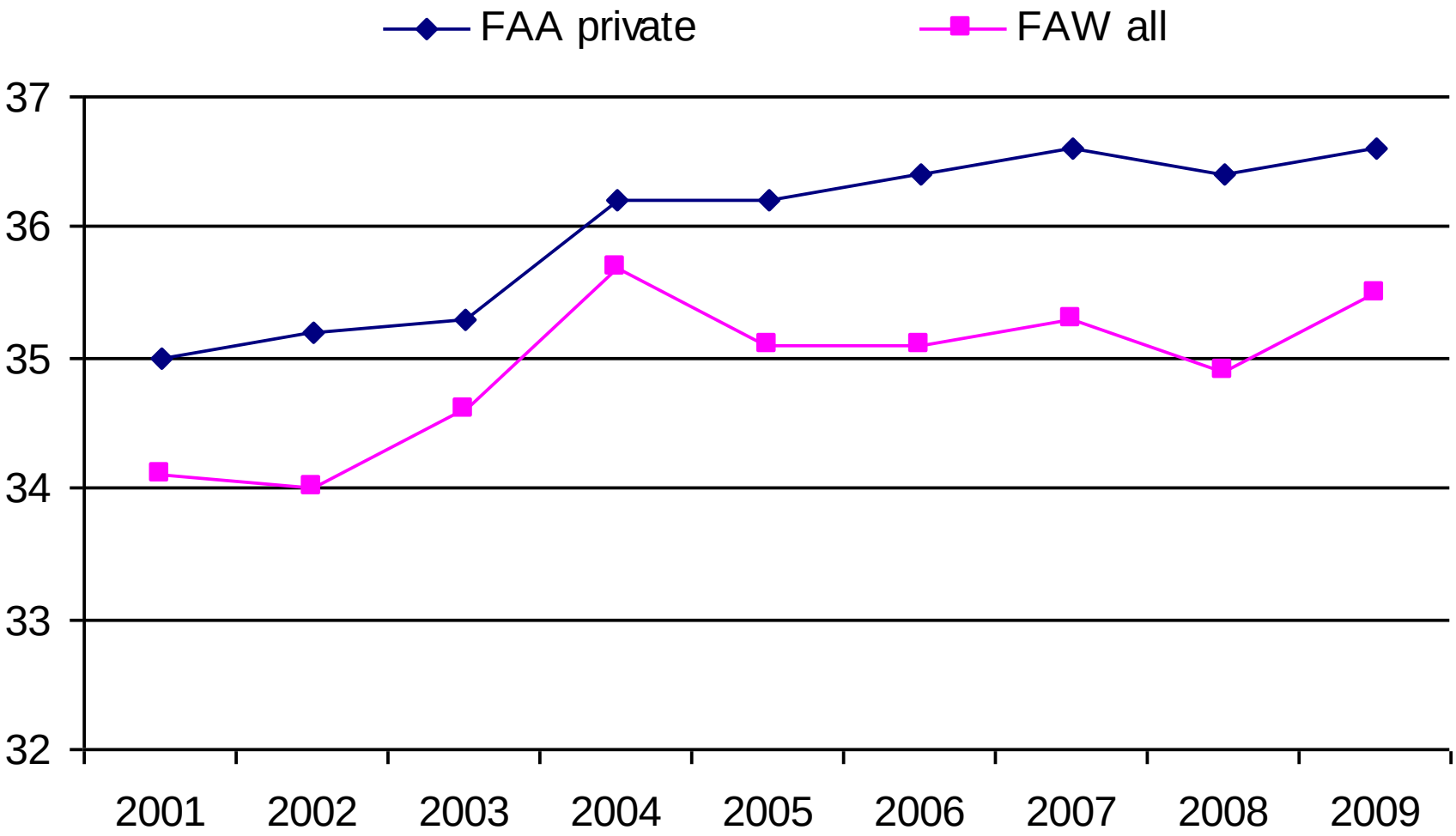
Age is a significant issue

Figure 4 - Cohort mean age at first birth, selected countries, birth cohorts 1915-1971



Source: Max Planck Institute

Average age at consultation



Source: Fertility Associates

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

Cross border reproductive care

Oct 2010 to Sept 2011 AUCKLAND

- 28 Patients to San Diego Fertility Clinic alone
- Average age of egg donors around 23
- Clinical pregnancy rate of around 65%
- Returned for thawed embryo replacement 6
- Transport of frozen embryos

NZ Census 2006

Indication for Donor Insemination at FA

Social indicators

	Proportion of cycles			
Year	**Total**	**FAA**	**FAH**	**FAW**
2002	40%	48%	29%	33%
2003	46%	44%	36%	51%
2004	45%	40%	33%	55%
2005	58%	54%	49%	65%
2006	51%	51%	31%	57%
2007	58%	59%	56%	57%
2008	59%	61%	40%	59%
2009	59%	61%	40%	62%
2010	55%	57%	38%	55%
2011 to date	62%	61%	50%	57%

Average age of women at the time of DI treatment

- Social causes 38.3
- Other causes 34.5

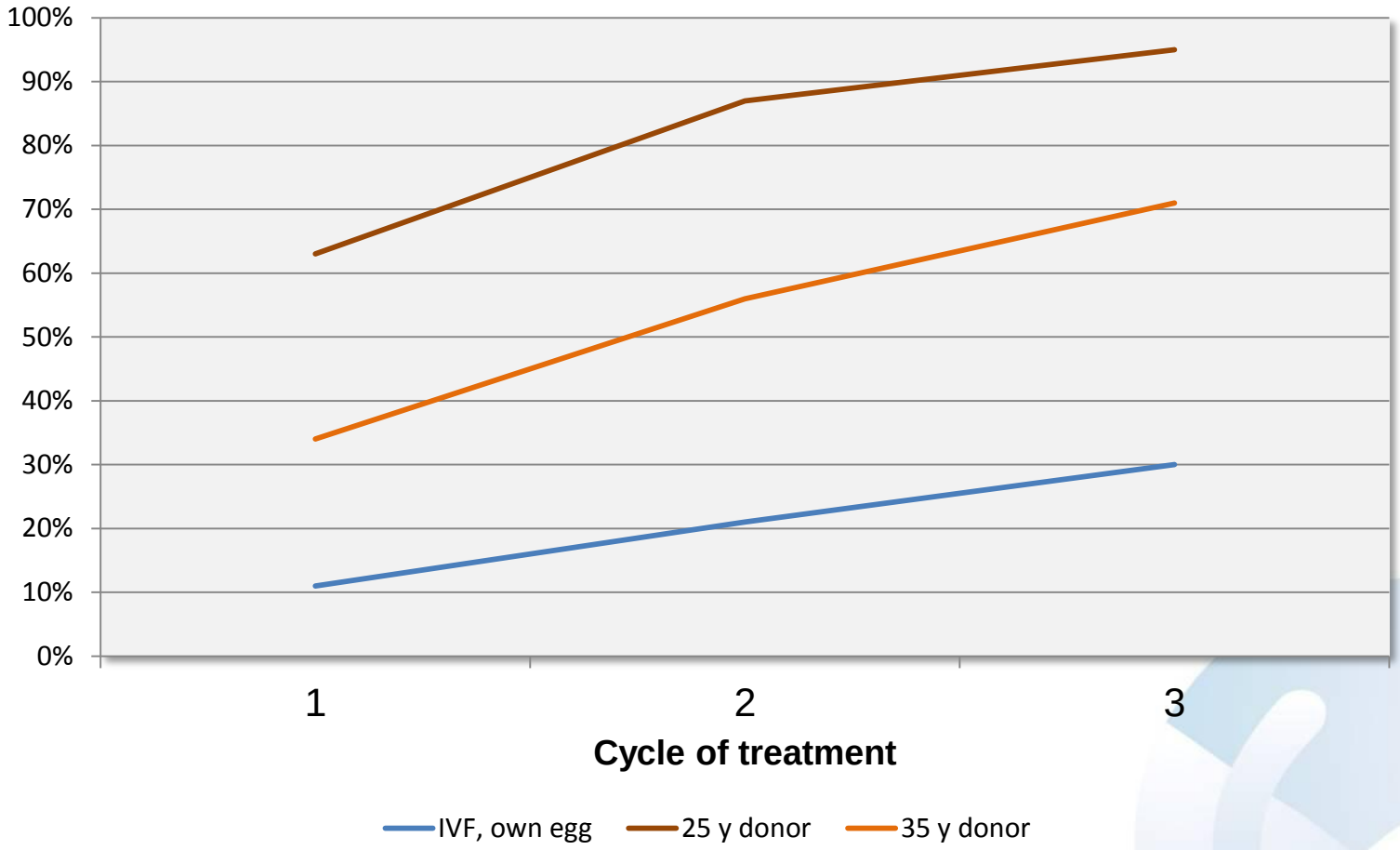
Families in NZ

- Couples with child(ren) 447,894
- One parent with child(ren) 193,635
- 30% of children are from one parent families

Statistic NZ 2006 Census

Thanks

Estimate cumulative birth rate, women 42y using donor eggs

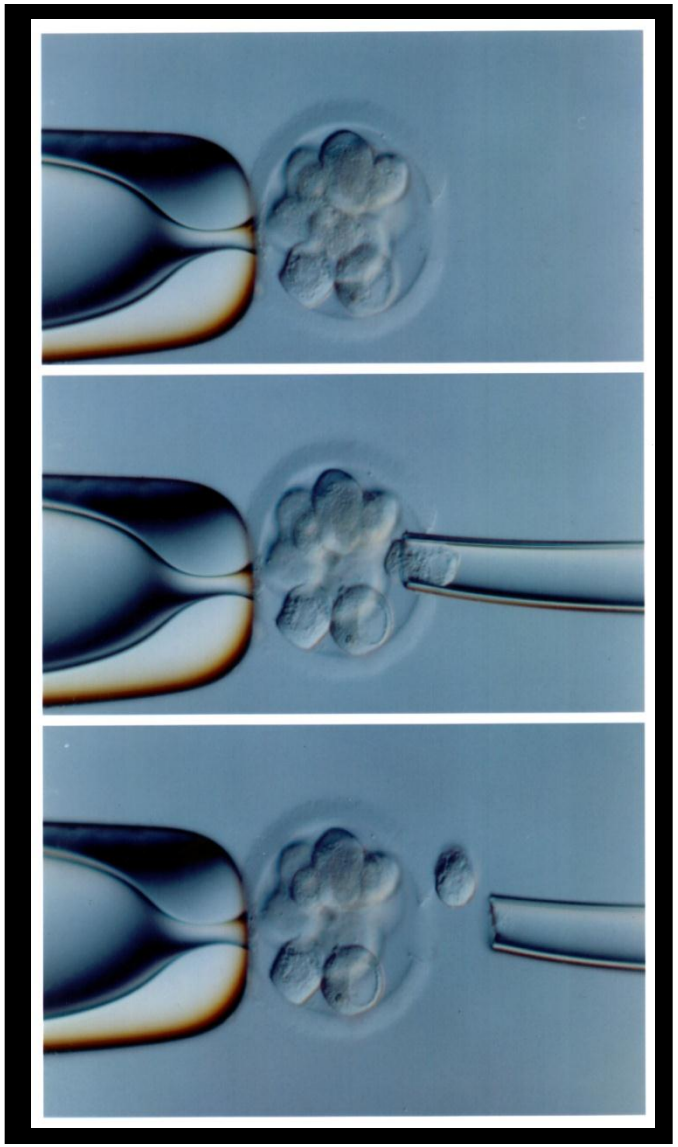


Ovarian reserve

- FSH
- AMH
- Antral follicle scan

PGD

Day 3 embryo (8 cells)

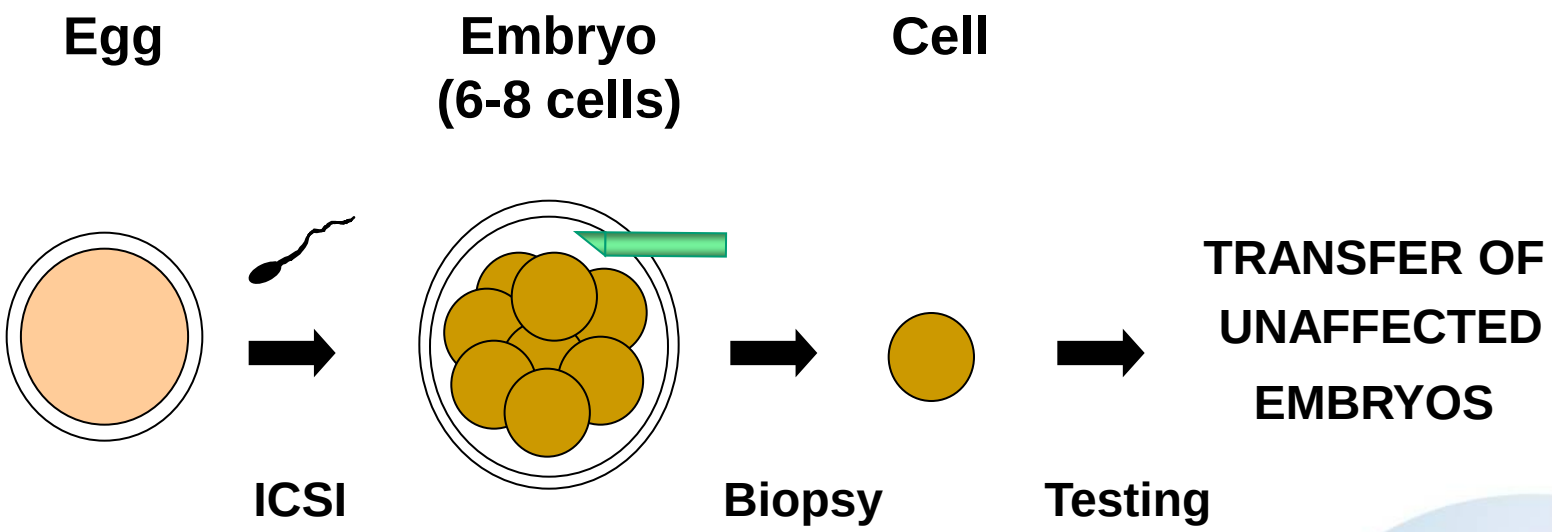


Hole in the zona pellucida by non-contact laser

Insertion of glass micropipette

Removal of a single blastomere for genetic analysis

Principle of PGD



Diagnosis

- Semen analysis
- History
- Examine
- FSH
- Testosterone
- Karyotype
- C.F. gene
- Y. microdeletion